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# Effects of 4% icodextrine, magnesium sulfate, and 0.9% sodium chloride on postoperative intraabdominal adhesions

*Efeitos da icodextrina a 4%, sulfato de magnésio e cloreto de sódio a 0.9% nas aderências intra-abdominais pós-operatórias*

Necip T. Baran<sup>1</sup>, Gokalp Okut<sup>1\*</sup>, and Mevlut R. Pekcic<sup>2</sup>

<sup>1</sup>Gastroenterology Surgery Department, Inonu University Turgut Ozal Medical Center, Malatya; <sup>2</sup>General Surgery Department, Ankara Research and Training Hospital, Ankara, Turkey

## Abstract

**Objective:** Postoperative intraabdominal adhesions are obvious cause of postoperative morbidity. In this experimental study, our aim is to compare the effects of 4% icodextrin produced for adhesion prevention, magnesium sulfate used as an anticonvulsant in obstetrics and also as a thickening lubricant in the detergent industry, and saline, which we use most frequently in abdominal irrigation, on adhesion formation. **Materials and methods:** A total of 4 groups were formed, 8 in the control group (K), 8 in the icodextrin group (I), 8 in the magnesium sulfate group (M), and 8 in the saline group (SF). Adhesions were quantitatively evaluated with the classification defined by Nair and microscopic grading defined by Zuhlke. **Results:** The macroscopic staging degree was statistically significantly lower in Group M, I, and SF compared to Group K. Again, the degree of microscopic staging was significantly lower in Group M and I compared to Group K. **Conclusions:** Three different materials were used in our study. It was observed that they significantly reduced adhesions. This study once again demonstrates the limited ability of these materials to prevent adhesion, despite the wide variety of materials used, and the need for careful adherence to tissue-respectful surgical techniques.

**Keywords:** Intra-abdominal adhesions. Magnesium sulfate. Icodextrine.

## Resumen

**Objetivo:** As aderências intra-abdominais pós-operatórias (PIA) são causa óbvia de morbidade pós-operatória. Neste estudo experimental, nosso objetivo é comparar os efeitos da icodextrina 4% produzida para prevenção de aderências, sulfato de magnésio usado como anticonvulsivante em obstetrícia e também como lubrificante espessante na indústria de detergentes e soro fisiológico, que usamos mais frequentemente em abdominais irrigação, na formação de aderências. **Materiais e Métodos:** Foram formados 4 grupos, 8 no grupo controle (K), 8 no grupo da icodextrina (I), 8 no grupo sulfato de magnésio (M) e 8 no grupo solução salina (SF). As aderências foram avaliadas quantitativamente com a classificação definida por Nair e graduação microscópica definida por Zuhlke. **Resultados:** O grau de estadiamento macroscópico foi estatisticamente significativamente menor no Grupo M, I e SF em comparação com o Grupo K. Novamente, o grau de estadiamento microscópico foi significativamente menor nos Grupos M e I em comparação com o Grupo K. **Conclusões:** Três materiais diferentes foram usados em nosso estudo. Foi observado que eles reduziram significativamente as aderências. Este estudo demonstra mais uma vez a capacidade limitada desses materiais em prevenir a adesão, apesar da grande variedade de materiais usados, e a necessidade de uma adesão cuidadosa a técnicas cirúrgicas que respeitem o tecido.

**Palabras clave:** Aderências intra-abdominais. Sulfato de magnésio. Icodextrina.

### Correspondence:

\*Gokalp Okut

Elazığ Yolu 15. Km Bulgurlu Mahallesi

P.C. 44280, Malatya, Turkey

E-mail: gokalp.okut@gmail.com

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## Introduction

Postoperative intraabdominal adhesions (PIA) are an undesirable and frequent complication of modern surgery. It is also an obvious cause of postoperative morbidity. Postoperative adhesions are usually asymptomatic. In the early postoperative period, they may cause difficult-to-treat infections, mechanical obstructions, and anastomosis complications. In the late postoperative periods, they can cause many complications such as chronic abdominal pain, adhesive ileus, and infertility. 54-74% of all intestinal obstruction cases develop due to intraabdominal adhesions<sup>1</sup>. This situation is seen in 1-3% of patients who admit to general surgery clinics. 3-8% of patients who have undergone abdominal surgery are reoperated for brid ileus<sup>2</sup>. Medical problems caused by adhesion also cause loss of workforce and increase in health expenses in patients. For PIA, various solutions (steroids, some antibiotic drugs, heparin solution, tissue plasminogen activators, icodextrin, hyaluronic acid solution, protein concentrates, transforming growth factor-beta isoforms, and neurokinin-1 receptors, etc.) have been studied for many years and minimal invasive surgical procedures have been adopted<sup>3-5</sup>. Despite the advancement of minimally invasive surgical techniques, the presence of adhesions has revealed the necessity of using substances that prevent or suppress adhesion.

In this experimental study, our aim is to compare the adhesion prevention effects of 4% icodextrin, which has been studied in recent years on its anti-adhesion effect, with magnesium sulfate, which has a lubricating effect, and saline, which is the most commonly used in routine surgery.

## Materials and methods

This study is a single-center, prospective, randomized controlled clinical trial, which has been carried out in the Department of General Surgery, Ankara Research and Training Hospital. This study was conducted with the permission of the ethics committee (No:2010-0377) in our center to investigate the effects of 4% icodextrin, magnesium sulfate, and saline in the prevention of PIA. Also, the protocol of the experiment was approved by the Local Animal Experiments Committee. The experimental procedures were performed in accordance with the Guide to the Care and Use of Laboratory Animals (National Institutes of Health Publications

No. 8023, revised 1978). The number of rats was calculated by Mead method<sup>3</sup>.

Thirty-two male Wistar Albino rats weighing between 250 and 350 g were used in the study. A total of four groups were formed, eight in the control group, eight in the icodextrin group, eight in the magnesium sulfate group, and eight in the saline group.

Standard surgical instruments were used for surgical procedures. Relaparotomy was performed on the 14<sup>th</sup> day for histopathological evaluation. In the presence of adhesion, the adhesive tape was resected together with the affected organs. In cases without adhesion, the anterior cecum was resected together with the parietal peritoneum and studied in the pathology laboratory.

All rats used in the study were kept in the same laboratory environment for a week before the experiment. During the experiment, rats were fed with city water and standard commercial rat food in cages. The rats were housed in a light and dark environment for 12 h before and after surgery, between 20-24 degrees and 30-70% humidity.

15 mg/kg intramuscular anesthesia with ketamine hydrochloride was applied to the subjects after 12 h of fasting. The abdominal skin was shaved and the field was cleaned with povidin-iodine. In order to apply the adhesion model, laparotomy was performed with a standard midline incision following anesthesia in rats. After it was determined that there was no adhesion in the abdomen, the cecum was revealed.

The anterior wall of the cecum taken outside the abdomen was determined, and wipings were made with gauze until serosal punctate hemorrhage occurred. After the cecum abrasion, it was kept for 5 min before being returned to the abdomen, and it was cooled and dried.

Then, 1 cm long incision were applied on the peritoneum on both sides of the incision, perpendicular to the incision, one on the right and left, and bleeding was ensured.

Group K: After the described surgical procedures were performed, the organs were returned to the abdomen.

Group M: In the Magnesium Sulfate group, after the mentioned surgical procedures were performed, the organs were returned to the abdomen and intraperitoneally under the incision, 1 ml of magnesium sulfate diluted in 1 in 1 distilled water was given.

Group I: After surgical procedures were performed in the 4% icodextrin group, the organs were returned to the abdomen and 1 ml of 4% icodextrin was given intraperitoneally under the incision.

Group SF: After performing the mentioned surgical procedures in the saline (SF) group, the organs were returned to the abdomen and 1 ml of SF was given to the area under the incision.

In all patients, the anterior abdominal wall muscle layer was sutured with continuous sutures with 4/0 round vicryl and the skin was sutured with 4/0 round prolene.

Considering the potential cardiac side effects of Magnesium Sulphate, magnesium sulfate was diluted with 1 in 10 distilled water and then 1 ml was preferred.

Following the sacrifice of all rats with high doses of ether on the 14<sup>th</sup> day in accordance with the Helsinki agreement, a U incision was made in the abdomen and the abdominal walls were retracted downwards to provide maximum vision. Then, adhesions were quantitatively evaluated with the classification defined by Nair et al. (Table 1 and Fig. 1). The evaluation was carried out by two separate persons, in accordance with the classification previously described to them, and in a double-blind manner. The average of the two evaluations was used for statistical evaluation.

Following macroscopic evaluation, the affected organs were excised together with the adhesion band in rats that developed adhesion, while in those without adhesion, the cecum anterior wall and parietal peritoneum were excised for pathological sampling, including all layers except skin. Pathological pieces were fixed in 10% buffered formol. Sections with a thickness of 5 micrometers were taken on a slide. The pathologist conducting the examination did not know from which group the plays were taken. After histopathological evaluation, the plays were subjected to microscopic grading defined by Zuhlke<sup>4</sup> (Table 2 and Fig. 2).

All operations, scoring and evaluation of findings were carried out by the same team.

## Statistical analysis

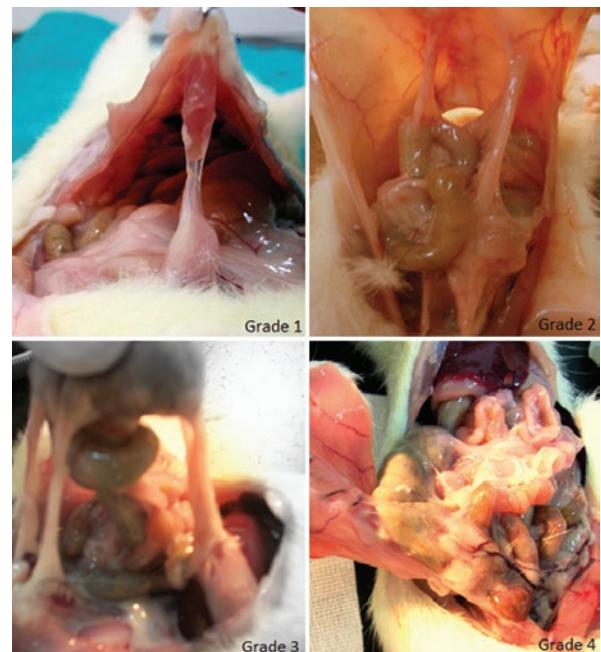
All statistical analyzes were performed using SPSS software version 22 for Windows (SPSS Inc., Chicago, IL, USA) and the results were considered statistically significant if  $p < 0.05$ . Descriptive statistics were shown as median (minimum-maximum). The significance of the difference in macroscopic and microscopic staging between the groups was investigated with the Kruskal-Wallis test.

## Results

During the study period, no rats in the groups died. There were no rats in poor health that would require

**Table 1. "Nair" macroscopic adhesion classification**

<b>Grade 0 No adhesion</b>		
Insubstantial Adhesion	Grade 1	Single band of adhesions between viscera or from one viscus to the abdominal Wall
Substantial Adhesion	Grade 2	Two bands between viscera or between viscera and abdominal Wall
	Grade 3	More than two bands between viscera or between viscera and abdominal wall, or the entire intestine forming a mass adhering to the abdominal wall to the abdominal wall
	Grade 4	Viscera directly attached to the abdominal wall, regardless of number or extent of bands



**Figure 1.** Images according to the Nair Classification in our own study.

sacrifice. Surgical procedures and administration of drugs were well tolerated during the study period.

Macroscopic evaluation results according to the Nair classification are shown in table 3 and microscopic evaluation results according to Zuhlke classification are shown in table 4.

According to the comparison results of the groups among themselves (Table 5);

The macroscopic staging degree was statistically significantly lower in Group M, I, and SF compared to Group K ( $p = 0.005$ ;  $p < 0.001$  and  $p < 0.001$ ). Again, the degree of microscopic staging was significantly lower in Groups M and I compared to Group K ( $p = 0.030$  and  $p < 0.001$ ). With Group M, respectively; no

**Table 2. "Zuhlke" microscopic adhesion classification**

Grade 1	Weak, connective tissue, rich cell, new and old fibrin, thin reticulin fibriles
Grade 2	Connective tissue which has cells and capillaries. Few collagen fibers
Grade 3	Thicker connective tissue. Few cells and elastic and smooth muscle fibers, more vessels
Grade 4	Old and thick granulation tissue, poor cells, difficult separation of serosal surfaces

**Table 5. Results of multiple comparison between groups regarding macroscopic and microscopic staging**

Multiple comparisons	Macroscopic	Microscopic
Group K – Group M	p = 0.005	p = 0.030
Group K – Group I	p < 0.001	p < 0.001
Group K – Group SF	p < 0.001	p = 0.053
Group M – Group I	p = 0.119	p = 0.207
Group M – Group SF	p = 0.638	p = 0.788
Group I – Group SF	p = 0.267	p = 0.129

**Table 3. Macroscopic staging according to groups**

Groups	Macroscopic Staging median (min-max)
Group K	3 (2-4) <sup>a,b,c</sup>
Group M	2 (1-4) <sup>a</sup>
Group I	1.5 (1-3) <sup>b</sup>
Group SF	2 (1-4) <sup>c</sup>

<sup>a</sup>The difference between Group K and Group M is statistically significant (p = 0.005).<sup>b</sup>The difference between Group K and Group I is statistically significant (p < 0.001).<sup>c</sup>The difference between Group K and Group SF is statistically significant (p < 0.001).**Table 4. Microscopic staging according to groups**

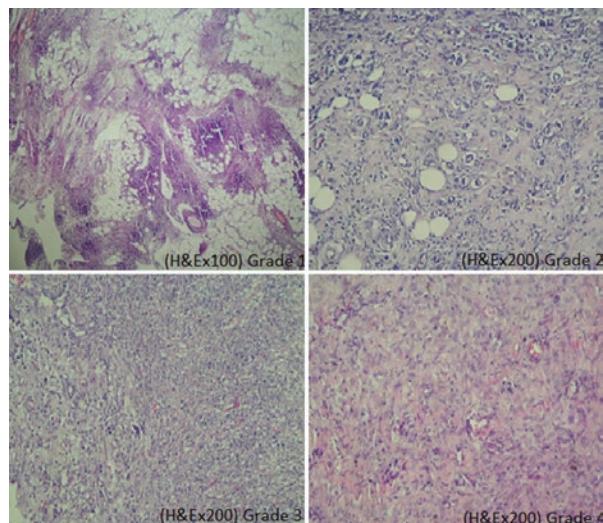
Groups	Microscopic Staging median (min-max)
Group K	3 (2-4) <sup>a,b</sup>
Group M	2 (2-3) <sup>a</sup>
Group I	2 (1-3) <sup>b</sup>
Group SF	2.5 (1-3)

<sup>a</sup>The difference between Group K and Group M is statistically significant (p = 0.030).<sup>b</sup>The difference between Group K and Group I is statistically significant (p < 0.001).

statistically significant difference was found between Group I and Group SF in terms of macroscopic staging (p = 0.053; p = 0.207). With Group M, respectively; no statistically significant difference was found between Group I and Group SF in terms of microscopic staging (p = 0.207; p = 0.788). No statistically significant difference was found between Group I and Group SF in terms of macroscopic staging (p = 0.267). No statistically significant difference was found between Group I and Group SF in terms of microscopic staging (p = 0.129).

## Discussion

PIA is an important cause of long-term morbidity. Strategies such as the use of various pharmacological

**Figure 2.** Images according to the Zuhlke Classification in our own study.

agents as well as rigorous surgical techniques have been adopted to prevent adhesion formation. Currently, available knowledge suggests that three major methods have the potential to reduce PIA: (I) reduction of peritoneal trauma using minimally invasive approaches; (II) use of pharmacological agents to inhibit fibrin formation; and (III) reducing contact between intraabdominal organs and peritonized structures after dissection using film or fluid barriers. However, none of these approaches have been adopted as standard therapy, and research is still ongoing for a final solution<sup>5</sup>.

There are studies showing that 4% Icodextrin reduces primary PIA and their recurrence by separating the damaged area during the healing phase<sup>6,7</sup>. A prospective randomized controlled study by Catena et al. showed that the use of icodextrin in small bowel obstructions due to adhesions is safe and reduces the risk of PIA formation and re-obstruction. Icodextrin

causes less scarring by stimulating the local inflammatory and immunological response, not as a simple physicochemical barrier that reduces cell activation and invasion. The authors concluded that the application of 4% Icodextrin to extensively deserosalized surfaces is more suitable than other non-adherent barriers. In contrast to these studies, there are articles in the literature showing that 4% Icodextrin does not reduce adhesion formation. Ditzel et al. and Bellon et al. investigated 4% Icodextrin in two different studies and failed to show a significant reduction in PIA<sup>8,9</sup>. In our study, it was seen that 4% Icodextrin reduced adhesion macroscopically and microscopically.

In our study, three different liquid materials were used, based on the adhesion prevention effect, keeping the adhesion foci away and forming fluid surfaces and preventing adhesion. Recently, many studies have been carried out on intraabdominal barriers to keep possible adhesion surfaces away from each other to prevent adhesion formation<sup>10-12</sup>. These substances keep the damaged ischemic tissues separate from each other. It also inhibits the binding of free macrophages and reduces local fibroblastic infiltration. In this way, it is thought that the process that results in the development of adhesion is prevented by preventing ischemic tissues from approaching neighboring organs for blood supply<sup>13</sup>. The most appropriate anti-adhesive material should not be permanent; It should not contain adhesiogenic properties; should continue its effect in the presence of blood and should not adversely affect wound healing<sup>14</sup>. All of these have required the investigation of agents that are more effective, cheaper, relatively free of side effects and toxicity, and easy to apply and make them suitable for clinical use<sup>13</sup>. One of the agents developed for this purpose is Icodextrin. It is a disposable, sterile, clear, colorless to pale yellow liquid containing icodextrin at 4% concentration in an electrolyte solution for intraperitoneal administration. It is an iso-osmolar and biologically degradable, high molecular weight (12,000-20,000 dalton) kind of glucose polymer solution. It is used intraperitoneally to reduce adhesions after abdominal surgery.

Although there are studies in the literature with adhesion inhibitors containing icodextrin, there is no study comparing this substance with saline and magnesium sulfate. Magnesium sulfate was chosen both because it is in the icodextrin solution and because it is a lubricant and thickener.

In our study, 4 groups were formed as the icodextrin group (Group I), the saline group (Group SF), and the

magnesium sulfate group (Group M), one of which is a control (Group K). There was no statistically significant difference between Group K and Group SF in terms of microscopic staging. The high degree of both microscopic and macroscopic adhesion in the control group compared to the other three groups indicates that our anti-adhesion model was successful.

When the adhesion prevention potentials of magnesium sulfate, icodextrin, and saline applications were compared; although it has been observed that icodextrin reduces adhesions more at the macroscopic level, it is revealed that these three substances are not statistically superior to each other in terms of adhesion prevention.

The success of icodextrin solution in preventing adhesions compared to the control group is an expected result. Compared to the relatively more professional 4% icodextrin produced for adhesion prevention, it is important that the adhesion prevention effect of magnesium sulphate used for the 1<sup>st</sup> time is as high as icodextrin, since it is a new material used for this purpose. Considering the potential cardiac side effects during the study, we think that the fact that it prevents adhesion, although it is diluted every 10 times, will allow the planning of new studies for this substance.

Icodextrin shows some local and systemic side effects in case of high amount and prolonged contact with the peritoneum. Some of those; abdominal pain, peritonitis, nausea, vomiting, sweating, flu-like symptoms, headache, hypertension, and hyperglycemia. It may interact with adefovir, blood pressure medications, digoxin, entecavir, insulin, metformin, or HIV or AIDS medications. It is not recommended for use in pregnant women<sup>15</sup>. Magnesium sulfate has side effects such as chest pain, respiratory distress, confusion, decreased reflexes, hypotension, and anxiety. It can be used in pregnant women<sup>16</sup>.

The small sample group is one of the weak points of our study. The reason for this is the insufficient facilities in the animal laboratory at the time of the study and different animal experiments were carried out in the same period.

## Conclusion

Despite all the new scientific developments, due to the fact that auxiliary techniques for postoperative adhesions are not fully accepted, new research focuses on finding intraperitoneally applicable materials that significantly reduce adhesions, are affordable and do not cause side effects such as wound healing, infection, and bleeding.

Three different materials were used in our study. It was observed that they significantly reduced adhesions. Although the magnesium sulfate used for the 1<sup>st</sup> time was diluted, its adhesion prevention effect was comparable to that of 4% icodextrin and SF. In this respect, we think that magnesium sulfate is a material that needs to be studied for its anti-adhesion effect.

This study once again demonstrates the limited ability of these materials to prevent adhesion, despite the wide variety of materials used, and the need for careful adherence to tissue-respectful universal surgical techniques.

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## Conflicts of interests

The authors of the manuscript certify that all authors of the article do not have commercial associations (e.g. consultancies, stock ownership, equity interests, patent licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article.

The corresponding author is in possession of this document.

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# Distribution of peripheral blood cells after splenectomy in immune thrombocytopenia patients

*Distribución de glóbulos periféricos después de la esplenectomía en pacientes*

Arife Simsek\*

Department of General Surgery, Inonu University, School of Medicine, Malatya, Turkey

## Abstract

**Background:** There are some difficulties regarding the evaluation of the post-splenectomy state. **Objective:** The objective of the study is to compare the post-splenectomy blood changes of immune thrombocytopenia (ITP) patients with those of trauma patients, 1 month and  $\geq 6$  months after surgery. **Methods:** Medical records of patients, who had undergone total splenectomy for ITP and trauma at a tertiary center between January 2009 and December 2019, were retrospectively reviewed. **Results:** The current study included 52 patients, who had undergone splenectomy for ITP (57.7%), and trauma (42.3%). Splenectomy, irrespective of the indications, resulted in an increase in hemoglobin concentration, hematocrit, and platelet levels. Neutrophils were responsible for the preoperative leukocytosis in ITP patients, and neutrophilia was ameliorated by splenectomy and also withdrawal of the steroid therapy in some patients. Decreased neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio supported the finding that splenectomy ameliorated inflammation in ITP patients. **Conclusions:** Splenectomy, irrespective of the indications, resulted in an increase in hemoglobin concentration, hematocrit and platelet levels, lymphocyte, monocyte, and eosinophil counts. Splenectomy ameliorated inflammation in ITP patients and resulted in a change in percentages of leukocytes in favor of basophils.

**Keywords:** Immune thrombocytopenia. Neutrophil-to-lymphocyte ratio. Peripheral blood cells. Splenectomy. Trauma.

## Resumen

**Antecedentes:** Existen algunas dificultades con respecto a la evaluación del estado post-esplenectomía. **Objetivo:** Comparar los cambios sanguíneos post-esplenectomía de pacientes con PTI con los de pacientes traumatizados, 1 mes y  $\geq 6$  meses después de la cirugía. **Métodos:** Se revisaron retrospectivamente las historias clínicas de los pacientes que habían sido sometidos a esplenectomía total por PTI y trauma en un centro terciario entre enero de 2009 y diciembre de 2019. **Resultados:** El presente estudio incluyó a 52 pacientes, que habían sido sometidos a esplenectomía por PTI (57.7%) y traumatismo (42.3%). La esplenectomía, independientemente de las indicaciones, resultó en un aumento de la concentración de hemoglobina, hematocrito y niveles de plaquetas. Los neutrófilos fueron responsables de la leucocitosis preoperatoria en pacientes con PTI, y la neutrofilia mejoró mediante esplenectomía y también la suspensión de la terapia con esteroides en algunos pacientes. La disminución de NLR y PLR apoyó el hallazgo de una disminución de la inflamación en la esplenectomía en pacientes con PTI. La esplenectomía resultó en un cambio en los porcentajes de leucocitos a favor de los basófilos en

## Correspondence:

\*Arife Simsek

Bulgurlu, Malatya Elaziğ Yolu

10.KM, 44210

C.P. 44000, Battalgazi/Malatya, Turkey

E-mail: draksimsek@yahoo.com.tr

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pacientes con PTI. **Conclusiones:** La esplenectomía, independientemente de las indicaciones, resultó en un aumento de la concentración de hemoglobina, niveles de hematocrito y plaquetas, recuentos de linfocitos, monocitos y eosinófilos. Una disminución de la inflamación en la esplenectomía en pacientes con PTI resultó en un cambio en los porcentajes de leucocitos a favor de los basófilos.

**Palabras clave:** Trombocitopenia inmune. PTI. NLR. Glóbulos periféricos. Esplenectomía. Trauma.

## Introduction

As a major lymphoid organ, receiving 5% of cardiac output every minute, the spleen has a fundamental role in the reticuloendothelial system. It removes antigens, aging platelets, and erythrocytes from the circulation and participates in iron recycling, as well as in the production of lymphocytes, immunoglobulins, and opsonins<sup>1</sup>. It serves as a storage site for blood components and supplies erythrocytes and platelets in increased demand, such as trauma<sup>1</sup>.

The knowledge of splenic functions is mostly based on murine studies. However, morphological and physiological differences between humans and other non-primate species may obscure understanding of splenic functions<sup>1,2</sup>. *Ex-vivo* studies are preferred, due to limitations in *in-vivo* human testing, to analyze the interactions between the functioning spleen and circulating blood components. *Ex-vivo* studies are performed in splenectomized patients by comparing preoperative conditions with postoperative ones. However, there are some difficulties regarding the evaluation of the post-splenectomy state. Along with surgical stress, any indication itself for splenectomy may interfere with the evaluation process by promoting cellular abnormalities<sup>3</sup>.

Immune thrombocytopenia (ITP) is an acquired form of thrombocytopenia that is characterized by autoantibody-mediated destruction of platelets and suppression of platelet production<sup>4</sup>. As a primary site of platelet removal, the spleen plays a critical role in the pathogenesis of ITP. It also participates in the production of anti-platelet antibodies<sup>4</sup>. Although splenectomy is associated with a better outcome than any other therapy, it is generally reserved (as second-or third-line therapy) for patients who fail medical therapy, as it poses short and long-term risks<sup>4</sup>. Although several efforts have been made to predict splenectomy responses, they have not been fully successful<sup>4</sup>.

This study aimed to compare the post-splenectomy blood changes of ITP patients with those of trauma patients, 1 month and  $\geq 6$  months after surgery. The comparison of ITP patients with trauma patients, who

are hematologically normal people, may clarify the post-splenectomy changes in patients with ITP.

## Material and method

Medical records of patients, who had undergone total splenectomy for ITP and trauma at a tertiary center between January 2009 and December 2019, were retrospectively reviewed. Exclusion criteria included partial splenectomies, patients younger than 18 years of age, patients with congestive heart failure, patients with chronic pulmonary diseases, patients with chronic liver diseases, patients with malignant diseases, and patients with autoimmune diseases other than ITP. The patients, who had not had a blood test in the 1<sup>st</sup> month and/or  $\geq 6$  months after surgery and/or who had died before the blood samplings were also excluded.

The diagnosis of ITP was based on isolated thrombocytopenia in the absence of other causes of thrombocytopenia. In cases where platelet counts were  $< 30 \times 10^9/L$  and/or patients had signs and symptoms of bleeding, first-line therapy was administered with 1 mg/kg/day oral methylprednisolone. In addition to steroid therapy, some patients had taken danazol, azathioprine, cyclosporine, cyclophosphamide, vin-cristine, thrombopoietin receptor agonists, intravenous immunoglobulin. For the management of ITP, medical treatment was applied initially, and splenectomy was indicated when medical treatment was exhausted in long-term follow-up. Appropriate preparation of patients for surgery was performed.

The data included demographics, clinical findings, laboratory findings, and therapeutic interventions. The following characteristics were recorded:

- Demographics: Age and gender;
- Clinical findings: Comorbid factors, postoperative hospital stay, and perioperative complications;
- Laboratory findings: Preoperative and postoperative (1<sup>st</sup> month and/or  $\geq 6$  months after surgery) complete blood counts (hematocrit, hemoglobin, white blood cell, platelet, and mean corpuscular volume [MCV], and percentages of neutrophils, lymphocytes, eosinophils, basophils, and monocytes) and

inflammatory markers (neutrophil-to-lymphocyte ratio [NLR] and platelet-to-lymphocyte ratio [PLR], which were calculated based on complete blood count results; and

- Therapeutic interventions: Surgical technique (open or laparoscopic), and transfusion of blood components.

The study was conducted according to the principles set forth by the Helsinki Declaration of 1975. Approval from the Human Ethics Committee of the Institution was obtained.

### **Statistical analysis**

Data were analyzed using SPSS 17.0 for Windows. Continuous variables were presented as means with SDs; categorical variables were presented as numbers with percentages. The Shapiro-Wilk test was used to analyze the normality of the groups. For intergroup comparison, the Chi-squared test or Fisher's exact test was used for categorical variables. The Student's t-test was used for continuous variables with normal distribution. The Mann-Whitney U-test was applied for non-normally distributed variables. The paired-sample t-test was used to compare the changes of laboratory values, at the 1<sup>st</sup> month and ≥ 6 months after surgery. The level of significance was accepted as 0.05.

## **Results**

The current study included 52 patients, who had undergone splenectomy for ITP (57.7%), and trauma (42.3%). The mean age was  $37.1 \pm 15.4$  (range: 18-76) years. Of the 52 patients, 33 (63.5%) had one or more systemic diseases including ITP (n: 30), hypertension (n: 2), diabetes mellitus (n: 2), coronary artery diseases (n: 1), and psychiatric disease (n: 1, depression). All trauma cases were operated on with open technique. Of the ITP cases, 80% were operated with laparoscopic technique. Transfusion of blood components was required in 48.1% of the cases. The mean length of hospitalization was  $9.9 \pm 15.8$  (range: 2-96 days) (Table 1). All ITP patients had a complete response to splenectomy, which means platelet count >  $100 \times 10^9/L$  and the absence of bleeding without any treatment after splenectomy.

### **Hematocrit and hemoglobin count**

One month after surgery, we did not find any significant change in hematocrit and hemoglobin levels

in both groups (Table 2). However, at least 6 months after surgery, there was a significant increase in hematocrit and hemoglobin levels in both groups (Table 2). There was not a significant difference between the groups in terms of preoperative and postoperative hematocrit levels (Table 1). Although preoperative and postoperative 1<sup>st</sup>-month hemoglobin concentration was not different between the groups, it was significantly lower in the ITP group 6 months after surgery (Table 1).

### **MCV**

The preoperative and postoperative MCVs were lower in the ITP group compared to the trauma group (Table 1). One month after surgery, there was a significant increase in MCVs in the trauma group. However, these declined to preoperative values after 6 months (Table 2).

### **Platelet count**

There was a significant increase in postoperative platelet counts in both groups (Table 2). One month after surgery, the increase in platelet count was more prominent in the trauma group but declined slightly overtime. The preoperative and postoperative 1<sup>st</sup>-month platelet counts were statistically higher in the trauma group. However, the difference disappeared after 6 months (Table 1).

### **Leukocyte count**

The preoperative leukocyte count was statistically higher in the trauma group. There was no statistical difference between the groups on postoperative courses (Table 1). There was a significant decrease in postoperative leukocyte counts in the trauma group, although they were still above the normal range (Table 2). However, we did not find any significant change in leukocyte count in the ITP group.

### **Neutrophil count**

The pre-operative neutrophil count was statistically higher in the trauma group (Table 1). There was no statistical difference between the groups on post-operative courses (Table 1). There was a significant decrease in post-operative neutrophil counts in both groups (Table 2).

**Table 1. The characteristics of the patients and comparison of the laboratory values of ITP patients with those of trauma patients**

Laboratory findings	Total (n: 52) mean ± SD or n (%)	Trauma (n: 22) mean ± SD or n (%)	ITP (n: 30) mean ± SD or n (%)	p
Age (years)	37.1 ± 15.4	35.6 ± 18.8	38.2 ± 12.5	0.176
Gender				
Male	25 (48.1)	17 (77.3)	8 (26.7)	0.000
Female	27 (51.9)	5 (22.7)	22 (73.3)	
Pre - operative				
Hematocrit value	37.6 ± 6.2	35.5 ± 6.6	39.2 ± 5.5	0.035
Hemoglobin value	12.5 ± 2.07	11.9 ± 2.2	12.9 ± 1.9	0.112
Platelet value	189.7 ± 101.8	247 ± 64.9	147.7 ± 104.2	0.000
White blood cell count	15.2 ± 6.5	19.4 ± 6.2	12.1 ± 4.9	0.000
Neutrophil count	11.47 ± 6.4	15.4 ± 6.3	8.56 ± 4.8	0.000
Lymphocyte count	2.75 ± 1.4	2.8 ± 2.05	2.7 ± 0.76	0.304
Neurophil percentage	70.4 ± 16.6	77.5 ± 15.07	65.2 ± 15.9	0.005
Lymphocyte percentage	20.6 ± 11.9	15.5 ± 12.7	24.4 ± 9.9	0.005
Eisonphil percentage	1 ± 1.29	0.37 ± 0.38	1.46 ± 1.52	0.011
Basophil percentage	0.53 ± 0.78	0.54 ± 1.13	0.53 ± 0.37	0.032
Monocyte percentage	6.35 ± 5.6	6.03 ± 8.43	6.6 ± 1.9	0.000
Neutrophil-to-lymphocyte ratio	6.1 ± 6.1	9.4 ± 7.6	3.72 ± 3.2	0.005
Platelet-to-lymphocyte ratio	94.1 ± 97.2	141.2 ± 115.8	59.6 ± 49.7	0.001
Mean corpuscular volume	84.6 ± 6.7	87 ± 6.4	82.8 ± 6.5	0.002
Post- operative 1 <sup>st</sup> month				
Hematocrit value	39.5 ± 5.2	38.3 ± 4.6	40.4 ± 5.58	0.156
Hemoglobin value	12.8 ± 1.7	12.5 ± 1.4	13.1 ± 1.86	0.279
Platelet value	496.7 ± 298.7	692.4 ± 301.7	353.26 ± 201.7	0.000
White blood cell count	11.6 ± 4.3	12.4 ± 5.1	11.05 ± 3.64	0.251
Neutrophil count	6.8 ± 4.08	8.03 ± 5.1	6.06 ± 2.9	0.067
Lymphocyte count	3.15 ± 1.06	2.8 ± 1.03	3.4 ± 0.96	0.027
Neurophil percentage	56.6 ± 12.9	60.1 ± 14.4	53.1 ± 10.85	0.021
Lymphocyte percentage	28.5 ± 11.6	24.6 ± 11.8	31.4 ± 10.7	0.036
Eisonphil percentage	3.02 ± 2.68	2.8 ± 3.1	3.1 ± 2.3	0.541
Basophil percentage	1.36 ± 1.79	1.3 ± 2.04	1.4 ± 1.6	0.224
Monocyte percentage	9.7 ± 2.72	9.5 ± 3.1	9.9 ± 2.4	0.664
Neutrophil-to-lymphocyte ratio	2.6 ± 2.4	3.5 ± 3.3	1.89 ± 0.98	0.009
Platelet-to-lymphocyte ratio	187.8 ± 152.5	292.7 ± 171	110.9 ± 72.6	0.000
Mean corpuscular volume	85.9 ± 6.1	89.05 ± 3.7	83.6 ± 6.5	0.001
Post- operative ≥ 6 month				
Hematocrit value	42.6 ± 5.3	44.3 ± 5.3	41.4 ± 5.16	0.052
Hemoglobin value	13.9 ± 1.9	14.6 ± 1.7	13.4 ± 1.92	0.021
Platelet value	375.2 ± 138.7	412 ± 75.7	348.3 ± 167.1	0.295
White blood cell count	11.2 ± 2.9	12.1 ± 3.4	10.57 ± 2.4	0.071
Neutrophil count	5.6 ± 1.9	6.1 ± 2.1	5.26 ± 1.6	0.122
Lymphocyte count	4.1 ± 1.4	4.3 ± 1.6	3.9 ± 1.2	0.447
Neurophil percentage	49.8 ± 8.3	50.2 ± 8.5	49.4 ± 8.2	0.731
Lymphocyte percentage	36.8 ± 8.4	36.3 ± 8.9	37.1 ± 8.1	0.754
Eisonphil percentage	2.4 ± 1.8	2.1 ± 1.8	2.58 ± 1.85	0.364
Basophil percentage	0.9 ± 0.6	0.86 ± 0.75	1.04 ± 0.55	0.038
Monocyte percentage	9.9 ± 2.8	10.2 ± 3.37	9.7 ± 2.5	0.774
Neutrophil-to-lymphocyte ratio	1.5 ± 0.74	1.5 ± 0.89	1.46 ± 0.6	0.704
Platelet-to-lymphocyte ratio	104.7 ± 62.4	105.5 ± 38.9	104.1 ± 75.9	0.604
Mean corpuscular volume	85.9 ± 7.33	88.6 ± 4.6	83.7 ± 8.29	0.012
Surgical technique				
Open	28 (53.8)	22 (100)	6 (20)	0.000
Laparoscopic	24 (46.2)	-	24 (80)	
Transfusion of blood components				
Yes	25 (48.1)	19 (86.4)	6 (20)	0.000
No	27 (51.9)	3 (13.6)	24 (80)	
Lenght of hospitalization (day)	9.9 ± 15.8	17.8 ± 22	4.1 ± 2.2	0.000

## Lymphocyte count

The pre-operative lymphocyte counts were not different between the groups (Table 1). One month after surgery, there was no change in lymphocyte count in the trauma group. However, it increased significantly after 6 months (Table 2). There was a significant increase in post-operative lymphocyte counts in the ITP group, which was predominant 6 months after surgery (Table 2). The post-operative 1<sup>st</sup>-month lymphocyte count was significantly higher in the ITP group, but the difference disappeared within 6 months (Table 1).

## *The percentages of neutrophils, lymphocytes, monocytes, eosinophils, and basophils*

The pre-operative percentages of neutrophils and basophils were significantly higher in the trauma group. The pre-operative percentages of lymphocytes, eosinophils, and monocytes were significantly higher in the ITP group (Table 1).

In the trauma group, there was a significant decrease in the percentage of neutrophils, while an increase in the percentages of lymphocytes and eosinophils. Although the percentage of monocytes increased, it was statistically significant 6 months after surgery. The changes in the percentages of neutrophils, lymphocytes, and monocytes were more prominent 6 months after surgery. Although the percentage of basophils increased, it was not statistically significant (Table 2).

In the ITP group, there was a significant decrease in the percentages of neutrophils, while there was an increase in the percentages of lymphocytes, eosinophils, basophils, and monocytes. The changes in the percentages of eosinophils, basophils, and monocytes were more prominent 1 month after surgery, while the changes in the percentages of neutrophils and lymphocytes were more prominent 6 months after surgery (Table 2).

The percentage of neutrophils decreased, while the percentage of lymphocytes increased in both groups (Table 2). The percentage of neutrophils was significantly higher in the trauma group, while the percentage of lymphocytes was significantly higher in the ITP group 1 month after surgery (Table 1). There were no statistical differences between the groups in terms of postoperative percentages of eosinophils and monocytes (Table 1). Six months after surgery, there was no significant difference between the groups in terms of neutrophils, lymphocytes,

eosinophils, and monocytes. Only the percentage of basophils was significantly higher in the ITP group 6 months after surgery (Table 1).

## NLR

The preoperative NLR was significantly higher in the trauma group (Table 1), but it decreased over time in both groups (Table 2). The NLR of the trauma group was significantly higher 1 month after surgery, but the difference disappeared over time (Table 1).

## PLR

The preoperative PLR was significantly higher in the trauma group (Table 1). It increased in both groups 1 month after surgery and was more prominent in the trauma group (Table 2). Although the change in PLR in the ITP group remained stable over time, it declined to preoperative values in the trauma group (Table 2). Thus, PLR values were comparable between the groups 6 months after surgery (Table 1).

## Discussion

It was not surprising that hematocrit and hemoglobin values increased within the normal range after therapy in both groups. The post-operative 1<sup>st</sup>-month increase in MCVs in trauma patients was thought to be a compensatory mechanism for blood loss. ITP, as a chronic inflammatory disease, had lower hematocrit, hemoglobin, and MCV levels compared to those of trauma patients in the post-operative period even after iron repletion.

Thrombocytosis is defined as a platelet count  $>500 \times 10^9/L$ , and extreme thrombocytosis is defined as a platelet count  $>1,000 \times 10^9/L$ . Thrombocytosis is either a reactive process (secondary to infection, trauma, surgery, and malignancy) or is caused by a clonal bone marrow disorder<sup>5</sup>. It is a normal physiologic response to splenectomy, which may persist in up to 30% of splenectomized patients, and cessation of splenic sequestration is thought to be a major participatory mechanism<sup>6</sup>. In the current study, 1 month after surgery, the increase in platelet count was more prominent in the trauma group but declined slightly overtime. The pre-operative and postoperative 1<sup>st</sup>-month platelet counts were statistically higher in the trauma group. However, the difference disappeared  $\geq 6$  months after. All ITP patients had a complete response to splenectomy.

Leukocytes constitute the cellular components of the immune system and participate in host defense.

**Table 2.** The paired-sample t-test for comparison of the changes of laboratory values, at the 1<sup>st</sup> month and ≥ 6 months after surgery

Laboratory findings	Pre-operative mean ± SD	Post-operative 1 <sup>st</sup> month mean ± SD	p	Post-operative ≥ 6 month mean ± SD	p
Trauma Patients					
Hematocrit value	35.5 ± 6.6	38.3 ± 4.6	0.118	44.3 ± 5.3	0.000
Hemoglobin value	11.9 ± 2.2	12.5 ± 1.4	0.288	14.6 ± 1.7	0.000
Platelet value	247 ± 64.9	692.4 ± 301.7	0.000	412 ± 75.7	0.000
White blood cell count	19.4 ± 6.2	12.4 ± 5.1	0.000	12.1 ± 3.4	0.000
Neutrophil count	15.4 ± 6.3	8.03 ± 5.1	0.000	6.1 ± 2.1	0.000
Lymphocyte count	2.8 ± 2.05	2.8 ± 1.03	0.927	4.3 ± 1.6	0.006
Neurophil percentage	77.5 ± 15.07	60.1 ± 14.4	0.001	50.2 ± 8.5	0.000
Lymphocyte percentage	15.5 ± 12.7	24.6 ± 11.8	0.007	36.3 ± 8.9	0.000
Eisonphil percentage	0.37 ± 0.38	2.8 ± 3.1	0.001	2.1 ± 1.8	0.000
Basophil percentage	0.54 ± 1.13	1.3 ± 2.04	0.156	0.86 ± 0.75	0.289
Monocyte percentage	6.03 ± 8.43	9.5 ± 3.1	0.082	10.2 ± 3.37	0.049
Neutrophil-to-lymphocyte ratio	9.4 ± 7.6	3.5 ± 3.3	0.001	1.5 ± 0.89	0.000
Platelet-to-lymphocyte ratio	141.2 ± 115.8	292.7 ± 171	0.002	105.5 ± 38.9	0.206
Mean corpuscular volume	87 ± 6.4	89.05 ± 3.7	0.047	88.6 ± 4.6	0.124
ITP Patients					
Hematocrit value	39.2 ± 5.5	40.4 ± 5.58	0.123	41.4 ± 5.16	0.005
Hemoglobin value	12.9 ± 1.9	13.1 ± 1.86	0.449	13.4 ± 1.92	0.050
Platelet value	147.7 ± 104.2	353.26 ± 201.7	0.000	348.3 ± 167.1	0.000
White blood cell count	12.1 ± 4.9	11.05 ± 3.64	0.342	10.57 ± 2.4	0.092
Neutrophil count	8.56 ± 4.8	6.06 ± 2.9	0.034	5.26 ± 1.6	0.001
Lymphocyte count	2.7 ± 0.76	3.4 ± 0.96	0.002	3.9 ± 1.2	0.000
Neurophil percentage	65.2 ± 15.9	53.1 ± 10.85	0.003	49.4 ± 8.2	0.000
Lymphocyte percentage	24.4 ± 9.9	31.4 ± 10.7	0.006	37.1 ± 8.1	0.000
Eisonphil percentage	1.46 ± 1.52	3.1 ± 2.3	0.001	2.58 ± 1.85	0.012
Basophil percentage	0.53 ± 0.37	1.4 ± 1.6	0.008	1.04 ± 0.55	0.000
Monocyte percentage	6.6 ± 1.9	9.9 ± 2.4	0.000	9.7 ± 2.5	0.000
Neutrophil-to-lymphocyte ratio	3.72 ± 3.2	1.89 ± 0.98	0.007	1.46 ± 0.6	0.001
Platelet-to-lymphocyte ratio	59.6 ± 49.7	110.9 ± 72.6	0.002	104.1 ± 75.9	0.012
Mean corpuscular volume	82.8 ± 6.5	83.6 ± 6.5	0.302	83.7 ± 8.29	0.435
Total					
Hematocrit value	37.6 ± 6.2	39.5 ± 5.2	0.030	42.6 ± 5.3	0.000
Hemoglobin value	12.5 ± 2.07	12.8 ± 1.7	0.186	13.9 ± 1.9	0.000
Platelet value	189.7 ± 101.8	496.7 ± 298.7	0.000	375.2 ± 138.7	0.000
White blood cell count	15.2 ± 6.5	11.6 ± 4.3	0.001	11.2 ± 2.9	0.000
Neutrophil count	11.47 ± 6.4	6.8 ± 4.08	0.000	5.6 ± 1.9	0.000
Lymphocyte count	2.75 ± 1.4	3.15 ± 1.06	0.088	4.1 ± 1.4	0.000
Neurophil percentage	70.4 ± 16.6	56.6 ± 12.9	0.000	49.8 ± 8.3	0.000
Lymphocyte percentage	20.6 ± 11.9	28.5 ± 11.6	0.000	36.8 ± 8.4	0.000
Eisonphil percentage	1 ± 1.29	3.02 ± 2.68	0.000	2.4 ± 1.8	0.000
Basophil percentage	0.53 ± 0.78	1.36 ± 1.79	0.005	0.9 ± 0.6	0.003
Monocyte percentage	6.35 ± 5.6	9.7 ± 2.72	0.000	9.9 ± 2.8	0.000
Neutrophil-to-lymphocyte ratio	6.1 ± 6.1	2.6 ± 2.4	0.000	1.5 ± 0.74	0.000
Platelet-to-lymphocyte ratio	94.1 ± 97.2	187.8 ± 152.5	0.000	104.7 ± 62.4	0.508
Mean corpuscular volume	84.6 ± 6.7	85.9 ± 6.1	0.031	85.9 ± 7.33	0.121

Normal levels of leukocytes are 4.000-11.000 per microliter of blood. Leukocytosis is an expected finding after splenectomy; thus, the diagnosis of postoperative infection in those patients may be a challenge<sup>7-9</sup>. Leukocyte count rises, irrespective of the reason for splenectomy<sup>7</sup>. The increase is initially confined to neutrophils. However, neutrophil count returns to within the normal range within weeks or months, and lymphocyte and monocyte counts rise steadily<sup>7</sup>.

Leukocytosis is a well-known response of the body to trauma. It is mainly due to neutrophilia, caused by redistribution of neutrophils from the storage pool to the circulation, and not due to increased production<sup>10</sup>. Neutrophils are one of the first defenders of inflammatory cells to migrate toward the site of injury. So, leukocytosis, especially neutrophilia, is an expected finding in trauma patients as in the current study. In trauma patients, the leukocyte count decreased compared to that

recorded preoperatively, but it was still above the normal range. In ITP patients, the leukocyte count did not change statistically following splenectomy, though leukocytosis was present already before the surgery. Neutrophil counts decreased permanently in both groups during the period of recovery from surgery. The change in lymphocyte and monocyte counts followed a different pattern between the groups. In trauma patients, lymphocyte and monocyte counts initially did not change but increased  $\geq$  6 months after surgery. However, in ITP patients, lymphocyte and monocyte counts increased gradually overtime. The postoperative 1<sup>st</sup>-month lymphocyte count was significantly higher in the ITP group, but the difference disappeared within 6 months.

Which mechanism, therefore, is responsible for leukocytosis after splenectomy? The spleen participates in the regulation of leukocytes. Along with the preservation of lymphoid tissue, it may also sequester leukocytes produced elsewhere<sup>7</sup>. Thus, the removal of the spleen causes the leukocyte count to rise. Could there be any mechanism other than the cessation of sequestration that could cause leukocytosis? In order to determine this, several questions must be answered. First: why does the leukocyte count not change significantly in ITP patients, while it remains stable above the normal range in trauma patients? Second: why do lymphocyte and monocyte counts in trauma patients increase several months later than those of ITP patients? Third: could the high basophil level in ITP patients be a unique finding?

ITP is an autoimmune disease, and inflammation plays a central role in pathogenesis. It was clear that neutrophils were responsible for the preoperative leukocytosis in ITP patients, and neutrophilia was ameliorated by both splenectomies, and also the withdrawal of steroid treatment in some patients. Thus, despite the increase in lymphocytes, monocytes, eosinophils and basophiles, total leukocyte count, which was already above the normal range, did not change in this group. The NLR and PLR have been found to be potential markers of systemic inflammation and used to predict prognosis and treatment response in various benign and malign diseases<sup>11-13</sup>. The NLR was used in a small number of studies for the prediction of treatment response to medical therapy in ITP patients, and their results were contradictory<sup>14,15</sup>. In a recent study, it was concluded that splenectomy might improve the weakened immune system of patients with cirrhosis, possibly by reducing suppressive cell fractions and amplifying the effector cell population. In that study, splenectomy was found to decrease NLR<sup>16</sup>. We supposed that, based on the decrease in the NLR and

PLR, splenectomy did not only eliminate sequestration but also ameliorated the inflammation in ITP patients.

In ITP patients, the effect caused by the cessation of sequestration on lymphocytes and monocytes is likely to emerge several weeks to months later as in the trauma patients. It seems there was another mechanism responsible for the early increase in lymphocyte and monocyte counts. This mechanism, causing lymphocyte and monocyte counts to increase without inflammatory effects, must be particularly complex, and its effect must not have lasted longer than a few months as the leukocyte counts were comparable with those of the trauma patients,  $\geq$  6 months after splenectomy. Furthermore, it must have been negated in the presence of a spleen. Although the mechanism that triggers inflammation in ITP has not yet been determined, direct interaction of monocytes with stimulated T-lymphocytes might be a major pathway for the production of proinflammatory cytokines and their inhibitors in monocytes, which has been postulated as a possible mechanism in the pathogenesis of any chronic inflammation<sup>17,18</sup>. Depending on T-cell type and T-cell stimulus, multiple ligands/counter-ligands are involved in the contact-mediated activation of monocytes, and the outcome of the inflammatory process is determined by the balance between proinflammatory cytokines and their inhibitors, which are produced in the monocytes. We suppose that ITP, as a chronic inflammatory disease, might possess similar inflammatory processes<sup>17,18</sup>. Further research is needed to identify inhibitory and/or stimulatory molecules involved in the inflammatory process.

Basophils are the least common type of leukocytes, constituting about 0.5-1% of circulating leukocytes. In the current study, basophils were the only leukocyte type, which was significantly higher in the ITP group  $\geq$  6 months after surgery. Basophils participate in the regulation of immune response and allergic reactions by producing histamine and serotonin. They also secrete endogenous heparin for anticoagulation<sup>19</sup>. Low basophil percentages or counts are thought to be responsible for the increased risk of thrombosis<sup>20</sup>. Although patients with ITP have a low platelet count with a tendency to bleeding, they occasionally develop venous and/or arterial thromboembolic events by a mechanism, which has not yet been fully elucidated. It may occur as a result of inflammatory processes acting on thrombosis, or as a result of complications of medical and/or surgical treatment. Comorbid diseases may also increase the risk for thromboemboli in ITP patients<sup>21</sup>. It

was not known whether the increase in basophil percentage was a compensatory mechanism in the protection of ITP patients against thromboembolism or whether it was a participant in the inflammatory process itself. Only three patients of the study population, two patients with ITP and the other with trauma, developed thromboembolic complications following splenectomy. Further research is needed for clarification.

Small case numbers and a retrospective design were weaknesses of the current study, while the comparison with a normal population (trauma patients) was a strength.

## Conclusions

Splenectomy, irrespective of the indications, resulted in an increase in hemoglobin concentration, hematocrit, and platelet levels. It did not alter leukocyte count in ITP patients but led to leukocytosis in trauma patients. Although lymphocyte, monocyte, and eosinophil counts increased after splenectomy in both groups, total leukocyte count, which was already above the normal range, did not change in ITP patients. Neutrophils were responsible for the preoperative leukocytosis in ITP patients, and neutrophilia was ameliorated by splenectomy and also withdrawal of the steroid therapy in some patients. Decreased NLR and PLR supported the finding that splenectomy ameliorated inflammation in ITP patients. Splenectomy resulted in a change in percentages of leukocytes in favor of basophils in ITP patients, but did not result in any change in trauma patients. It is not known whether the increase in basophil percentage was a compensatory mechanism to protect ITP patients against thromboembolism or whether it was a participant in the inflammatory process itself. There are many issues that require clarification with regard to the inhibitory and/or stimulatory molecules involved in the inflammatory process in ITP patients. Our knowledge of the spleen is encompassed by the literature, and everything we don't yet know falls outside of that repository. Further research is needed to illuminate this mysterious organ.

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## Conflicts of interest

The author reports no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The author declares that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The author declares having followed the protocols in use at their working center regarding patients' data publication.

**Right to privacy and informed consent.** Patients were informed that their data could be used for research and informed consents were obtained from all patients prior to surgery. The corresponding author is in possession of this document.

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# Impact of COVID-19 on surgical residency training programs in Mexico City: The third victim of the pandemic. A resident's perspective

*Impacto del COVID-19 en los programas de residencias quirúrgicas en la Ciudad de México: La tercera víctima de la pandemia. Perspectiva de los residentes*

Mariano Oropeza-Aguilar<sup>1</sup>, José de Jesús Cendejas-Gómez<sup>1</sup>, Alejandro Quiroz-Compeán<sup>1</sup>, Gabriela A. Buerba<sup>2</sup>, Ismael Domínguez-Rosado<sup>2</sup>, and Carlos E. Méndez-Probst<sup>1\*</sup>

<sup>1</sup>Department of Urology; <sup>2</sup>Division of Surgery. Instituto Nacional de Ciencias Médicas y Nutrición. Salvador Zubiran, Mexico City

## Abstract

**Objective:** The aim of this study is to assess the perceptions of the impact of health-care disruption due to COVID-19 on the academic training and skills of surgical trainees. **Material and Methods:** We developed a 32-question survey assessing the clinical and surgical impact of COVID-19 on surgical training programs and proposals to compensate for the decrease in surgical education. We got 453 responses of surgical trainees in Mexico City. **Results:** Sixty-six percent of the respondents answered that their centers had converted to the exclusive attention of COVID-19 patients. Ninety-five percent reported a decrease in surgical skills learning and 91.8% reported a decrease to clinical exposure. On proposals, 75.6% reported that it is essential to take the necessary measures to recover the clinical and surgical milestones lost. In the binary logistic regression analysis, we found that the postgraduate year ( $\geq$  PG-Y3) was statistically significant factor ( $p \leq 0.000$ ) related to a favorable opinion to developing an academic contingency plan and postponing the end of the academic residency year. **Conclusion:** More than 90% of the survey respondents reported having been affected by COVID-19 mitigation strategies. Our data calls for urgent training adjustments by hospital and university program leaders to mitigate downstream educational repercussions.

**Keywords:** COVID-19. Mexico. Surgery. Surgical residency programs.

## Resumen

**Objetivo:** Evaluar las percepciones del impacto de la interrupción de la atención médica por COVID-19 en la formación académica y las habilidades de los residentes quirúrgicos. **Material y Métodos:** Realizamos una encuesta de 32 preguntas, evaluando el impacto clínico y quirúrgico del COVID-19 en los programas de entrenamiento quirúrgico y propuestas para compensar la disminución de la educación quirúrgica. Obtuvimos 453 respuestas de residentes quirúrgicos en la Ciudad de México. **Resultados:** El 66% respondió que sus centros se convirtieron en atención exclusiva de pacientes con COVID-19. El 95% presentó una disminución en el aprendizaje de habilidades quirúrgicas y el 91.8% presentó una disminución de la exposición clínica. El 75.6% consideró fundamental tomar las medidas necesarias para recuperar las destrezas clínicas perdidas. En el análisis de regresión logística binaria, encontramos que el año de posgrado ( $>$  PG-Y3) fue un factor estadística-

## Correspondence:

\*Carlos E. Méndez-Probst

Avda. Vasco de Quiroga, 15

Col. Belisario Domínguez Sección XVI Tlalpan

C.P. 14080 Mexico City, Mexico

E-mail: probstmc@hotmail.com

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mente significativo ( $p <0,000$ ) relacionado con una opinión favorable para desarrollar un plan de contingencia académica y posponer el final del año de residencia académica. **Conclusión:** Más del 90% de los encuestados fueron afectados por las estrategias de mitigación de COVID-19. Nuestros datos exigen ajustes urgentes por parte de los líderes de programas de hospitales y universidades para mitigar las repercusiones educativas posteriores.

**Palabras clave:** COVID-19. México. Cirugía. Programas de residencia quirúrgica.

## Introduction

Since the beginning of the SARS-CoV-2 pandemic in late 2019<sup>1</sup>, worldwide medical care has been dramatically impacted. Medical centers across the globe have adopted multiple coping strategies, either directly prioritizing patients affected with COVID-19, or indirectly by reducing elective surgical procedures<sup>2,3</sup>, and the care of patients in outpatient areas. All in a desperate effort to increase the surge capacity to avoid or mitigate the swamping of health-care facilities and also to steward as many scarce resources as possible and reduce the risk of contagion for health personnel and patients<sup>1</sup>.

One of the drawbacks of the world's massive response to COVID-19 has been a widespread disruption of medical education. Surgical cases have plunged, leading to very limited hands on training, loss of external rotations, and educational opportunities such as specialty meetings<sup>4-6</sup>. However, residency programs have either partially or totally changed to a remote education, and surgical simulation.

As the pandemic unfolds there is also a growing uncertainty about the future of surgical training and a real potential for future epidemic outbreaks, limited data exist on the residents perception of COVID-19 mitigation measures on the safety, continuity, and efficacy of their training, especially since in some countries academic calendar, the disease has already used up to 30-40% of their academic year (e.g., In Mexico the academic year runs from March to February).

We sought to collect information on surgical trainees, using a qualitative approach to document if a reduced clinical (office consults and operative time) exposure would lead to a decreased perception of surgical preparedness among the different surgical specialty programs in our city. The secondary objective was to explore proposals to compensate for the decrease in learning opportunities of the different surgical specialties and different hospital centers in Mexico City.

## Materials and methods

After ethics committee approval (URO-3406-20-21-1), we performed a cross-sectional survey of surgical trainees in Mexico City; the target population was extracted from the 18 surgical programs accredited by the National Autonomous University of Mexico (UNAM), which is the largest university in the state. The study universe comprised 3015 eligible residents or fellows affiliated to a general surgery, gynecology/obstetrics, ENT, orthopedics, vascular surgery, urology, oncological surgery, plastic surgery and pediatric surgery, and related fellowships. A sample size of 341 subjects was calculated using a 95% confidence interval and a 5% margin of error using an online sample size calculator (<http://fluidsurveys.com>).

We recruited participants through a closed group direct invitation to all the surgical residents and fellows of the UNAM, otherwise the survey was not publicly announced or open on the internet, participation was voluntary, and no incentives were provided for study participation. The survey was administered through electronic means only (Google Forms and Google LLC) and informed consent was tacitly requested at the initial page of the survey, which included an information letter informing the purpose and length of the survey, no personal data or identifiers were collected from the subjects, and the study was performed according to the precepts of the Helsinki Declaration.

The survey was available for response from April 27, 2020, and closed on May 11, 2020.

## Survey design

We developed an ad hoc 32-question survey divided into eight domains assessing demographic, outpatient, and emergency care, surgical exposure, and skills development, educational modifications (academic and research), perceptions of the impact of COVID-19 on surgical their training programs and proposals to compensate for the decrease in the learning opportunities due to the COVID-19.

The survey was then uploaded to the survey program for distribution and automatic response collection; this also allowed the use of special features such as adaptive questioning, review, and answer change. The survey was composed of two electronic pages (page 1 informed consent and page 2 actual survey).

Incomplete surveys, from residents from non-surgical specialties and from different states than Mexico City, were excluded from further analysis.

### **Statistical analysis**

Responses were exported from Google Forms to Microsoft Excel database and all statistical analyses were performed with Statistical Package for the Social Sciences 26<sup>th</sup> version (SPSS, Chicago, IL, USA).

All survey questions responses were coded as binary or categorical variables. Descriptive statistics of the overall cohort were performed.  $p < 0.05$  was considered significant.

## **Results**

### **Demographics**

We received 453 (15% of the study universe) survey responses from 18 surgical programs from Mexico City. Of the total participants, 287 (63.4%) were male and 166 (36.6%) were female. The mean age was  $29 \pm 2$  years. Most responses came from general surgery residents (21.4%). An important proportion was junior residents (44.4% post graduate year [PGYs] 1-2). We describe the rest of demographics and details in table 1.

### **Impact of the COVID-19 pandemic**

Of all the responders 302 (66.7%) answered that their centers had been converted to the exclusive attention of COVID-19 patients (COVID-19 Centers). Only 7% responded that they work normally, the rest are not involved in daily hospital work. Patient care is mostly performed through telemedicine and the majority of elective surgical cases have been canceled. Not surprisingly, the number of Non-COVID-19 cases in the outpatient clinics and in the emergency department has significantly declined, as shown in figures 1 and 2, respectively.

### **Resident training and academics**

A worrisome finding was that most of the residents reported a decrease in surgical skill learning,

**Table 1. Demographics details**

Year of residency	Percentage (n)
PGY1	23.2 (105)
PGY 2	21.2 (96)
PGY 3	17.4 (79)
PGY 4	15.2 (69)
PGY 5	9.1 (41)
PGY 6	0.4 (2)
PGY 7	0.2 (1)
1 <sup>st</sup> year Fellow	10.2 (46)
2 <sup>nd</sup> year Fellow	3.1 (14)
Residency program	Percentage (n)
General Surgery	21.4 (97)
Fellowship	11 (55)
Neurosurgery	9.5 (43)
Oncology Surgery	7.3 (33)
Gynecology and obstetrics	7.5 (34)
Urology	6.8 (31)
Traumatology and Orthopedics	6 (27)
Plastic Surgery	6 (27)
Pediatric Surgery	6 (27)
Otorhinolaryngology	4.9 (22)
Ophthalmology	2.6 (12)
Vascular Surgery	2.2 (10)
Cardiothoracic surgery	1.3 (6)
Others	7.5 (29)

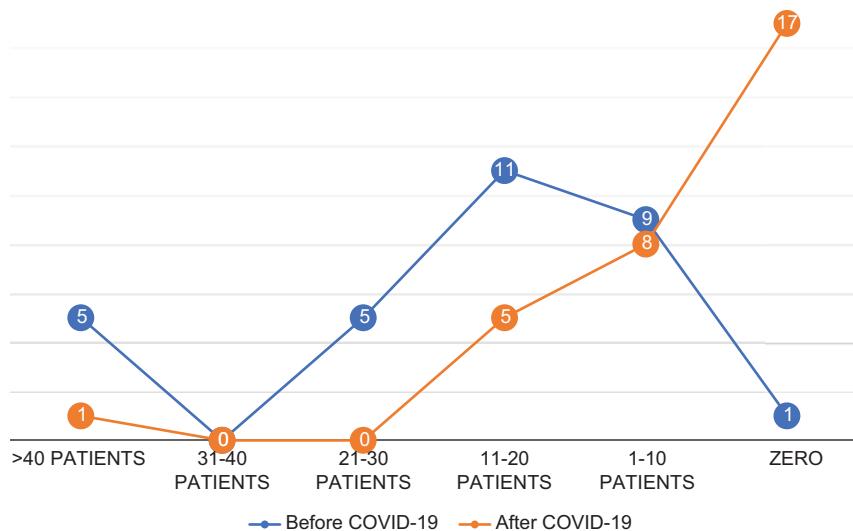
275 (60.8%) felt completely affected and 154 (34.1%) as partially affected (Figure 3). In addition, the vast majority (91.8%) reported a decrease in clinical exposure (Figure 4). Only (41.2%) of the respondents were practicing surgical skills in simulators outside of hospital settings (e.g., at home), and just 53% of the responders use their time to research activities.

All respondents reported discontinuation of in-person conferences, with most (82.4%) transitioning to distance learning through virtual platforms (e.g., Zoom, WebEx, Google Meets, or Hang outs), this last scenario had a positive impact with 70.4% of respondents reporting at least the same or an increased quality of virtual classes compared to traditional ones.

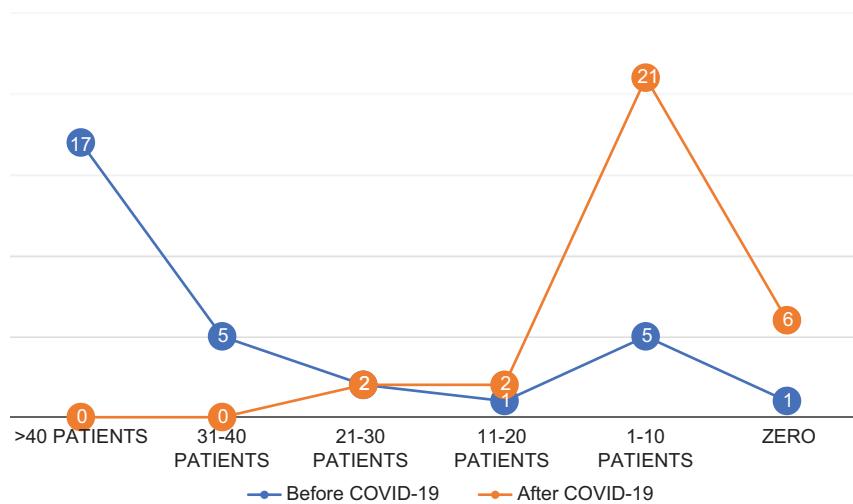
As a perception of the negative downstream effects on surgical training programs, most residents reported being in agreement with the statement indicating that converting into COVID-19 centers had negatively impacted their surgical training.

### **Proposals and alternatives to reach the objectives in the academic programs**

Due to negative concerns about their training, 75.6% of the surveyed cohort reported that it is essential to take necessary measures to recover the clinical and



**Figure 1.** Comparison between the patient volume in outpatient clinics before and after COVID-19 pandemic.



**Figure 2.** Comparison between the patient volume for non COVID-19 cases in emergency department before and after COVID-19 pandemic.

surgical milestones lost during pandemic. The most common expressed proposals were related exclusively to recovering surgical exposure (48.7%), and (34.1%) related to recovering surgical exposure and increasing theoretical learning (Figure 5). Drastically 52% of the responders thought that the most feasible alternative to achieve this is to postpone the end of the academic residency year.

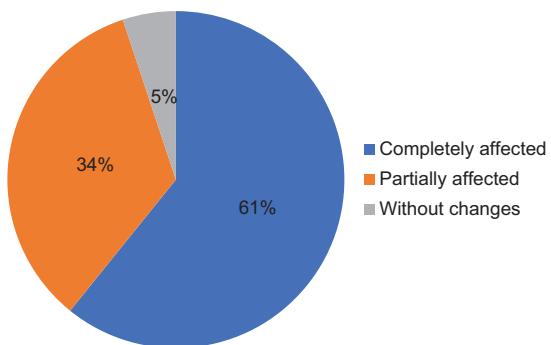
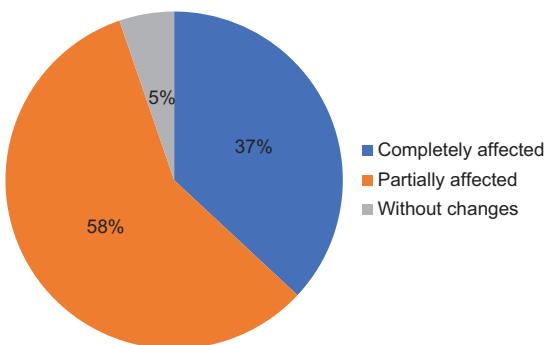
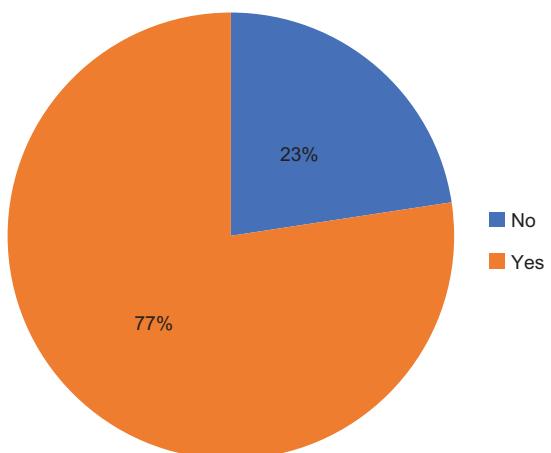
### Inferential analysis

Since almost a quarter of the trainees were not in favor of developing an academic contingency plan and

slightly  $< \frac{1}{2}$  of the respondents were against extending the academic year, we performed univariate and multivariate binary logistic regression analysis looking for factors that correlated with this choice, we found that the PGY was the only statistically significant factor (Tables 2-5).

### Discussion

We report a survey of surgical residency programs assessing the modifications and their impact on trainees. Our main findings show that 66% of the surveyed programs had undergone conversion to COVID-19

**Figure 3.** Impact on surgical skill learning.**Figure 4.** Impact on theoretical learning.**Figure 5.** Residents in favor of the extension in the academic year of residence.

only centers, the respondents felt that this had impacted their surgical training, either by partially/totally disrupting their surgical skills (94.9%), or their clinical exposure and theoretical learning (91.8%). During the pandemic, many of the surveyed surgical residents

**Table 2.** Predictive factors to agreeing to the question: that some measures should be taken to recover the objectives. Results of the univariate analysis of binary logistic regression

Factors	p value	OR	95% CI
Sex	0.376	0.813	0.513-1.287
Male (reference)			
Female			
Age dicotomical	0.057	0.653	0.422-1.012
≥29 years (reference)			
≤ 28 years			
Year of residency dicotomical	<b>0.000</b>	<b>0.366</b>	<b>0.233-0.574</b>
≥PGY 3 (reference)			
PGY 1/PGY2			
COVID-19 Centre	0.530	1.157	0.733-1.826
No (reference)			
Yes			

**Table 3.** Predictive factors to agreeing to the question: that some measures should be taken to recover the objectives. Results of the multivariate analysis of binary logistic regression

Factors	p value	OR	95% CI
Sex	0.381	0.808	0.768-1.995
Male (reference)			
Female			
Age dicotomical	0.637	0.891	0.696-1.809
≥29 years (reference)			
≤ 28 years			
Year of residency dicotomical	<b>0.000</b>	<b>0.378</b>	<b>0.234-0.611</b>
≥PGY 3 (reference)			
PGY 1/PGY2			
COVID-19 Centre	0.307	1.279	0.487-1.54
No (reference)			
Yes			

have been assigned to provide first-line care for patients with suspected SARS-CoV2 at their emergency departments. All national and international meetings and hands-on courses have been so far canceled, this data allow us postulate that surgical residents have become the third major victim of the COVID-19 (after patients and health-care workers respectively).

Recent studies have shown similar findings, a study at a tertiary care hospital in Pakistan evaluated the impact of surgical residency programs on 112 surgical residents from all departments of surgery. They observed that 86.6% stated that their surgical exposure duration was adversely affected by the pandemic<sup>5</sup>. In addition, in a survey of urological training programs in the United States, 26% reported being asked to

**Table 4. Predictive factors for agreeing to postpone residency graduation. Results of the univariate analysis of binary logistic regression**

Factors	p value	OR	95% CI
Sex	0.627	0.909	0.619-1.335
Male (reference)			
Female			
Age dicotomical ≥29 years (reference) ≤ 28 years	0.126	0.745	0.512-1.086
Year of residency dicotomical ≥PGY 3 (reference) PGY 1/PGY2	<b>0.000</b>	<b>0.419</b>	<b>0.286-0.612</b>
COVID-19 Centre No (reference)	0.716	0.930	0.628-1.376
Yes			

**Table 5. Predictive factors for agreeing to postpone residency graduation. Results of the multivariate analysis of binary logistic regression**

Factors	p value	OR	95% CI
Sex	0.792	1.055	0.636-1.412
Male (reference)			
Female			
Age dicotomical ≥29 years (reference) ≤ 28 years	0.960	1.011	0.669-1.528
Year of residency dicotomical ≥PGY 3 (reference) PGY 1/PGY2	<b>0.000</b>	<b>0.419</b>	<b>0.278-0.630</b>
COVID-19 Centre No (reference)	0.934	0.983	0.656-1.474
Yes			

redeploy residents. Nearly all urology programs were willing to send residents for redeployment if needed, with the corresponding impact in clinical and surgical exposure.

Our data also parallels the Italian experience, where surgical training was also severely affected. All weekly lessons were suspended, as well as seminars, workshops, and practical courses (e.g., suture courses, laparoscopic simulators, and cadaver lab). Moreover, due to the interruption of the elective surgery (mostly benign pathology), which are most frequently performed by residents as the operator, there was a failure in achieving the minimum number of interventions required for surgical certification<sup>7</sup>. In our study, we

found that only the 41% of responders practice their surgical skills with simulators. Nowadays, the use of simulators training (e.g., laparoscopic or virtual reality) can provide a safe and standardized method for training in surgery without the risks that come with operating on real patients during this pandemic<sup>8,9</sup>.

One of the possible solutions could be the use of technology to continue clinical and academic tasks, such as virtual lectures or in real-time videoconferencing, journal clubs, and watching surgical videos followed by discussing the surgical steps with the attending professors. We found that the 87.9% of the residents are taking virtual lectures to attain the theoretical goals of their different residency programs.

In this era of competency based certification, the pandemic has the potential to derail the current trainees cohort (PGY 4-5), by making surgical milestones unattainable, although each surgical residency program has its own objectives and requirements<sup>10-12</sup>, surgical authorities like the American Board Of Surgery in United States<sup>6,13</sup>, require that candidate applicants have had performed at least 200 surgical procedures during their senior year. Furthermore, this may also impact downstream cohorts as well, since it also requires that trainees perform at least 850 operative procedures as the surgeon over 5 years, and at least 250 operations (including as operating surgeon or first assistant) by the beginning of PGY-3 year<sup>13</sup>.

Our study has some limitations. As a survey study, it is subject to response bias, although we accrued a robust sample size, the study population only comprises 15% of the resident population currently training to become a surgical specialist, our target population was limited to a geographical region (the State of Mexico City) so our findings might not apply to surgical programs outside this area; however, this region comprises most of the surgical infrastructure and academic programs of the country as well as hospital beds, making it by far the major medical hub nation-wide. The strengths of our study are that we exceeded our calculated sample size thus can conclude that our sample was a representative portion of the surgical residents currently undergoing training in the state of Mexico City.

As the long-term effects of this outbreak on worldwide health systems are still unknown, we believe it is crucial to incorporate the trainee's worldview. Our data serves as a potential guide for education policy makers, as it reflects the worries and anxieties of the

COVID-19 surgical resident. New strategies involving trainees should be developed that consider the training needs of the residents. Appropriate modifications to the format and timing of the current residency paradigm should be considered, including restructuring the academic programs (e.g., adapting and extending the academic year program or replacing the time-based standards with volume-based or competency-based standards).

Despite this pandemic, many programs have not established plans for the post-COVID-19 world. Faculty leaders, universities and governing bodies (Health authorities) should consider options to compensate the missed hands-on exposure, providing didactic resources (e.g., medical simulators and access to on-line content, in addition to personal, and workplace safety).

## Conclusions

During the spring and summer of 2020 due to the COVID-19 pandemic, surgical residency programs in Mexico City underwent significant modifications, including a marked decrease in surgical procedures. More than 90% of the survey respondents report having been affected by these mitigation strategies, mostly by the lack of surgical, academic, and clinical exposure, thus surgical residents have become the pandemic's third casualty. Our data calls for urgent training adjustments by hospital and university program leaders to mitigate downstream educational repercussions.

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## Conflicts of interest

The authors declare that they have no conflicts of interest in this manuscript.

## Ethical disclosures

**Protection of human and animals subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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# Mortality after kidney transplantation: 10-year outcomes

## *Mortalidad después del trasplante de riñón: resultados a 10 años*

Turgut Piskin<sup>1</sup>, Arife Simsek<sup>1\*</sup>, Sait Murat-Dogan<sup>1</sup>, Bahar T. Demirbas<sup>2</sup>, Bulent Unal<sup>1,3</sup>, Ismail O. Yildirim<sup>1</sup>, Sibel A. Toplu<sup>1</sup>, Haci B. Berktaş<sup>1</sup>, Hatice Can<sup>1</sup>, Ebru I. Coskun<sup>1</sup>, Mukadder Sanli<sup>1</sup>, Huseyin Gurbuz<sup>1</sup>, Mehmet S. Arslan<sup>1</sup>, Zeynep Piskin<sup>1</sup>, Julide Yagmur<sup>1</sup>, Fatih Oguz<sup>1</sup>, Yasemin Bayindir<sup>1</sup>, Ozkan Ulutas<sup>1</sup>, Hulya Taskapan<sup>1</sup>, and Idris Sahin<sup>1</sup>

<sup>1</sup>Division of Kidney Transplantation Inonu University, School of Medicine, Turgut Ozal Medical Center, Malatya; <sup>2</sup>Department of General Surgery, Marmara University Pendik Training and Research Hospital, Istanbul; <sup>3</sup>Division of Kidney Transplantation, Eskisehir Osmangazi University Faculty of Medicine, Eskisehir, Turkey

### Abstract

**Objectives:** In the past decade, advances in immunological therapy have increased the survival of kidney recipients and their grafts. However, it has not achieved the desired level of improvement. This study aims to reveal the mortality among kidney recipients. **Methods:** Medical data of the patients, who had undergone kidney transplantation (KT) between November 2010 and December 2020, were retrospectively reviewed. Inclusion criteria were adult kidney recipients, who had died. Exclusion criteria were pediatric recipients, recipients of en bloc and dual KT, recipients with missing data, and recipients with a primary non-functioning graft. The recipients were grouped according to their donor type; Group 1 (from a living donor) and Group 2 (from a deceased donor). Subgroup analyses were done for mortality by time-period post-transplant and for infectious causes of mortality. **Results:** Of 314 recipients, 35 (11.14%) died. Twenty-nine recipients were included in the study (Group 1: 17 and Group 2: 12). The most common cause of mortality was infection (58.6%), and the second was cardiovascular disease (CVD) (24.1%). Sepsis developed in 29.4% of infection-related deaths, while COVID-19 constituted 23.5% of infection-related deaths. **Conclusion:** Early diagnosis and treatment of infectious and CVD are important to improve survival in kidney recipients.

**Keywords:** Cardiovascular. COVID-19. Infection. Kidney transplantation. Mortality.

### Resumen

**Objetivos:** En la última década, los avances en la terapia inmunológica han aumentado la supervivencia de los receptores de riñón y sus injertos. Sin embargo, no se pudo lograr el nivel de mejora deseado. Este estudio tiene como objetivo revelar la mortalidad entre los receptores de riñón. **Materiales y métodos:** Se revisaron retrospectivamente los datos médicos de los pacientes, que se habían sometido a un trasplante de riñón entre Noviembre de 2010 y Diciembre de 2020. Los criterios de inclusión fueron los receptores de riñón adultos, que habían fallecido. Los criterios de exclusión fueron los receptores pediátricos, los receptores de trasplantes de riñón dual y en bloque, los receptores con datos faltantes y los receptores con un injerto primario no funcinante. Los receptores se agruparon según su tipo de donante; Grupo 1 (de un donante vivo) y Grupo 2 (de un donante fallecido). Se realizaron análisis de subgrupos para la mortalidad por período de tiempo posterior al

### Correspondence:

\*Arife Simsek

Bulgurlu, Malatya Elazığ Yolu

10.KM, 44210

C.P. 44000, Battalgazi/Malatya, Turkey

E-mail: draksimsek@yahoo.com.tr

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trasplante y para las causas infecciosas de mortalidad. **Resultados:** De 314 beneficiarios, 35 (11,14%) fallecieron. Se incluyeron 29 receptores en el estudio (Grupo 1:17; Grupo 2:12). La causa más común de mortalidad fue la infección (58,6%) y la segunda fue la enfermedad cardiovascular (24,1%). La sepsis se desarrolló en el 29,4% de las muertes relacionadas con la infección, mientras que el COVID-19 constituyó el 23,5% de las muertes relacionadas con la infección. **Conclusión:** El diagnóstico y tratamiento tempranos de enfermedades infecciosas y cardiovasculares es importante para mejorar la supervivencia de los receptores de riñón.

**Palabras clave:** Cardiovascular. COVID-19. Infección. Trasplante de riñón. Mortalidad.

## Introduction

Kidney transplantation (KT) is the best treatment option for patients with end-stage renal disease (ESRD) compared with dialysis therapy. It is associated with improved quality of life and better survival in patients with ESRD<sup>1-3</sup>. Advances in immunological therapy and management strategy have increased the survival of kidney recipients and their grafts. Despite short-term increases in graft and patient survival, long-term outcomes are still not as expected<sup>4-12</sup>. Mortality after KT is still a serious problem.

In developed countries, underlying causes of deaths among kidney recipients have changed over time, and infection-related mortality has decreased, while cardiovascular diseases (CVDs) have become the leading causes of mortality<sup>13,14</sup>. Since the incidence of fatal infections after KT has decreased over time, current data on specific infectious causes of mortality are scarce<sup>13</sup>.

This study aims to share 10-year outcomes after KT and reveal the diseases leading to death among kidney recipients.

## Materials and methods

Medical data of the patients, who had undergone KT at a tertiary center between November 2010 and December 2020, were retrospectively reviewed. Inclusion criteria were adult kidney recipients, who had died. Exclusion criteria were pediatric recipients, recipients of en bloc and dual KT (EBDK), recipients with missing data, and recipients, who had died with a primary non-functioning graft (PNFG). Figure 1 shows the flowchart of the recipients. Six recipients, who had died (2 pediatric recipients, 2 recipients of EBDK, 1 recipient with missing data, and 1 recipient, who died with a PNFG) were excluded from the study. The recipients were grouped according to their donor type: Group 1 (from a living donor) and Group 2 (from a deceased donor). Subgroup analyses were done for mortality by time-period post-transplant (within the

1<sup>st</sup> year and after the 1<sup>st</sup> year) and for infectious causes of mortality.

## Evaluation of living donors and recipients

All recipients and living kidney donors (LKD) underwent detailed clinical examination. A six-step process (Malatya Algorithm) was used for evaluation of both potential LKDs and recipients<sup>15</sup>. The evaluation of LKDs with standard criteria was conducted according to the principles set out by the Amsterdam Forum<sup>16</sup>. Due to serious organ shortage, as is the case globally, kidneys were recovered from the donors with both standard criteria and extended criteria (ECD). There are no universal criteria defining ECD. This refers to a higher risk when compared to that with a standard donor. The risk could be a disadvantage in the future not only for recipients, but also for LKDs. Table 1 provides a definition for ECD, which was applied and/or recommended by our clinic.

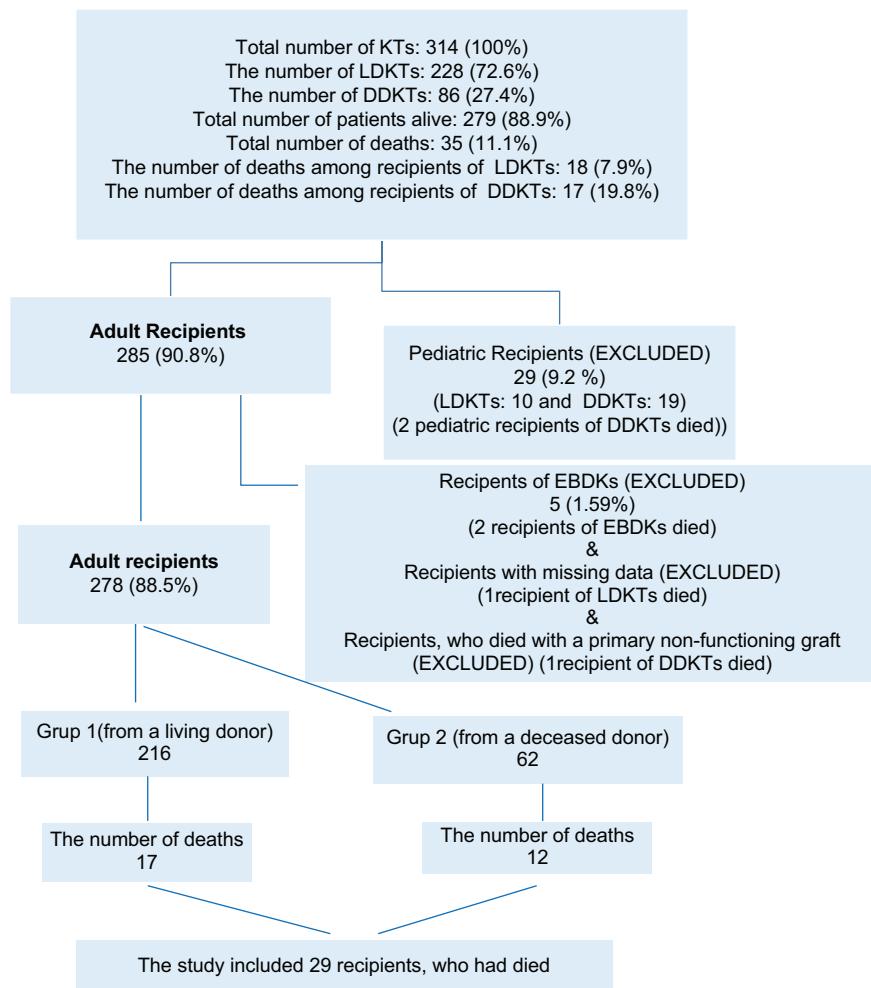
Delayed graft function (DGF) was defined as the need for dialysis within the 1<sup>st</sup> week of transplantation. The recipients were followed by the Nephrology Outpatient Clinic after having been discharged.

## Immunosuppressive regimen

Immunosuppressive regimen included induction therapy with a polyclonal antibody preparation (anti-thymocyte globulin) or an anti-CD25 monoclonal antibody (basiliximab) and maintenance therapy (triple therapy with a calcineurin inhibitor [tacrolimus], an adjunctive agent [mycophenolate mofetil or mycophenolic acid], and corticosteroids). Short courses of “rescue” therapy were also required to treat episodes of acute rejection in some recipients.

## Antimicrobial prophylaxis and treatment

All kidney donors received a single-dose of 2 g Cefazolin IV. Kidney recipients either received a Cefazolin 1 g IV



**Figure 1.** Flowchart of the patients in the study.

every 8 h for 24 h (before 2013) or a single-dose of 1 g Cefazolin IV (through 2013 and beyond). In addition to Cefazolin prophylaxis, both empirical and adjusted anti-microbial therapies were given to recipients of donors with microbial growth on urine/blood/tracheal aspirate cultures and recipients with any infectious complications.

All kidney recipients received 3 months of Valganciclovir prophylaxis for CMV infection and 1-2 years of Trimethoprim/Sulfamethoxazole prophylaxis for *Pneumocystis carinii* infection. Kidney recipients, who were at a high risk of developing tuberculosis (Tbc), received 9 months of isoniazid prophylaxis. Kidney recipients, who required AntiHBV therapy, received Entecavir or Tenofovir.

## Ethics

The study was conducted according to the principles set forth by the Helsinki Declaration of 1975.

Approval from the Human Ethics Committee of the Institution was obtained (approval number: 2021/1767).

## Statistical analysis

The data were analyzed using SPSS 17.0 for Windows (SPSS Inc., Chicago, USA). Continuous variables were presented as means with standard deviations (SDs), categorical variables were presented as numbers with percentages. The Shapiro-Wilk test was used to analyze normality of the groups. The Student's t-test was used for continuous variables with normal distribution. The Mann-Whitney U-test was applied for non-normally distributed variables. The Chi-squared test or Fisher's exact test was used for categorical variables.

**Table 1. The definition of the extended criteria donor**

<b>Deceased donor</b>	<b>Living donor</b>
Donor aged ( $\geq 60$ and $< 5$ )	Donor aged $\geq 60$
Vascular or anatomic variations	Vascular or anatomic variations
Kidney with simple cysts and/or stones	Simple kidney cysts and/or stones in one kidney, which is planned to be recovered. Donors with multiple cysts in one kidney or simple cysts and/or stones in both kidneys are not eligible for donation.
Presence of infection (except sepsis)	
Ischemia time longer than 24 h	ABO incompatible donors
Grafts with ATN (especially when CPR applied)	* It is not applicable in our country
ABO incompatible donors	
* It is not applicable in our country	
Donation after cardiac death	
* It is not applicable in our country	
Donor aged ( $\geq 50 - < 60$ ), who have at least two of the following criteria	Donor aged ( $\geq 50 - < 60$ ), who have at least one but no more than two of the following criteria
– Cerebrovascular accident	– Previous history of cerebrovascular accident without serious sequelae
– Hypertension	– Hypertension (uncomplicated)
– Diabetes Mellitus	– Diabetes Mellitus (uncomplicated)
– Serum creatinine $> 1.5$ mg/dL at time of donation	– Connective tissue disease (uncomplicated)
Donor aged ( $\geq 5 - < 50$ ), who have at least one of the following criteria	Donor aged ( $\geq 30 - < 50$ ), who have only one of the following criteria.
– Cerebrovascular accident	Donation is not eligible if the potential donors have two or more of the criteria.
– Hypertension	– Hypertension (uncomplicated)
– Diabetes Mellitus	– Diabetes Mellitus (uncomplicated)
– Serum creatinine $> 1.5$ mg/dL at time of donation	– Connective tissue disease (uncomplicated)
*** Our clinic recommends not to recover kidney from the potential living donor aged ( $\geq 18 - < 30$ ) securing donor interests If it is preferred, it would be appropriate for donor not to have additional diseases	

ATN: acute tubular necrosis, CPR: cardiopulmonary resuscitation.

## Results

Three hundred and fourteen patients had undergone KT between November 2010 and December 2020. Of these, 228 were living-donor KT (LDKT) and 86 were deceased-donor KT (DDKT). Of 314 recipients, 35 (11.14%) died. Twenty-nine recipients with a mean age of  $51.7 \pm 11.9$  years (12 females and 17 males) were included in the study.

Immunosuppressive regimen included induction therapy with an antithymocyte globulin ( $n = 25$ ) or basiliximab ( $n = 4$ ) and maintenance therapy (triple therapy with a tacrolimus ( $n = 29$ ), an adjunctive agent (mycophenolate mofetil ( $n = 16$ ) or mycophenolic acid ( $n = 13$ ), and corticosteroids ( $n = 29$ ). Twenty recipients (68.9%) remained on their discharge immunosuppressive regimens, while nine recipients (31.1%) not. Short courses of "rescue" therapy were required to treat episodes of acute rejection in 6 recipients. Seven kidney recipients received a Cefazolin 1 g IV every 8 h for 24 h, eight recipients received a single-dose of 1 g Cefazolin IV. In addition to Cefazolin prophylaxis, both empirical and adjusted antimicrobial therapies were

given to seven recipients of donors with microbial growth on urine/blood/tracheal aspirate cultures and seven recipients with any infectious complications.

The number of recipients in Group 1 and Group 2 was 17 and 12, respectively. The mean follow-up period of recipients was  $34.41 \pm 35.30$  months and  $25.25 \pm 34.41$  months in Group 1 and Group 2, respectively. The difference was not statistically significant ( $p = 0.478$ ) (Table 2).

There was not significant differences between the groups in terms of recipients' gender ( $p = 0.471$ ) and donors' gender ( $p = 0.449$ ). The mean age of recipients was significantly higher in Group 2 ( $60.25 \pm 7.87$  years) compared to that in Group 1 ( $45.76 \pm 10.68$  years) ( $p = 0.000$ ). The mean age of donors was  $48.76 \pm 10.34$  years and  $53.08 \pm 22.77$  years in Group 1 and Group 2, respectively. The difference was not statistically significant ( $p = 0.495$ ) (Table 2). The mean warm ischemic time was  $196.2 \pm 74.7$  s in Group 1. The mean cold ischemic time was  $1204.25 \pm 246.9$  min in Group 2.

Twenty-five recipients had comorbid diseases, while four recipients did not. Comorbid diseases

**Table 2. The characteristics of the recipients and donors according to type of donors**

<b>Characteristics</b>	<b>Total (n = 29)</b>	<b>Group I (n = 17)</b>	<b>Group II (n = 12)</b>	<b>(p)</b>
Age (recipient)	51.75 ± 11.93	45.76 ± 10.68	60.25 ± 7.87	0.000
Age (donor)	50.55 ± 16.41	48.76 ± 10.34	53.08 ± 22.77	0.495
Gender (recipient)				
Female	12	6	6	0.471
Male	17	11	6	
Gender (donor)				0.449
Female	10	7	3	
Male	19	10	9	
Ischemia time		196.2 ± 74.7 (WIT, s)	1204.25 ± 246.9 (CIT, min)	
Follow-up time (months)	30.62 ± 34.62	34.41 ± 35.30	25.25 ± 34.41	0.478
Causes of ESRD				
Idiopathic	14	8	6	
DM	7	5	2	
HT	2	(-)	2	
GN	3	2	1	
Others	3	2	1	
Comorbid disease (recipient)				
Yes	25	17	8	0.021
No	4	(-)	4	
Pre-transplantation RRT				
Preemptive	4	4	(-)	
HD	18	9	9	
PD	4	3	1	
HD-PD	3	1	2	
Mean duration of RRT (month)	74.08 ± 66.29	22.07 ± 26.52	130.4 ± 46.5	0.000
Extended criteria donor	16	5	11	0.001
Delayed graft function	12	3	9	0.006
Death with functioning graft	23	13	10	1.000
Gender (recipients with functioning graft)				
Female	6	2	4	0.002
Male	17	11	6	
Return to dialysis	6	4	2	1.000
RRT options from graft loss to mortality				
HD	5	3	2	
HD-PD	1	1	(-)	
Gender of recipients, who return to dialysis				
Female	6	4	2	0.002
Male	(-)	(-)	(-)	
Gender of donors, whose recipients return to dialysis				
Female	1	1	(-)	0.633
Male	5	3	2	

LDKT: living donor kidney transplantation, DDKT: deceased donor kidney transplantation, WIT: warm ischemia time, CIT: cold ischemia time, ESRD: end stage renal disease, DM: diabetes mellitus, HT: hypertension, GN: glomerulonephritis, RRT: renal replacement therapy, HD: hemodialysis, PD: peritoneal dialysis.

were more common in Group 1 (n = 17) compared to Group 2 (n = 8) (p = 0.021). The most common cause of ESRD was idiopathic (n: 14), the second was diabetes mellitus (DM) (n = 7). Hemodialysis was the

most applied dialysis type before KT. The mean duration of pre-transplantation dialysis was significantly higher in Group 2 (130.4 ± 46.5 months) compared to that in Group 1 (22.07 ± 26.52 months) (p = 0.000)

(Table 2). ECDs were preferred in 16 recipients, which was significantly higher in Group 2 ( $n = 11$ ) compared to Group 1 ( $n = 5$ ) ( $p = 0.001$ ). DGF developed in 12 recipients, which was significantly higher in Group 2 ( $n = 9$ ) compared to that in Group 1 ( $n = 3$ ) ( $p = 0.006$ ). Thirteen recipients in Group 1 and 10 recipients in Group 2 died with a functioning graft (DWFG). The difference was not statistically significant ( $p = 1.000$ ). The female-to-male ratio of DWFG recipients was 6/17. This ratio was 2/11 and 4/6 in Group 1 and Group 2, respectively. The difference was statistically significant ( $p = 0.002$ ). Only six patients, all of whom were female, returned to dialysis before death ( $p = 0.002$ ). Four of them were in Group 1, and two patients were in Group 2 ( $p = 1.000$ ) (Table 2).

About 52% of the deaths occurred within the 1<sup>st</sup> year of KT. Underlying causes of mortality were not different between the two groups ( $p = 0.407$ ), with infection the leading cause (58.6%), followed by CVD (24.1%). Although infection-related mortality was higher within the 1<sup>st</sup> year, it was not statistically significant ( $p = 0.396$ ). It was noteworthy that infection ( $n = 5$ ) was the only cause of mortality within the first 2 months of KT. Malignancy developed only in the late period (> 1 year) (Table 3). Sepsis developed in 29.4% of infection-related deaths. COVID-19 constituted 23.5% of infection-related deaths. Two recipients in Group 1 and three recipients in Group 2 died from sepsis, while two recipients in Group 1 and two recipients in Group 2 died from COVID-19 infection. One recipient in Group 1 and two recipients in Group 2 died from bacterial pneumonia/sepsis. One recipient in Group 2 died from meningitis. One recipient in Group 2 died from invasive fungal infection (IFI) + Tbc. One recipient in Group 1 died from IFI. Two recipients in Group 1 died from viral infection (Table 4).

Both empirical and adjusted antimicrobial therapies were used during the peritransplant period in 59% (10/17) of the infection-related deaths, half of which were administered for donor-derived infections. They were used in 33.3% (4/12) of the non-infectious deaths, half of which were also administered for donor-derived infections.

## Discussion

Despite the short-term increase in graft and patient survival, long-term outcomes are still not as expected<sup>4-12</sup>. The survival of kidney recipients is still shorter than that of the general population<sup>2</sup>. We

**Table 3. The causes of death according to the both mortality by the time period post-transplantation and donor type**

Donor type	Mortality by the time period post-transplantation					
	$\leq 1$ year ( $n = 15$ )		> 1 year ( $n = 14$ )		Total death ( $n = 29$ )	
	Group 1 ( $n = 7$ )	Group 2 ( $n = 8$ )	Group 1 ( $n = 10$ )	Group 2 ( $n = 4$ )	Group 1 ( $n = 17$ )	Group 2 ( $n = 12$ )
Causes of death						
Infection/ Sepsis	4	6	4	3	8	9
CVD	2	1	3	1	5	2
CVA	1	1	1	-	2	1
Malignancy	-	-	2	-	2	0

CVD: cardiovascular disease, CVA: cerebrovascular accident.

**Table 4. Infectious causes of death according to the both mortality by the time period post-transplantation and donor type**

Donor type	Mortality by the time period post-transplantation					
	$\leq 1$ year ( $n = 10$ )		> 1 year ( $n = 7$ )		Total death ( $n = 17$ )	
	Group 1 ( $n = 4$ )	Group 2 ( $n = 6$ )	Group 1 ( $n = 4$ )	Group 2 ( $n = 3$ )	Group 1 ( $n = 8$ )	Group 2 ( $n = 9$ )
Causes of death						
Sepsis	1	2	1	1	2	3
COVID-19	-	1	2	1	2	2
infection						
Bacterial pneumonia/ Sepsis	1	1	-	1	1	2
Menengitis	-	1	-	-	-	1
IFI+Tbc	-	1	-	-	-	1
IFI	1	-	-	-	1	-
Viral infections	1	-	1	-	2	-

IFI: invasive fungal infection, Tbc: tuberculosis.

evaluated the mortality after KT among kidney recipients, comparing several parameters. There was no statistical difference between two groups in terms of donor age, gender (both recipients and their donors) and mean follow-up time. However, the mean age of recipients in Group 2 was significantly higher than in Group 1, which might be attributed to the prolonged waiting period for DDKT. There is a serious organ shortage in our country as well as globally<sup>3</sup>. Patients have to wait for many years to be transplanted from deceased donors, which leads to an increase in the pre-transplantation dialysis period, as in the current study. As a result of this, the

pre-transplantation dialysis period was longer in Group 2 than in Group 1.

Due to organ shortage, we perform KTs from ECDs, as with many transplant centers<sup>3</sup>. There are no universal criteria defining ECD. The current study shared the definition of ECD, which was applied and/or recommended by our clinic. Sixteen recipients (55.1%) had received kidney grafts from ECDs, the majority of whom were in Group 2. It was not surprising that the development of DGF was more common in Group 2, which included deceased donors. Mortality after KT, especially with a functioning graft, is still a serious problem<sup>2,4-6,8,9,11,12</sup>. Of all cases, 79.3% died with a functioning graft. DWFG was not associated with donor type. However, it was more common in male recipients, especially those who had received kidneys from living donors. This might be attributable to underlying health problems in males, irrespective of their grafts. Only six patients, all were female, returned to dialysis before death. Neither donor type nor donor gender affects the rate of return to dialysis. Female recipients had experienced higher graft loss.

Some authors have revealed that infection is the leading cause of mortality after KT, followed by gastrointestinal disease and CVD<sup>7,8</sup>. Others have reported that CVD is the most common cause of mortality and neoplasia the second<sup>9</sup>. Mazuecos et al. stated that infection was the most common cause of mortality within 1 year of KT, while CVD was the leading cause of mortality thereafter. They found that malignancy was the second common cause of mortality 1-year post-transplant<sup>6</sup>. According to the current study, causes of mortality after KT were similar to those in some studies, but not to those in others<sup>6-9</sup>. Almost over half of deaths occurred within the 1<sup>st</sup> year of KT and infection was the leading cause, which was followed by CVD in both groups. Not only recipient-derived microorganisms but also donor-derived microorganisms led to infections after KT. The current study showed that, in a developing country such as Turkey, infection continued to be a major cause of death after KT, both within the 1<sup>st</sup> year of transplantation and thereafter. This was a descriptive study without a comparator, and thus cannot be used to make conclusions on the efficacy and safety of immunosuppressive therapies. However, it was clear that infection was the only cause of mortality within the first 2 months of KT, in which immunosuppressive therapy was used intensively. Thus, modulation of immunosuppressive regimen and antimicrobial therapy according to supposed risk of recipient and donor-derived

infections may be necessary. Optimization and standardization of donor management are also essential. It was noteworthy that mortality due to COVID-19, which has been present for the last year, constituted almost 25% of infection-related mortality after KT over 10 years.

Retrospective design and small case number were the limitations of the study. It was a descriptive research, and presented the characteristics of the kidney recipients, who had died. However, it did not reveal the underlying causes of mortality. While the findings from the current study were not evidence of causality, they helped to distinguish variables that might be important in explaining mortality after KT from those that were not. Thus, it can be used to generate hypotheses that should be tested using more rigorous designs, including immunosuppressive regimen, antimicrobial therapy, recipient and donor-derived infections.

## Conclusion

To reduce mortality after KT, KT recipients should be encouraged to increase their preventive measures against infections, and they should be educated about lifestyle and dietary habits, especially in developing countries. Modulation of immunosuppressive regimen and antimicrobial therapy according to supposed risk of recipient and donor-derived infections and early diagnosis and treatment of CVD is also important in decreasing mortality in KT recipients.

Within a relatively brief period of time, the current COVID-19 pandemic has resulted in a significant proportion of infection-related mortality after KT. As in the management of other infectious diseases, a multidisciplinary approach should be implemented in the management of COVID-19 infection.

## Conflicts of Interest

The authors report no conflicts of interest.

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## Ethical disclosures

**Protection of human and animal subjects.** The author declares that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The author declares having followed the protocols in use at their working center regarding patients' data publication.

**Right to privacy and informed consent.** Patients were informed that their data could be used for research and informed consents were obtained from all patients before surgery. The corresponding author is in possession of this document.

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# Coronary artery bypass on survival in patients with moderate ischemic mitral regurgitation: meta-analysis

*Derivación de la arteria coronaria en supervivencia de pacientes con insuficiencia valvular mitral isquémica moderada: un meta-análisis*

Jing Lv<sup>1</sup>, Kai Liu<sup>2</sup>, Ruoyi Lu<sup>2</sup>, Renliang He<sup>2</sup>, and Shaoxi Chen<sup>2\*</sup>

<sup>1</sup>Department of General Medicine; <sup>2</sup>Department of Cardiovascular Surgery, ZheJiang Hospital, Hangzhou, China

## Abstract

**Objective:** The objective of the study was to systematically evaluate the effect of coronary artery bypass grafting (CABG) or CABG combined with mitral valve surgery (cMVS) on post-operative survival in patients with moderate ischemic mitral valve regurgitation. **Materials and methods:** Databases including PubMed, Web of Science, COCHRANE LIBRARY, WanFang Data, and CNKI Data were searched from inception to January 2020. According to the inclusion criterion, relevant articles were screened. After that we extracted data, assessed quality, and performed meta-analysis using RevMan 5.2. **Results:** A total of 4 randomized controlled trial and 14 retrospective study involving 4476 patients were included in the study. The CABG group was 2278 and the cMVS group was 1698. The results of meta-analysis showed that compared with CABG group, there were no statistically significant differences in the recent mortality (odds ratio [OR] = 0.88,  $p = 0.62$ ), 1-year survival ( $OR = 1.03$ ,  $p = 0.82$ ), 1-year survival ( $OR = 1.07$ ,  $p = 0.62$ ), and long-term survival ( $OR = 0.95$ ,  $p = 0.61$ ) of the cMVS group. **Conclusion:** Current evidence indicates that patients in the cMVS group did not benefit from CABG group in survival after surgery.

**Keywords:** Ischemic mitral regurgitation. Coronary artery bypass grafting. Meta-analysis.

## Resumen

**Objetivo.** Evaluar sistemáticamente el efecto del injerto de derivación de la arteria coronaria (CABG) o el injerto de derivación de la arteria coronaria combinados con la cirugía de la válvula mitral (cMVS) sobre la supervivencia posoperatoria en pacientes con insuficiencia valvular mitral isquémica moderada. **Material y métodos.** Se realizaron búsquedas en bases de datos que incluyen Pubmed, Web of Science, COCHRANE LIBRARY, WanFang Data y CNKI Data desde el inicio hasta enero de 2020. De acuerdo con el criterio de inclusión, se seleccionaron los artículos relevantes. Después de eso, extrajimos los datos, evaluamos la calidad y realizamos el metanálisis con RevMan 5.2. **Resultados.** Se incluyó un total de 4 ensayos controlados aleatorios (ECA) y 14 estudios retrospectivos con 4476 pacientes. El grupo CABG fue 2278, el grupo cMVS fue 1698. Los resultados del metanálisis mostraron que, en comparación con el grupo CABG, no hubo diferencias estadísticamente significativas en la mortalidad reciente ( $OR = 0.88$ ,  $p = 0.62$ ), supervivencia a 1 año ( $OR = 1.03$ ,  $p = 0.82$ ), supervivencia a 1 año ( $OR = 1.07$ ,  $p = 0.62$ ) y supervivencia a largo plazo ( $OR = 0.95$ ,  $p = 0.61$ ) del grupo cMVS. **Conclusión.** La evidencia actual indica que los pacientes del grupo cMVS no se beneficiaron del grupo CABG en la supervivencia después de la cirugía.

**Palabras clave:** Insuficiencia mitral isquémica. Cirugía de revascularización coronaria. Metaanálisis.

### Correspondence:

\*Shaoxi Chen

Gudun Road, 1229  
C.P. 310007, Hangzhou, China  
E-mail: shxi\_c1110@21cn.com  
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## Introduction

Ischemic mitral regurgitation (IMR) is one of the common complications after myocardial infarction and an important factor leading to heart failure and death. At present, the surgical treatment of severe IMR has been clear, but it is still controversial whether surgical treatment should be performed in patients with moderate IMR. Relevant research results showed that the long-term survival rate of patients with IMR combined with surgery was low, the residual rate of mitral regurgitation, the recurrence rate of mitral regurgitation, and the incidence of postoperative adverse events were higher, so coronary artery bypass grafting (CABG) combined with mitral valve surgery was not recommended<sup>1-3</sup>. Hamouda et al. retrospective studies have found that CABG combined with valve surgery in IMR can significantly improve the cardiac function and prognosis<sup>4</sup> compared with CABG alone. At present, there are many studies on the choice of treatment for IMR, but the results are still not uniform. By searching the relevant literature at home and abroad, we meta analyzed the influence of CABG combined with mitral valve surgery (cMVS) on the survival rate of patients with IMR, and provided some reference for the selection of clinical treatment.

## Materials and methods

### Retrieval strategy

This study retrieves PubMed, Web of Science, COCHRANE LIBRARY, WanFang Data, and CNKI Data databases with the English keywords include “IMR,” “Ischemic mitral insufficiency,” “coronary artery bypass,” “off-pump coronary artery bypass surgery,” “OPCABG,” and “CABG” and the Chinese keywords include “ischemic mitral insufficiency,” “IMR,” “CABG,” “CABG,” and “non-stop CABG.” The year restriction is limited to the establishment of the library to January 2020, as an example of PubMed, the search is shown in figure 1.

### Permission and exclusion standard

All patients included in the study were moderate mitral regurgitation or insufficiency caused by coronary heart disease, excluding mild and severe and excluded patients with rheumatic heart valve disease, congenital

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((((coronary artery bypass[Title/Abstract] OR off-pump coronary artery bypass surgery[Title/Abstract]) OR OPCABG[Title/Abstract]) OR CABG[Title/Abstract]) AND "humans"[MeSH Terms]) AND (((ischemic mitral regurgitation[Title/Abstract] OR Ischemic mitral insufficiency[Title/Abstract]) AND "humans"[MeSH Terms]) AND "humans"[MeSH Terms])
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Figure 1. Meta-analysis results are represented by forest maps.

heart valve disease, infective endocarditis, and so on. All included studies had related follow-up results.

### Document extraction

The literature was selected by two authors (Chen Shao-chien and Lu Jing), If there are different opinions, the two authors will decide whether to be selected after discussion. The included literature was divided into randomized controlled trials or retrospective cohort controlled studies. The extraction results included: ① literature information: author, country, publication time of the literature; ② literature type: randomized controlled study, retrospective cohort controlled study; ③ literature characteristics: sample size, sex, age; and ④ observation events: post-operative perioperative mortality, the survival rate of 1 year after operation, the survival rate of 1-3 years after operation, and the survival rate of more than 3 years after operation.

### Statistical methods

The Revman 5.2 software provided by Cochrane Collaboration Network was used for meta-analysis, and the confidence level was set as 95%. The heterogeneity of the effect value of each independent study was tested. If there was no statistical heterogeneity ( $p > 0.1$ ), the fixed effect model was used; if there was statistical heterogeneity ( $p \leq 0.1$ ), and the random effect model was used. The results of meta-analysis were represented by forest map.

## Results

### Results and basic information of literature retrieval

There are 1466 documents were initially retrieved, remove the irrelevant research, review and repetitive literature by reading the article title and abstract. Finally, 4 randomized controlled studies and 15 retrospective

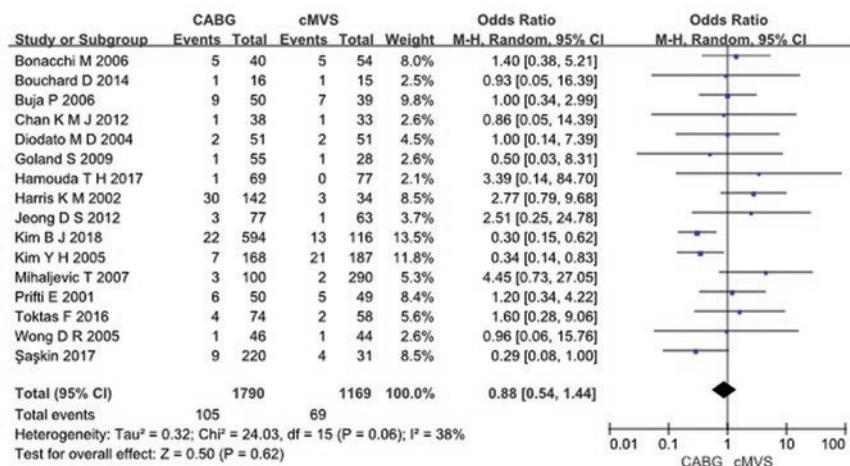


Figure 2. Meta-analysis of post-operative perioperative mortality two groups.

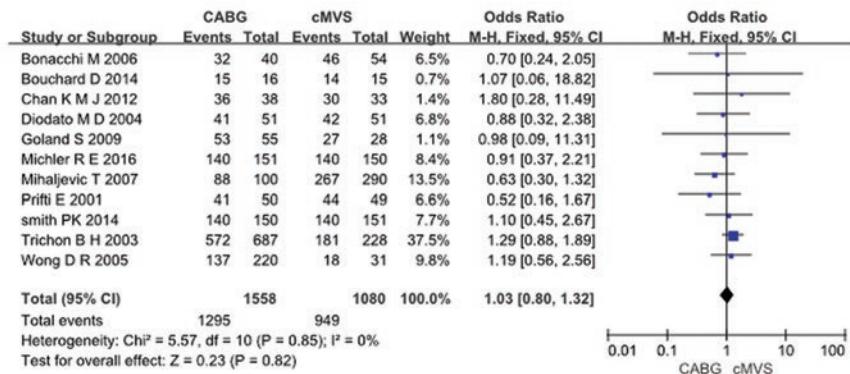


Figure 3. Meta-analysis of 1-year survival after operation in two groups.

controlled studies were included in the study from 2001 to 2018<sup>2-20</sup>. A total of 4476 patients were enrolled in this study, including 2778 patients in CABG group and 1698 patients in CMVs group. The baseline levels were compared between groups; there was no significant difference between the two groups. The basic information of the literature included is shown (Table 1).

## Meta-analysis results

### PERIOPERATIVE MORTALITY

The 16 studies<sup>4-13,15-18,20</sup> reported perioperative mortality after surgery, and the results showed statistical heterogeneity ( $p = 0.06$ ,  $I^2 = 38\%$ ), so the random effect model was used for meta-analysis. The results showed that there was no significant difference in perioperative mortality between CABG group and CMVs Group (odds

ratio [OR] = 0.88, 95% confident interval [CI] [0.54, 1.44],  $p = 0.62$ ) (Fig. 2).

### 1-YEAR POST-OPERATIVE SURVIVAL

The 11 studies<sup>3,5,6,8,9,14-16,19</sup> reported the survival rate of 1 year after operation, and the results of each study were not statistically heterogeneous ( $p = 0.85$ ,  $I^2 = 0\%$ ), so the fixed effect model was used for meta-analysis. The results showed that there was no significant difference in 1-year survival rate between CABG group and CMVs Group (OR = 1.03, 95% CI [0.80, 1.32],  $p = 0.82$ ) (Fig. 3).

### 1-3 YEARS AFTER SURGERY

The 11 studies<sup>5,9,14,16,17</sup> reported the survival rate of 1-3 years after surgery, and the results of each study

**Table 1. Inclusion of basic literature**

Author	Follow-up time (month)	Date of publication (year)	Country	Type of study	Age		Sample size		Observation of outcome
					CABG	cMVS	CABG	cMVS	
Goland, 2009 <sup>2</sup>	61.2 ± 43.2	2009	U.S.	Retrospective	69 ± 11	68 ± 9	55	28	①、②、④
Smith, 2014 <sup>3</sup>	12	2014	U.S.	Randomized	65.2 ± 11.3	64.3 ± 9.6	150	151	①、②
Hamouda, 2017 <sup>4</sup>	48	2017	Arabia	Retrospective	67 ± 7	63 ± 5	69	77	①、③
Bonacchi, 2006 <sup>5</sup>	32 ± 11	2006	Italy	Retrospective	64.5 ± 6	64.6 ± 6	40	54	①、②、③、④
Bouchard, 2014 <sup>6</sup>	12	2014	Canada	Randomized	65 ± 12	69 ± 7	16	15	①、②
Buja, 2006 <sup>7</sup>	34.9 ± 14.6	2006	Italy	Retrospective	75 ± 7.4	72 ± 9.1	50	39	①、②、④
Chan, 2012 <sup>8</sup>	12	2012	UK	Randomized	70.4 ± 7.9	70.9 ± 10.5	38	33	①、②
Diodato, 2004 <sup>9</sup>	50 ± 20	2004	U.S.	Retrospective	69 ± 11	65 ± 10	51	51	①、②、③、④
Harris, 2002 <sup>10</sup>	60	2002	U.S.	Retrospective	68.8 ± 9.8	65.6 ± 10.8	142	34	①、④
Jeong, 2012 <sup>11</sup>	96	2012	Korea	Retrospective	65.4 ± 9.1	63.9 ± 9.1	77	63	①、④
Kim, 2018 <sup>12</sup>	33.6–115.9	2018	Korea	Retrospective	65.2 ± 8.8	63.7 ± 9.4	594	116	①、④
Kim, 2005 <sup>13</sup>	60	2005	U.S.	Retrospective	71 ± 11	72 ± 9	168	187	①
Michler, 2016 <sup>14</sup>	24	2016	U.S.	Randomized	not described		151	150	②、③
Mihaljevic, 2007 <sup>15</sup>	120	2007	U.S.	Retrospective	66 ± 9.2	66 ± 9.6	100	290	①、②、④
Prifti, 2010 <sup>16</sup>	36	2001	Italy	Retrospective	64.5 ± 6	63.4 ± 5	50	49	①、②、③
Şaskin, 2017 <sup>17</sup>	51.3 ± 26.8	2017	Turkey	Retrospective	65.66 ± 9.95	64.1 ± 8.74	74	58	②
Toktas, 2016 <sup>18</sup>	17	2016	Turkey	Retrospective	63 ± 2.7	61 ± 3.2	46	44	①
Trichon, 2003 <sup>19</sup>	60	2003	UK	Retrospective	68 (61, 74)	68 (62, 74)	687	228	①、②、③、④
Wong, 2005 <sup>20</sup>	12	2005	U.S.	Retrospective	not described		220	31	①、②

CABG: coronary artery bypass grafting, cMVS: coronary artery bypass grafting mitral valve surgery. ①Postoperative perioperative mortality, ②1-year survival, ③1-year survival, ④3-year survival greater than 3-year survival.

were not statistically heterogeneous ( $p = 0.41$ ,  $I^2 = 2\%$ ), so the fixed effect model was used for meta-analysis. The results showed that there was no significant

difference in 1-3-year survival rate between CABG group and cMVS group ( $OR = 1.07$ , 95% CI [0.83, 1.37],  $p = 0.62$ ) (Fig. 4).

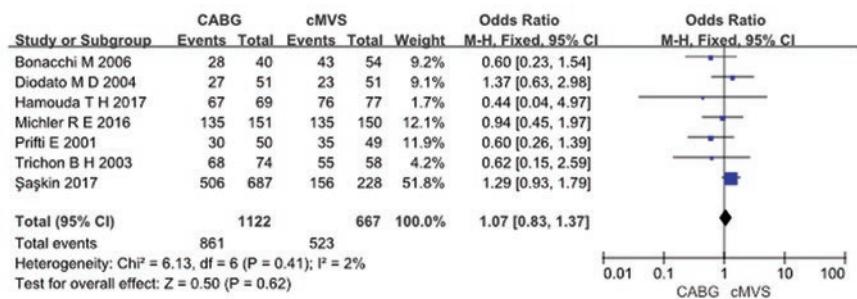


Figure 4. Meta-analysis of 1-3-year survival rate between the two groups.

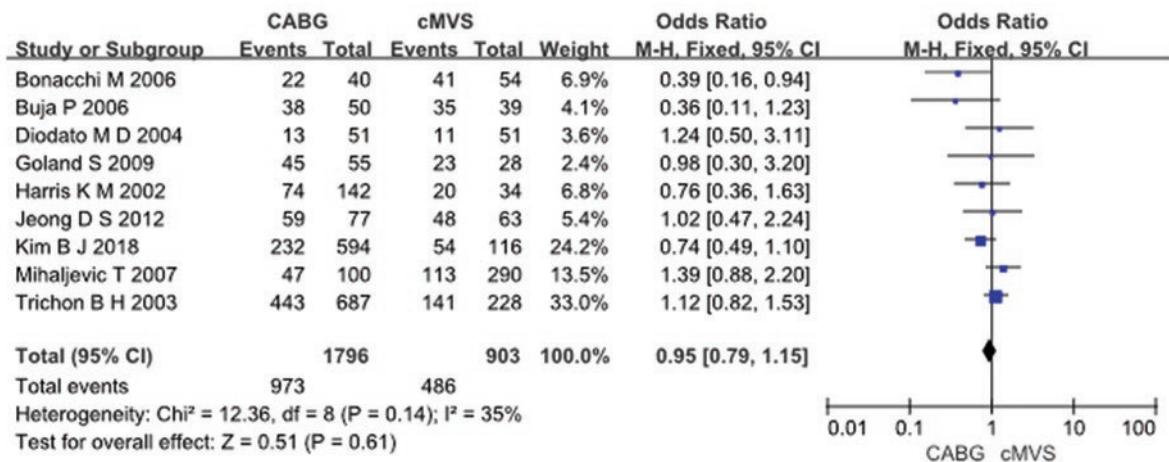


Figure 5. Meta-analysis of survival rate greater than 3 years after operation in both groups.

### POSTOPERATIVE SURVIVAL RATE GREATER THAN 3 YEARS

The 11 studies<sup>5,7,9-12,15</sup> reported the survival rate of more than 3 years after operation, and the studies of each study were not statistically heterogeneous ( $p = 0.14$ ,  $I^2 = 35\%$ ), so the fixed effect model was used for meta-analysis. The results showed that there was no significant difference in post-operative survival rate of more than 3 years between CABG group and cMVS group ( $OR = 0.95$ , 95%CI [0.79, 1.15],  $p = 0.61$ ), ( $p = 0.61$ ) (Fig. 5).

### Discussion

IMR is one of the common complications after ischemic heart disease and myocardial infarction caused by coronary atherosclerosis. It can be divided into acute and chronic IMR. The IMR is an important factor leading to heart failure and death. There were no typical pathological

changes in the mitral lobe and subvalvular structure of IMR patients. Patients with acute IMR were mainly due to acute papillary muscle infarction and rupture, which causes increased left heart volume load and left heart function decompensation, which can lead to heart source Sexual shock. Chronic IMR patients are secondary to the phenomenon of left ventricular remodeling caused by local myocardial ischemia, resulting in the expansion and deformation of the mitral valve annulus, subvalvular structural displacement or traction, which are involved in the formation of IMR, so IMR is considered to be a function Sexual mitral regurgitation<sup>21,22</sup>. The current surgical treatment of IMR mainly includes three surgical methods: simple CABG, CABG combined with mitral valve replacement, and CABG combined with mitral valve repair. At present, there are many clinical studies on the choice of surgical methods for moderate IMR, but the post-operative effects of different surgical methods are still controversial.

The results of meta-analysis of this study showed that there was no significant difference in perioperative mortality, 1-year survival rate, 1-3-year survival rate, and

more than 3-year survival rate between the two groups!compared with simple CABG, CMVs group had no obvious advantage in post-operative survival rate. Mallidi et al.<sup>23</sup> studies found that the perioperative risk of CMVs group was nearly 2 times higher than that of CABG alone. Complications caused by cardiopulmonary bypass cannot be avoided to a great extent with the development of CABG technology, especially the development and promotion of off-pump coronary artery bypass technology. Mallidi et al.<sup>23</sup> research found that the perioperative risk of cMVS group increased nearly 2 times compared with simple CABG. With the development of CABG, in particular, the development and promotion of CABG, complications due to cardiopulmonary bypass cannot be avoided to a great extent. Fatouch et al.<sup>24</sup> randomized controlled study results showed that CMVs group had more advantages in NYHA cardiac function classification and left ventricular diameter reduction, and mitral regurgitation was significantly improved in patients with postoperative mitral regurgitation. However, 40% of patients in CABG group had residual moderate to severe mitral regurgitation during long-term follow-up. Jeong et al.<sup>11</sup> found that for patients with IMR with a left ventricular ejection fraction <40%, cMVS can improve their post-operative residual mitral regurgitation, which is conducive to postoperative recovery and improves the quality of life, but its opening to exposed heart and longer turnaround time increase the risk of perioperative death. Kim et al.<sup>12</sup> found that cMVS increased the risk of early post-operative death and complications compared with simple CABG, and there seems to be no significant clinical benefit in long-term clinical and echocardiographic results.

Minghui et al.<sup>25</sup> suggested that individualized surgical scheme should be formulated for each patient, which is more favorable for the long-term prognosis of patients. For patients with multiple coronary artery disease, short life expectancy (< 5 years), and with large area of viable myocardium or normal papillary muscle function, simple CABG operation can be considered; for young patients with good pre-operative basic condition and stable condition, simple CABG can be considered, and CMVs should be considered actively.

The shortcomings of this study are as follows: (1) most of the references are retrospective controlled studies, which have some limitations. (2) The annual span of this study is large. Although the relevant literature is widely searched, there will still be unpublished literature and conference literature not included. Therefore, larger sample randomized controlled studies are needed to further verify this conclusion.

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## Conflicts of interest

The authors declare that they have no conflicts of interests.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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# The increased ratio of Treg/Th2 in promoting metastasis of hepatocellular carcinoma

*El aumento de la proporción de Treg/Th2 en la promoción de la metástasis del carcinoma hepatocelular*

Chuanzhi Li, Shuying Li, Jing Zhang, and Fenglei Sun\*

Department of Hepatobiliary and Pancreatic Surgery, Jinan Central Hospital, Cheeloo College of Medicine, Shandong University, Shandong, China

## Abstract

**Objective:** Liver cancer is the fifth most common cancer in the world. Research on the pathogenesis and detailed molecular mechanisms of liver cancer is very important. The immune system plays an important role in regulating the incidence and metastasis of liver cancer. **Materials and methods:** This work collected 20 blood samples from patients with clinical hepatocellular carcinoma without metastasis, 20 blood samples from patients with metastatic hepatocellular carcinoma, and 20 blood samples from healthy subjects. Flow cytometry was used to analyze the content of Treg and Th2 cells in the three groups of blood samples. Immunofluorescence was applied to analyze the relative expression of CTLA-4 and CD28 in lymphocytes of each group of blood samples. Western blot was used to analyze the T cell surface protein CTLA-4, CD28, GATA3, and FOXP3 expression in each group of blood samples. **Results:** The expression of CD28 and GATA3 in the blood of patients with hepatocellular carcinoma without metastasis was obviously higher than that of patients with metastasis of hepatocellular carcinoma, which is contrary to the expression trend of CTLA-4 and FOXP3, and corresponds to the content ratio of Treg and Th2 cells, thus verifying the relationship between Treg/Th2 ratio and metastasis of hepatocellular carcinoma. **Conclusions:** In the microenvironment of liver cancer, the ratio of Treg/Th2 will increase significantly, thereby promoting the metastasis of hepatocellular carcinoma.

**Keywords:** Hepatocellular carcinoma. Treg cells. Th2 cells. CTLA-4. CD28.

## Resumen

**Objetivo:** El cáncer de hígado es el quinto cáncer más común en el mundo. La investigación sobre la patogenia y los mecanismos moleculares detallados del cáncer de hígado es muy importante. El sistema inmunológico juega un papel importante en la regulación de la incidencia y metástasis del cáncer de hígado. **Material y métodos:** Este trabajo recogió 20 muestras de sangre de pacientes con carcinoma hepatocelular clínico sin metástasis, 20 muestras de sangre de pacientes con carcinoma hepatocelular metastásico y 20 muestras de sangre de sujetos sanos. Se utilizó citometría de flujo para analizar el contenido de células Treg y Th2 en los tres grupos de muestras de sangre. Se aplicó inmunofluorescencia para analizar la expresión relativa de CTLA-4 y CD28 en linfocitos de cada grupo de muestras de sangre. Se utilizó Western blot para analizar la expresión de la proteína de superficie de células T CTLA-4, CD28, GATA3, FOXP3 en cada grupo de muestras de sangre. **Resultados:** La expresión de CD28 y GATA3 en la sangre de pacientes con carcinoma hepatocelular sin metástasis fue obviamente mayor que la de pacientes con metástasis de carcinoma hepatocelular, lo cual es contrario a la tendencia de

## Correspondence:

\*Fenglei Sun

Jiefang Road, 105

C.P. 250013, Jinan, Shandong, China

E-mail: flei\_s0723@126.com

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expresión de CTLA-4 y FOXP3, y corresponde al contenido relación de células Treg y Th2, verificando así la relación entre la relación Treg/Th2 y la metástasis del carcinoma hepatocelular. **Conclusiones:** En el microambiente del cáncer de hígado, la proporción de Treg/Th2 aumentará significativamente, promoviendo así la metástasis del carcinoma hepatocelular.

**Palabras clave:** Carcinoma hepatocelular. Células Treg; Células Th2. CTLA-4. CD28.

## Introduction

Liver cancer is the fifth most common cancer in the world, and liver cancer is the main cause of death in patients with liver cirrhosis<sup>1,2</sup>. Hepatocellular carcinoma is one of the common malignant tumors in our country, with a high incidence in the southeast coastal areas. The median age of liver cancer patients in our country is 40-50 years old, and it is more common in men than women. Under normal circumstances, the immune system can recognize and eliminate tumor cells in the tumor microenvironment. However, to survive and grow, tumor cells can adopt different strategies to suppress the body's immune system and not be killed normally<sup>3</sup>. Therefore, research on the pathogenesis and detailed molecular mechanisms of liver cancer is very important, and research in this area has been a hot spot for many years<sup>4</sup>.

Regulatory T cells (Tregs) are a type of T cell subgroup that controls autoimmune reactivity in the body and were also called suppressor T cells in the early stage<sup>5</sup>. Regulatory T cells are one of the important factors for maintaining immune tolerance of the body. They are secreted by thymus, exported to the periphery, and inhibit the potential self-reactivity existing in the normal body through active regulation. The activation and proliferation of T cells regulate the body's immunity<sup>6,7</sup>. At present, the immunosuppressive function of tumor-related Treg cells is the main obstacle to improving the effectiveness of immunotherapy<sup>8</sup>.

T helper2 cell (Th2) is a subset of T cells that can secrete Th2-type cytokines (such as interleukins [IL-4], IL-5, IL-10, and IL-13). These cytokines can promote the proliferation of Th2 cells and inhibit the proliferation of Th1 cells, and, at the same time, assist B cell activation and exert humoral immunity<sup>9</sup>. T helper cells play a central role in the regulation of immune responses. In addition to effector cells, Th cells are also regulated by regulatory T cells<sup>10</sup>.

Cytotoxic T Lymphocyte Associated Protein-4 (CTLA-4) is a protein receptor that acts as an immune checkpoint and downregulates the immune

response. CTLA-4 is constitutively expressed in regulatory T cells but is only upregulated in conventional T cells after activation and this phenomenon is particularly pronounced in cancer<sup>11</sup>. When it binds to CD80 or CD86 on the surface of antigen presenting cells, it acts as a "off" switch. CTLA-4 is the target gene of the transcription factor Forkhead Box P3 (FOXP3) and a protein on the surface of T lymphocytes, which plays an important role in downregulating the immune response<sup>12</sup>. CD28 is a specific glycoprotein on the surface of T cells, involved in inducing T cell activation, T cell proliferation and cytokine production, and promoting T cell survival<sup>13</sup>.

Both CD28 and CTLA-4 can bind ligands CD80 and CD86 to regulate the function of T cells. Therefore, in the liver cancer microenvironment, the balance between the expression of CTLA-4 and CD28 on the surface of T cells determines the immune surveillance of T cells<sup>14</sup>.

This work collected 20 blood samples from patients with clinical hepatocellular carcinoma without metastasis, 20 blood samples from patients with metastatic hepatocellular carcinoma, and 20 blood samples from healthy subjects. Flow cytometry (FCM) was used to analyze the content of Tregs and Th2 cells in each group of blood samples. Immunofluorescence was used to analyze the relative expression of CTLA-4 and CD28 in lymphocytes of each group of blood samples. Western blot was used to analyze the T cell surface protein CTLA-4, CD28, GATA-binding protein 3 (GATA3), FOXP3 expression in each group of blood samples.

## Materials and methods

### Experiment design

Twenty blood samples were collected from patients with clinical hepatocellular carcinoma without metastasis (Ca-N-M), 20 blood samples from patients with metastatic hepatocellular carcinoma (Ca-M), and 20 blood samples from healthy subjects (NC). The content of Treg and Th2 cells in each group of blood

samples was detected by FCM. The relative expression of CTLA-4 and CD28 in lymphocytes of each group of blood samples were analyzed by immunofluorescence technology. Finally, the expression of T cell surface proteins CTLA-4, CD28, GATA3, and FOXP3 in each group of blood samples was determined by Western Blot analysis.

### **FCM analysis**

The single cell suspension was added to a 2 ml centrifuge tube, centrifuged at 1500 rpm for 5 min, and the supernatant was discarded. Use 4% paraformaldehyde (PFA) to fix at 4°C for 30 min, and then use 0.1% Triton X-100 to fix at room temperature for 10 min. Add 200 ul of the primary antibody diluted with PBA, incubate at 4°C for 2 h, then centrifuge to remove the supernatant and wash with PBS. Add 200 ul of fluorescein-labeled secondary antibody diluted with PBA, and incubate for 30 min at 4°C in the dark. Finally, the cells were re-suspended in 500 ul PBS, placed in a flow tube, and detected by FCM.

### **Immunofluorescence analysis**

Select the appropriate fluorescein-labeled antibody to stain CTLA-4 and CD28 in the lymphocytes of each group of blood samples, and then use DAPI to stain the nuclei in dark environment and observe through a fluorescence microscope.

### **Western blot analysis**

Collect T cells from each blood sample group, and add 200 µl of cell lysate to each six-well plate. After sonication, the cells were lysed on ice for 1 h. The lysed cell sample was centrifuged at 12,500 rpm for 15 min at 4°C. Then, transfer the supernatant in the centrifuge tube to a clean centrifuge tube. BCA protein quantification kit was used to quantify protein concentration. The measured protein samples were stored at -80°C. In Western blot electrophoresis, the protein loading concentration was 50 µg per well. After SDS-PAGE electrophoresis, the membrane was transferred and blocked. CTLA-4, CD28, GATA3, FOXP3, and B-actin (1: 500, anti-human, Abcam, USA) primary antibody were diluted to the concentration which can be used. The samples were incubated overnight on a shaker at 4°C. After washing with PBS, the samples were incubated with the secondary antibody (1: 1000,

anti-human, Abcam, USA) for 30 min at room temperature in the dark. Finally, the developer was used for development and photography.

### **Statistical analysis**

The experimental results are expressed as mean ± standard deviation. Statistical analysis was performed using SPSS 22.0 software. The figures were produced with Origin 2020 software.

## **Results**

### **The content of Treg and Th2 cells**

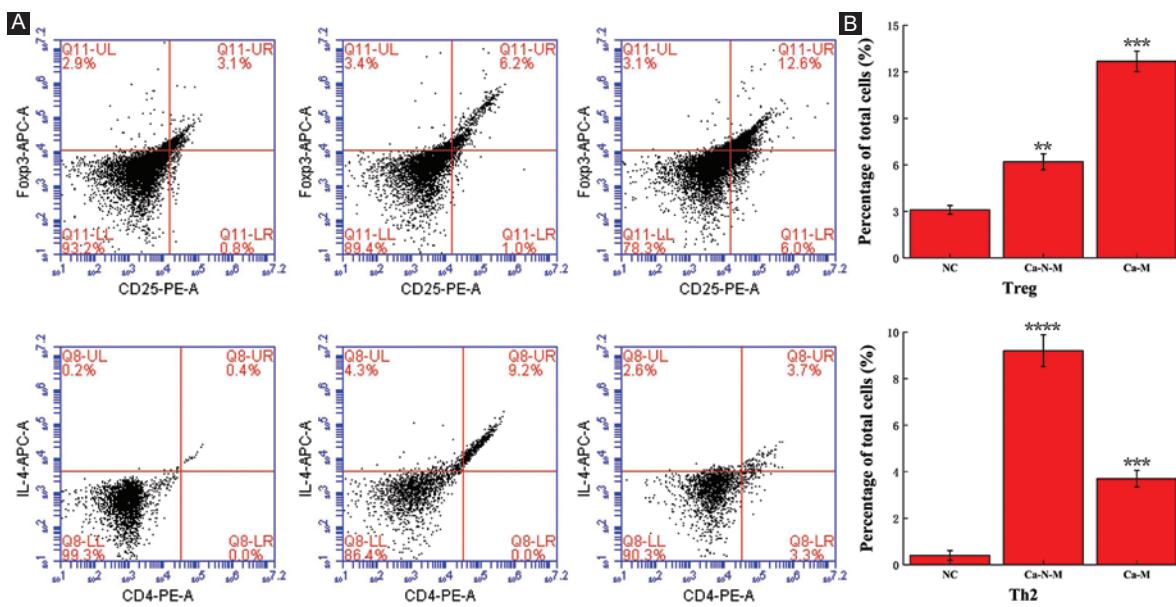
The data obtained by FCM showed that the content of Treg and Th2 cells showed different trends among the three groups. The content of Treg cells in the three groups from large to small was Ca-M group, Ca-N-M group, and NC group. The content of Th2 cells in the three groups from large to small was Ca-N-M group, Ca-M group, and NC group (Fig. 1).

### **Relative expression of CD28 and CTLA-4**

Immunofluorescence analysis technology was used to determine the relative expression of CTLA-4 and CD28 in lymphocytes of each blood sample group, and the results are shown in figure 2. It can be seen from the figure that the relative expression of CTLA-4 in Ca-M group is higher than that in Ca-N-M group, while the expression in Ca-N-M group is higher than NC group. For CD28, the relative expression in Ca-M group is lower than Ca-N-M group and at the same time higher than NC group.

### **The expression level of CD28, CTLA-4, GATA3, and FOXP3**

The expression level of CD28, CTLA-4, GATA3, and FOXP3 was obtained from Western blot analysis. B-actin was the internal reference protein in this Western blot analysis experiment (Fig. 3). For Ca-N-M group compared to NC group, the expression level of CTLA-4 and FOXP3 is higher, while that of CD28 and GATA3 are much higher. For Ca-M group, the expression level of CD28 and GATA3 is higher than that of NC group, and while that of CTLA-4 and FOXP3 is much higher.



**Figure 1.** The flow cytometry results of The content of Treg and Th2 cells. The data of NC group are all equivalent to that of healthy people. **A:** Treg cells (first row) and Th2 cells (second row) of NC, Ca-N-M, and Ca-M group. **B:** The percentage of target cells (Treg and Th2 cells) in total cells. The symbol \*\* means  $p < 0.01$ , \*\*\* means  $p < 0.001$ , \*\*\*\* means  $p < 0.0001$  (compared to the NC group).

## Discussion

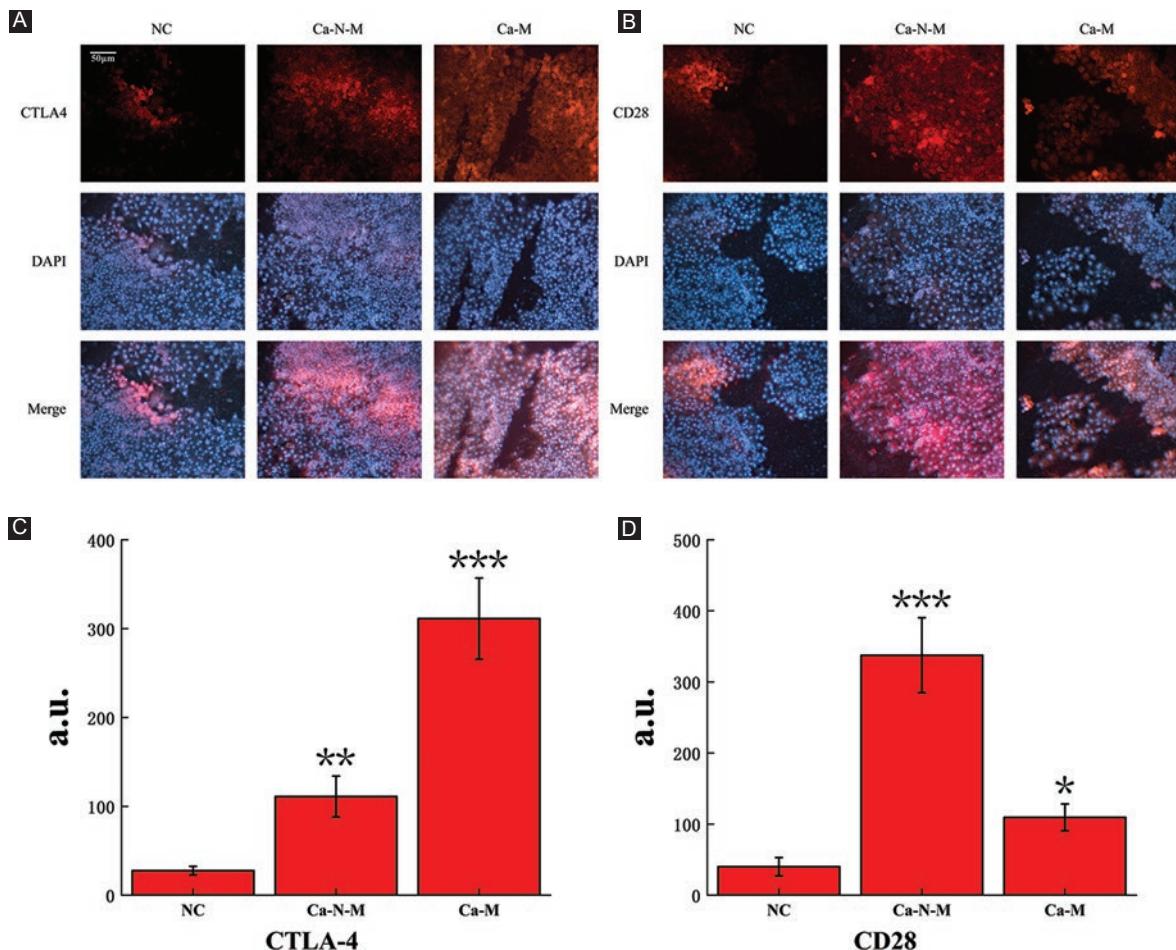
For Tc and Th cells, costimulatory signal transduction lowers the threshold of T cell activation and promotes the proliferation and differentiation of T cells. In the absence of CD28 co-stimulation, naive T cells will not be activated and will not respond<sup>15</sup>. The co-stimulation of CD28 has many important molecular effects: 1. Induces the expression of IL-2 receptor (IL-2R) on the surface of T cells, thereby allowing cells to receive the third signal; 2. Make Th cells begin to secrete a large number of cells Factors and chemokines; and 3. Induces and upregulates the expression of other co-stimulatory and regulatory molecules in Th and Tc cells<sup>16,17</sup>.

CTLA4 is homologous to the T cell costimulatory protein CD28, and these two molecules, respectively, bind to CD80 and CD86 (also known as B7-1 and B7-2) on antigen presenting cells. Compared with CD28, CTLA-4 has a higher affinity for CD80 and CD86, which makes it perform better than CD28 ligand. CTLA4 transmits inhibitory signals to T cells, while CD28 transmits stimulation signals<sup>18</sup>. CTLA4 is also present in regulatory T cells (Treg cells), which contributes to its inhibitory function. T cell activation through T cell

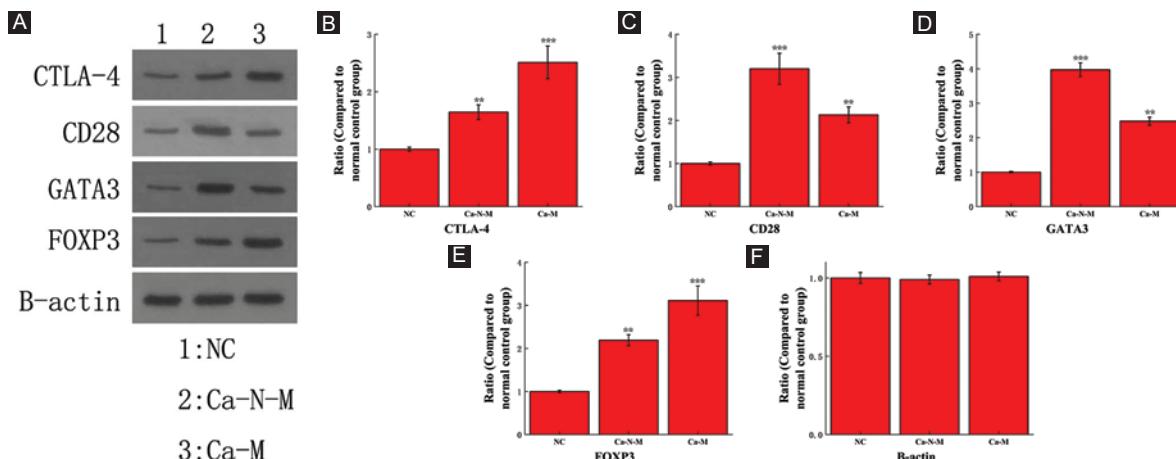
receptors and CD28 leads to the increased expression of CTLA-4<sup>19</sup>.

FOXP3 is a member of the fork-head transcription factor family and is considered to be a marker molecule of regulatory T cells (Treg)<sup>20,21</sup>. Mutations of FOXP3 gene can cause serious autoimmune diseases. Therefore, FOXP3 plays a key role in regulating the body's immune stability. As a transcriptional regulatory factor, FOXP3 regulates the activity of Treg by directly regulating a variety of genes<sup>22</sup>. FOXP3 cannot only be used as a marker molecule of CD+4T and CD+25T cells, but also a key factor that determines the function of CD+4T and CD+25T cells. FOXP3 secretes TGF-β and IL-10 for CD-127T, CD+4T, and CD+25T cells, which two are related to its immunoregulatory function<sup>23</sup>.

The transcription factor GATA3 is a key factor regulating cell differentiation and cytokine expression and is a specific transcription factor for Th2 cells<sup>24</sup>. Th2 cells express IL-4, IL-5, IL-13, and other cytokines, promote the production of antibodies, mediate humoral immune response, fight against pathogens outside the cell, and inhibit the function of anti-tumor immunity. GATA3 is critical in regulating the expression of cytokines in T cells and is limited in the expression of Th2 cells<sup>25</sup>.



**Figure 2.** The immunofluorescence results of relative expression of CTLA-4 and CD28. All pictures have the same magnification scale, and the scale bar is shown in A. The average fluorescence intensity was calculated by the software ImageJ. The data of NC group are all equivalent to that of healthy people. **A:** Relative expression of CTLA-4 in NC, Ca-N-M, and Ca-M group. **B:** Relative expression of CD28 in NC, Ca-N-M, and Ca-M group. **C:** The average fluorescence intensity of CTLA-4 (Red) in three groups. **D:** The average fluorescence intensity of CD28 (Red) in three groups. The symbol \* means  $p < 0.05$ , \*\* means  $p < 0.01$ , \*\*\* means  $p < 0.001$  (compared to the NC group).



**Figure 3.** The Western blot analysis results of protein CTLA-4, CD28, GATA3, and FOXP3. The data of NC group are all equivalent to that of healthy people. **A:** Original gel electrophoresis image. **B-F:** The ratio of protein CTLA-4, CD28, GATA3, and FOXP3 expression compared to NC group. The symbol \*\* means  $p < 0.01$ , \*\*\* means  $p < 0.001$  (compared to the NC group).

## Conclusions

CTLA-4, CD28, GATA3, and FOXP3 are all critical factors in regulating the expression level of Treg and Th2 cells. The expression of CD28 and GATA3 in the blood of patients with hepatocellular carcinoma without metastasis is obviously higher than that of patients with metastasis of hepatocellular carcinoma, which is contrary to the expression trend of CTLA-4 and FOXP3 and corresponds to the content ratio of Treg and Th2 cells, thus verifying the relationship between Treg/Th2 ratio and metastasis of hepatocellular carcinoma. The results indicate that in the microenvironment of hepatocellular carcinoma, the ratio of Treg/Th2 will increase significantly, thereby promoting the metastasis of hepatocellular carcinoma.

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## Conflicts of interest

The authors declared that they have no conflicts of interests.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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# Comparison of the non-absorbable polymer clips, knot-tying, and loop ligature appendiceal stump closure methods in laparoscopic appendectomy

*Comparación de los métodos de cierre del muñón apendicular con clips de polímero no absorbible, anudado y ligadura de bucle en la apendicectomía laparoscópica*

Hakan Ozdemir and Oguzhan Sunamak\*

Department of General Surgery, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey

## Abstract

**Objective:** In laparoscopic appendectomy (LA), closure of the appendix stump is important. This method must be safe and easy-to-use as well as an economical one. We compared three methods of the appendix stump closure in terms of safety, easiness, and financial cost. **Materials and methods:** Three-hundred and ten LA patients operated between January 2011 and December 2019 and appendix stump was closed using one of the three methods, namely, non-absorbable polymeric clips (Group 1, n = 126), knot-tying group (Group 2, n = 101), and laparoscopic loop ligature group (Group 3, n = 83) were retrospectively analyzed in terms of stump leakage, infection, operation, and hospital stay duration. **Results:** There were 148 female and 162 male patients. The mean age was  $33.57 \pm 12.60$  years. There was not any appendiceal stump leakage nor intra-abdominal infection in none of the groups. Local trocar site infection in 11 patients was medically treated. Surgical site infection and hospital stay period did not show statistically important difference among the groups. The operation duration in Group 1 was found to be shorter compared to the other groups. **Conclusions:** All three techniques are safe in LA. Non-absorbable polymer clips provide a shorter operation time. Extracorporeal knot-tying with knot-pusher provides the cheapest closure of the stump.

**Keywords:** Appendectomy. Laparoscopy. Clips. Ligature.

## Resumen

**Objetivo:** En la apendicectomía laparoscópica (LA), el cierre del muñón del apéndice es importante. Comparamos tres métodos de cierre de tocones del apéndice en términos de seguridad, facilidad y costo financiero. **Materiales y métodos:** Se incluyeron 310 pacientes de AL intervenidos entre 2011-2019 con cierre del muñón del apéndice mediante uno de los tres métodos: clips poliméricos no absorbibles (grupo 1), grupo de anudado (grupo 2) y grupo de ligadura de asa laparoscópica (grupo 3). Se analizaron las complicaciones, la operación y la duración de la estancia hospitalaria. **Resultados:** Hubo 148 pacientes mujeres y 162 hombres. La edad media fue de  $33.57 \pm 12.60$  años. No hubo ninguna fuga del muñón apendicular ni infección intraabdominal en ninguno de los grupos. La infección local del sitio del trocar en 11 pacientes fue tratada médica mente. La infección del sitio quirúrgico y el período de estancia hospitalaria no mostraron diferencias estadísticamente importantes entre

## Correspondence:

\*Oguzhan Sunamak,

Tibbiye Caddesi, 40

Uskudar C.P. 34668,

Istanbul, Turkey

E-mail: o.sunamak@yahoo.com.tr

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*los grupos. Conclusiones: Las tres técnicas son seguras en LA. Los clips de polímero no absorbible brindan un tiempo de operación más corto. El atado de nudos extracorpóreo con empujador de nudos proporciona el cierre más económico del muñón.*

**Palabras clave:** Apendicectomía. Laparoscopia. Clips. Ligadura.

## Introduction

Acute appendicitis (AA) is a common surgical emergency. Since its first use in 1983, laparoscopic appendectomy (LA) has become widely used<sup>1</sup>. There are lots of studies on the advantages of LA<sup>2-4</sup>. Among them, better cosmetic appearance, earlier return to daily life, and less pain feeling can be mentioned. Having been a safe and efficient method, LA is suggested as the first choice in the treatment of AA<sup>5</sup>.

In LA, closure of the appendix stump is an important step and various ligature methods have been used. Of course, this method must be safe and easy-to-use as well as an economical one. The most preferred ones in stump closure are non-absorbable polymeric clips, laparoscopic staplers, endoloop ligature, titanium endoclips, and knot-tying ligation<sup>6</sup>. Every center might use one closure method more frequently than others, depending on the habits of the surgeon and the preference of the center.

Certainly, the easiness to use and financial cost should be taken into consideration when choosing the technique. Despite knot-tying suture is of low cost, no absorbable polymer clips and end-loop ligature are preferred more due to their ease of use.

In this study, comparison of non-absorbable polymeric clips, knot-tying, and endoloop ligature closure of the appendix stump was aimed.

## Materials and methods

This retrospective study involved the AA patients older than 18 years of age who underwent LA between January 2011 and December 2019 and in whom the appendix stump was closed using one of three methods. Group 1 was non-absorbable polymeric clips (Click'a ligating clips, Grena, UK); Group 2 was knot-tying 0 polyglactin suture (Sterilactin, YU-CE, Turkey), and Group 3 was the endoloop ligature used patients, respectively. In Group 2, knot-pusher was used for ligation. In Group 3, laparoscopic loop ligature (Surgitie, Medtronics, US) was used.

The retrospective study approval was taken from the hospital education board. The informed consent of all patients was taken.

The data of 338 patients were analyzed and 28 of them were excluded as they could not be followed postoperatively.

The age, gender, surgical site infection, post-operative complication, and hospital stay periods were recorded.

SPSS 23.0 program was used for data analysis. Categorical parameters were number and per cent; continuous parameters were mean, standard deviation, minimum, and maximum.

The compatibility of parameters to normal distribution was analyzed using visual (histograms and possibility graphics) and analytic (Kolmogorov-Smirnov/Shapiro-Wilk Tests) methods. The categorical parameters were compared using the Chi-square test and Fischer's exact test. The parameters non-compatible to normal distribution were analyzed using the Kruskal-Wallis test. Bonferroni *post hoc* method was used to find the cause of difference among the groups. P < 0.05 was significant for all tests.

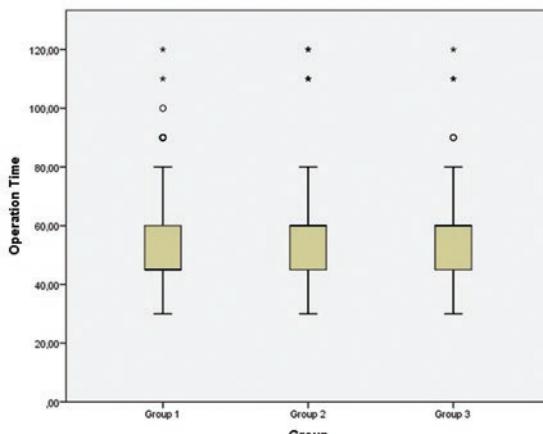
## Results

There were 310 patients of whom 148 (47.7%) were female and 162 (52.3%) were male. The mean age was  $33.57 \pm 12.60$  years. Group 1 was non-absorbable polymeric clips; Group 2 was knot-tying suture, and Group 3 was the endoloop ligature used patients, respectively. Non-absorbable polymeric medium and large clips were used in Group 1 and 2/0 coated polyglactin was used in Group 2, respectively. Endoloop ligature was 0 coated polyglactin.

There were 126, 101, and 83 patients in Group 1, 2, and 3, respectively (Table 1). There was neither appendiceal stump leakage nor intra-abdominal infection in none of the groups. There was a local trocar site infection only in 11 patients and was medically treated. There was not any statistically important difference in terms of surgical site infection among the groups (Table 2). Furthermore, hospital stay duration did not show any difference between the groups. However, operation duration in Group 1 was found to be shorter compared to the other groups (Table 3) (Fig. 1).

**Table 1. Patient demographics**

	Groups			Total	p
	Group 1	Group 2	Group 3		
Gender					
Female					
n	63	47	38	148	0.801
%	50.0%	46.5%	45.8%	47.7%	
Male					
n	63	54	45	162	
%	50.0%	53.5%	54.2%	52.3%	

**Table 2. Port-site infection**

	Group			Total	p
	Group 1	Group 2	Group 3		
Infection					
negative					
n	122	98	79	299	0.763
%	96.8%	97.0%	95.2%	96.5%	
positive					
n	4	3	4	11	
%	3.2%	3.0%	4.8%	3.5%	

**Table 3. Operation time and hospital stay period**

	n	Mean ± SD	p
Operation Time (min)			
Group 1	126	51.35 ± 16.95	
Group 2	101	55.99 ± 17.61	0.012
Group 3	83	54.94 ± 17.12	
Length of Hospital Stay (Day)			
Group 1	126	1.37 ± 0.55	
Group 2	101	1.30 ± 0.58	0.384
Group 3	83	1.36 ± 0.55	

## Discussion

The incidence of AA is said to be 8%<sup>7</sup>. Such a common cause of acute abdomen results in serious time and financial cost on emergency services and operation theatres. Having the advantages of decreasing hospital stay, post-operative pain, and return to daily life, LA should also be taken into consideration because of its cost. The closure of the appendix stump is an important step in LA<sup>1,8</sup>. The safety, cost-effectivity, and easy applicability of the closure technique are the reasons for preference. However, there is not a consensus on an optimum closure technique.

**Figure 1. Operation time graphics.**

The knot-tying suture is a more difficult technique to use and necessitates more experience compared to the others, which might prolong the operation time and results in less preference of it by the inexperienced surgeons<sup>6</sup>. It can be ligated either intracorporeally or extracorporeally using a knot-pusher. We used extracorporeal technique in our patients and it was easy to push and ligate it using the knot-pusher. We used 2/0 coated polyglactin and it was very cost-effective with its price of 0.48 US dollar and very advantageous.

Non-absorbable polymer clips have been reported to be preferred one as a safe, practical, and cost-effective method<sup>9-11</sup>. We detected that it was the most preferred method in our study with the number of 126 cases in Group 1. The lock system is its advantage making it safer.

It costs US\$ 16.9, and it is more expensive than that of the knot-tying suture. However, it shortened the operation duration significantly and seems to be its advantage<sup>6,10-12</sup>.

Endoloop ligature seems to be the most expensive technique with its cost of 24 US dollars in our study. Along with its cost, its easiness-to-use was found to be more difficult compared to that of clips; especially in extremely inflamed appendix tissue, its sliding from tip around the tissue to the base was reported not to be so easy<sup>13</sup>.

Another advantage of non-absorbable polymeric clips is the presence of five clips in one package compared to the one laparoscopic loop in a package, which enables us to re-try the closure using the content of the same package in clips use if any failure occurs or more ligatures are needed. However, we did

not find any superiority of the endoloop ligature to the clips in terms of operation duration in our study.

This study showed that all three techniques were safe in stump closure as any leakage or abscess formation was not observed in any of the groups. In light of this information, residents and inexperienced surgeons are better to use non-absorbable polymer clips or extracorporeal knot-tying during the learning period. The surgeons experienced in laparoscopic intracorporeal suture ligation might prefer intracorporeal tying. Still, the optimum one is extracorporeal knot-tying with knot pusher use in terms of financial cost and operation duration.

The shortest mean operation duration was found to be  $51.35 \pm 16.95$  min in Group 1 and it was significant in our study. This result reveals that non-absorbable polymer clips use provides a more practical and faster stump closure. This shorter operation duration means shorter operation room occupying, decreasing the operative cost per cases.

As a result, although all three techniques are safe in LA, having a shorter operation time, thus less general anesthesia exposure, less experience need, and being practical-to-use, non-absorbable polymer clips can be used. Another useful alternative, despite it prolongs the operation time, is extracorporeal knot-tying with knot-pusher use with the most economical cost.

## Conflicts of interest

The authors declare that does not exist conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant Clinical Research Ethics Committee and with those of the

Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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# Effectiveness of acute post-operative pain management by the acute pain service

*Efectividad del manejo del dolor agudo postoperatorio por el Servicio de Dolor Agudo*

Walter Osorio, Cesar Ceballos, and Jairo Moyano\*

Anesthesia Department, Pain Service, Hospital Universitario Fundación Santa Fe de Bogota, Bogota, Colombia

## Abstract

**Background:** Analgesia by specialists with formal training in pain management could be more effective, to find out, the results of a team of an acute pain service will be determined. **Methods:** Retrospective study ( $n = 108$ ) of post-operative (POP) analgesia; two evaluations were taken: before starting analgesics in the immediate POP period and the second at 24 h. A multivariate analysis was performed to establish independent risk factors associated with the effectiveness of the treatment. **Results:** The effectiveness was 81.48% at 24 h. The risk factors associated with poor management effectiveness were: a comorbidity, prevalence ratio (PR) = 1.22; fibromyalgia (PR = 8.47), and cancer (PR = 2.47). The duration of surgery was associated with poor control PR = 1.10 for each hour elapsed. Protective factors for poor pain control: administration of non-steroidal anti-inflammatory drugs during the POP period (PR = 0.11) and use of analgesia controlled by the patient (PR = 0.29). **Conclusion:** POP pain relief is multifactorial; the participation of specialists was very effective. Identification of risk factors led to closer follow-up.

**Keywords:** Acute pain. Analgesia. Pain postoperative. Treatment outcome

## Resumen

**Objetivo:** La analgesia por especialistas con entrenamiento formal en manejo del dolor podría ser más efectiva, para averiguarlo se determinarán los resultados de un servicio de dolor agudo. **Material y métodos:** Estudio retrospectivo ( $n = 108$ ) de analgesia postoperatoria; se tomaron dos evaluaciones: antes de iniciar analgésicos en el postoperatorio inmediato y la segunda a las 24 horas. Se realizó un análisis multivariado para establecer los factores de riesgo independientes asociados con la efectividad del tratamiento. **Resultados:** La disminución promedio fue 51,75% en el primer día postoperatorio. La efectividad fue del 81,48% a las 24 horas. Los factores de riesgo asociados con la mala efectividad del manejo fueron: una comorbilidad, razón de prevalencia (RP) = 1,22; fibromialgia (RP = 8,47) y cáncer (RP = 2,47). La duración de la cirugía se asoció con un mal control PR = 1,10 por cada hora transcurrida. Factores protectores para el mal control del dolor: administración de anti-inflamatorios no esteroideos durante el postoperatorio (RP = 0,11) y uso de analgesia controlada por el paciente (RP = 0,29). **Conclusión:** el alivio del dolor posoperatorio es multifactorial, la participación de especialistas fue muy eficaz. La identificación de los factores de riesgo condujo a un seguimiento más estrecho.

**Palabra clave:** Dolor agudo. Analgesia. Dolor postoperatorio. Resultado del tratamiento

## Correspondence:

\*Jairo Moyano

Carrera 7 117-15,

Bogota, Colombia

E-mail: jairo\_moyano@hotmail.com

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## Introduction

Managing post-operative (POP) pain can be challenging and continues to be a serious problem for health-care institutions around the world, even though there are many analgesia protocols. In this regard, it has been reported that 86% of surgical patients experience POP pain, and, out of these, 75% describe it as moderate or severe within the first 24 POP h<sup>1,2</sup>. Inadequate pain management leads to multiple cardiovascular, pulmonary, metabolic, immunological, and hematological complications, especially in elderly or obese patients, and in those with cardiovascular or pulmonary comorbidities<sup>3</sup>.

In the United States, hospitals with pain services range from 42% to 73%<sup>1,4</sup>, while in Europe, according to a survey conducted in European countries, only 34% have a pain service<sup>5</sup>.

Despite the implementation of pain services worldwide, about one-third of patients experience moderate-to-severe pain during their POP period, which can turn into chronic POP pain in 10-85% of these patients<sup>6,7</sup>. The evidence of poorly managed acute pain in most surgical patients, and wide variation in analgesic treatments, showed the need of formal standardized acute pain medicine services, based in anesthesiology. In this sense, a committee of experts has recommended basic quality criteria to be considered by pain services to have an efficient performance and, this way, achieving favorable outcomes in pain management. Somehow, in a survey conducted in European countries, found that < 10% of pain services met the quality criteria for being considered a “good pain service”<sup>8</sup>.

Worldwide, most pain services oversee nursing or anesthesia care<sup>9</sup>. Analgesic management may be more effective when a pain management specialist is responsible for it, yet, currently, there is not enough evidence supporting this association.

Taking this into account, the main objective of this study was to determine the effectiveness of the analgesic management provided by the pain management specialists of a pain service for reducing acute pain during the first 24 POP h. In addition, a second objective was to identify the independent risk factors associated with the effectiveness of said pain management.

## Materials and methods

### Study setting and design

This was a single-center retrospective service evaluation conducted at a 200 beds University Hospital. The

acute pain service (APS) is an anesthesiology-based POP pain service. Their responsibilities include coordinating hospital-wide acute POP pain services, teaching, implementation, and monitoring of acute pain guidelines.

### Study population

Patients over 18 years of age who received analgesic management by the pain specialists' team of the Pain Service of the University Hospital and who met the following inclusion criteria:

- Being in their immediate POP period (up to 24 h)
- Being classified as ASA I, ASA II, or ASA III patients according to the ASA Physical Status Classification System
- Having a pain score  $\geq 6/10$  in the Numerical Rating Scale (NRS) in the first pain assessment.

The following patients were excluded from the study: those who underwent an emergency surgical procedure, those with a history of dementia, schizophrenia, delirium, or cognitive deficit (Mini-Mental State Examination score  $\leq 24/30$ ), and women who underwent any surgical procedure other than a cesarean section during pregnancy. Effectiveness was defined as the reduction of 2 points in the NRS (from 0 to 10 points), a 20% decrease in the NRS score or achieving an NRS score  $\leq 4/10$  24 h after the establishment of the analgesic management.

### Statistical analysis

For the primary outcome, difference in pain intensity (NRS) between first and final pain assessments, differences of at least 20% were considered clinically relevant. A sample size of 108 patients was calculated using a  $\alpha < 0.05$  and a statistical power of 80%. A univariate analysis was performed to establish the occurrence of the events and their magnitude through the distribution of absolute and relative frequencies for qualitative variables; in the case of quantitative variables, data normality was determined by means of the Shapiro-Wilks test. A bivariate analysis was performed to evidence the relation between variables, and to identify possible associations. Then, a multivariate analysis was carried out using the Poisson regression model to calculate prevalence ratios (PR), establishing the independence of each risk or protective factor. A significance value of  $p < 0.05$  and a confidence interval of 95% were used for all statistical tests.

A simple random sampling of all patients treated at the pain service of the hospital from August 2016 to July 2017 was performed. Using these patients' medical records, a list of all those who were potentially eligible for the study was established, and out of this list, participants were randomly chosen using the Random.org service.

Variables that could be associated with the effectiveness of the analgesic treatment were assessed, namely: age; sex; history of smoking or being a smoker; having a comorbidity; history of anxiety, depression, chronic pain, chronic opioid use, and chronic benzodiazepine use; previous surgical procedures; surgical approach; surgical site; surgery duration; anesthetic technique used during the surgery; intraoperative use of opioids; intraoperative use of nonsteroidal anti-inflammatory drug (NSAID); intraoperative use of acetaminophen; POP administration of NSAID; POP use of acetaminophen; opioid PCA; scheduled opioid use and/or rescue doses use; administration of dexmedetomidine, analgesic lidocaine, ketamine, and gabapentinoids; POP NRS score; POP descriptive scale of pain; NRS score after 24 h; descriptive scale of pain after 24 h; opioid consumption within 24 h; POP nausea and/or vomiting; effectiveness of treatment at 24 h; and POP use of opioids. Data were entered into and stored in an Excel database (Microsoft Excel 2016TM), in which, all variables had already been preset. Data were processed using Stata software, version 12. A statistical significance higher than 95% with a type I error probability of < 5% ( $p < 0.05$ ) was considered in all statistical tests. We hypothesized that the pain management protocol offered by the pain service is effective for reducing acute POP pain within the first 24 h after the procedure.

## Results

A total of 1078 patients were treated by the pain service during the study period, from those patients, a sample of 108 was randomly selected for the study (Table 1).

### Univariate analysis

Participants' mean age was 58.2 years ( $SD = 15.37$ ) and most of them were male (67.59%); 25% had a history of smoking, either they were or had been smokers. In addition, 77.78% had had some comorbidity, being arterial hypertension (HT) and cancer the

**Table 1. Socio-demographic and clinical characteristics of the study population (n = 108)**

Feature	n (%)
Age <sup>†</sup>	58.20 (15.37)
Female	35 (32.41)
Male	73 (67.59)
Non-smoking	81 (75.00)
Smoking	27 (25.00)
Comorbidities*	84 (77.78)
High blood pressure	28 (25.93)
Mellitus diabetes	4 (3.70)
Fibromyalgia	3 (2.78)
Neoplasm	24 (22.22)
Other	25 (23.15)
Other chronic conditions	
Anxiety*	4 (3.70)
Depression*	5 (4.63)
Chronic pain*	20 (18.52)
Chronic opioid use*	12 (11.11)
Chronic benzodiazepine use*	2 (1.85)
Previous surgeries*	92 (85.19)

<sup>†</sup>S. Wilk = 0.0624

\*Absolute frequency (Relative frequency).

most frequent. Furthermore, 85.19% had undergone previous surgeries, and 18.52% and 11.11% had a history of chronic pain and chronic opioid consumption, respectively (Table 1).

The most frequently performed procedures were limbs surgeries which were done in 38.89% of patients followed by abdominal surgeries done in 37.96% (Table 2). Intraoperative remifentanil was used in the majority of patients, n = 98 (90.74%). General anesthesia was performed in 77 (77.3%) patients. Mean operative time was 204.5 min (interquartile range = 157.5-300.0).

Other findings observed in the POP follow-up include that 36 (33.33%) patients were administered NSAIDs, 100% were given acetaminophen, and that in 91.67%, intravenous opioid PCA was used. In addition, hydromorphone was the opioid most frequently used in the POP period (n = 64, 59.26%) followed by morphine (n = 32, 29.63%) and oxycodone (n = 9, 8.33%) and the median total consumption of oral morphine equivalents in 24 h was 31.5 mg (interquartile range = 13.5-58.5).

The average NRS score in the immediate POP period (first assessment) was 7.9/10 (standard deviation [SD] = 1.2), while in the second assessment (at 24 h of starting analgesia) it was 3.7/10 (SD = 2.4), that is,

**Table 2. Characteristics of the surgical patients (n = 108)**

Surgical site*	n (%)
CNS	2 (1.85)
Thorax	13 (12.04)
Abdomen	41 (37.96)
Spine	8 (7.41)
Urinary tract	2 (1.85)
Limbs	42 (38.89)
Endoscopic surgery*	20 (18.52)
Open surgery*	88 (81.48)
Regional anesthesia	8 (7.41)
General anesthesia	77 (71.30)
TIVA anesthesia	4 (3.70)
Combined (general and regional) anesthesia	19 (17.59)

\*Absolute frequency (Relative frequency).

ORL: Otorhinolaryngology, TIVA: Total intravenous anesthesia, CNS: Central nervous system

**Table 3. Pain intensity variations after surgery**

Variable	n = 108	S. Wilk
NRS POP <sup>t</sup>	7.89 (1.18)	0.9589
NRS 24H <sup>t</sup>	3.71 (2.39)	0.0633
NRS DIF <sup>t</sup>	4.18 (2.72)	0.9430
NRS DIF % <sup>t</sup>	51.75 (32.15)	0.3023
Effectiveness at 24H*	88.00 (81.48)	

\*Absolute frequency (Relative frequency), <sup>t</sup>Mean (Standard deviation).  
POP: post-operative, H: hours, DIF: percentual change.

an average decrease of 4.2 points at 24 h, which is equivalent to approximately a 52% decrease in pain intensity during the first POP day.

Based on the definition of effectiveness used in the present study, that is, a decrease of at least 2 points or a 20% decrease in the NRS score or having a NRS score  $\leq 4/10$ , an overall effectiveness of 81.48% was observed during the first 24 POP h (Table 3).

The independent risk factors associated with poor effectiveness of the analgesic management were having a comorbidity (PR = 1.22), having fibromyalgia (PR = 8.47), and being a cancer patient (PR = 2.47). The duration of the surgical procedure was also associated with poor pain control with a PR = 1.10 for

each hour elapsed. Furthermore, the administration of POP NSAIDs (PR = 0.11) and the use of opioid PCA (RP = 0.29) were factors for ineffective pain control (Table 4).

## Discussion

The results of this study suggest that POP pain management, when provided by a group of specialized anesthesiologists, is highly effective, since the overall effectiveness during the first 24 POP h was 81.48%. This high rate might be explained by several reasons. First, in the health institution where the study was carried out, there is an institutional pain management policy that guides health-care personnel to screen patients admitted to the hospital as well as POP patients with severe pain, looking for early recognition and proper treatment, this approach has been recommended to improve outcomes in hospitals<sup>10</sup>. Second, the POP pain management protocols and analgesic guidelines used by the pain service of the hospital are based on the best clinical evidence and the service works 24/7. It has been shown that evidence-based management recommendations provide better outcomes<sup>11</sup>. However, these good results cannot be attributed to one isolated factor, but to several variables, including the involvement of anesthesiologists in the pain management of patients. The participation of the anesthesia group supporting the acute pain group is essential because only the existence of protocols does not lead to an adequate treatment of pain as it was ratified in a study conducted in 1490 inpatients during their POP period; it was reported that 41% experienced moderate-to-severe pain during the first POP day and that, despite following analgesic protocols for POP pain control, this intensity remained until the 4<sup>th</sup> day in 14% of them. In addition, recent studies have found that up to 86% of surgical patients experience POP pain, and that, out of these, 75% rate it as moderate or severe in the first 24 h<sup>6</sup>. Identifying the risk factors associated with poor effectiveness of analgesic management (i.e., having a comorbidity, fibromyalgia, or cancer) allows establishing multimodal analgesia and close follow-up; however, this does not ensure adequate pain control. Additional studies are needed to improve clinical outcomes in this population.

Furthermore, since they require less time and cause less surgical trauma, minimally invasive surgical techniques should be preferred to achieve better POP pain control. Likewise, the implementation of multimodal analgesic management protocols that include the use of opioid patient controlled analgesia, NSAIDs, and

**Table 4. Independent prognostic factors associated with pain control**

Feature	PR	CI	P
Previous illness			
Fibromyalgia	1.22	1.04-1.42	0.028
Oncological disease	8.47	7.53-9.52	0.000
Duration of surgery	2.47	1.32-4.62	0.000
POP NSAID	1.10	1.03-1.15	0.005
PCA	0.11	0.02-0.79	0.028

PR: prevalence ratio, CI: confidence intervals, POP: post-operative, PCA: analgesia controlled by the patient.

non-pharmacological treatments is recommended for the proper management of pain in these patients. The limited use of NSAID indicates the need for further education in the use of non-opioid drugs. Similarly, the high number of patients who use opioids before their surgery indicates the need for multimodal therapies and institutional guidelines that promote the limitation of this type of medication.

In this study, the acute pain team services made an impact on pain management on surgical wards; in other words, the pain team is an option to improve pain relief as previously shown<sup>6</sup>. However, it is only a small percentage of surgical patients. To optimized resources, APS should provide pain treatment for carefully selected patients who undergo surgery. Although data appear to have benefited from the interventions of an APS, the data must be interpreted with care because of retrospective nature of the study and the small sample size. Despite these limitations, this service audit allows to show areas of improvement both in the monitoring of the services provided and in their outcomes. Similar pain services can find relevant data for their own practice.

## Conclusions

A hospital group of anesthesiologists specializing in the management of acute POP pain management can contribute to obtaining better results. The factors that contribute to these results are the institutional policy for the treatment of pain, the training of specialists, and timely access to services.

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## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

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# AZFa, AZFb, AZFc and gr/gr Y-chromosome microdeletions in azoospermic and severe oligozoospermic patients, analyzed from a neural network perspective

*Microdelecciones de las regiones AZFa, AZFb, AZFc y gr/gr del cromosoma Y en pacientes con azoospermia y oligozoospermia severa, análisis desde una perspectiva de red neuronal*

José Romo-Yáñez<sup>1</sup>, Rosalba Sevilla-Montoya<sup>2</sup>, Edith Pérez-González<sup>2</sup>, Josiff Flores-Reyes<sup>1</sup>, Estibalitz Laresgoiti-Servitje<sup>3</sup>, Salvador Espino-Sosa<sup>4</sup>, Mauricio Domínguez-Castro<sup>2</sup>, Guadalupe Razo-Aguilera<sup>2</sup>, Alberto Hidalgo-Bravo<sup>5</sup>, and Mónica Aguinaga-Ríos<sup>2\*</sup>

<sup>1</sup>Department of Cellular Development and Physiology, Instituto Nacional de Perinatología; <sup>2</sup>Department of Genetics and Human Genomics, Instituto Nacional de Perinatología; <sup>3</sup>Basic Medical Sciences, TEC-ABC School of Medicine, Tecnológico de Monterrey; <sup>4</sup>Clinical Research Sub-direction, Instituto Nacional de Perinatología; <sup>5</sup>Department of Genetics, Instituto Nacional de Rehabilitación. Mexico City, Mexico

## Abstract

**Aim:** Analysis of male infertility by molecular methods has increased since recognition of genetic risk factors. The AZFa, AZFb, AZFc, and gr/gr regions on the Y-chromosome can cause male infertility. The aim of this study was to determine the prevalence of Y-chromosome microdeletions in these regions in infertile Mexican patients. **Material and methods:** We recruited 57 infertile patients with abnormal sperm count (26 azoospermic and 31 oligozoospermic) and 55 individuals with normal sperm count. Analysis of the regions of interest was performed by PCR. **Results:** 15.8% of infertile patients presented Y-chromosome microdeletions, whereas no deletions were found in the control group. Deletions were observed in all the analyzed regions except in AZFa. Additionally, the neural network model revealed a mild genotype-phenotype correlation between deletion of the sY1191, sY1291 and sY254 markers with oligozoospermia, azoospermia and cryptozoospermia, respectively. **Conclusions:** Our data show that AZFb, AZFc, and gr/gr microdeletions are significantly associated with infertility in Mexican population. In addition, the neural network model revealed a discrete genotype-phenotype correlation between specific deletions and a particular abnormality. Our results reinforce the importance of the analysis of AZF regions as part of the clinical approach of infertile men.

**Keywords:** Male infertility. Y-Chromosome microdeletions. AZF region. Azoospermia. Oligozoospermia.

## Resumen

**Objetivo:** La utilización de técnicas moleculares para estudiar la infertilidad masculina se ha incrementado desde el reconocimiento de factores genéticos. Las regiones AZFa, AZFb, AZFc, y gr/gr del cromosoma Y son causa de infertilidad masculina. El objetivo de este estudio fue determinar la prevalencia de microdelecciones en estas regiones en pacientes infériles

### Correspondence:

\*Mónica Aguinaga-Ríos

Montes Urales, 800 Lomas-Virreyes,

Lomas de Chapultepec IV Secc.

C.P. 11000. Mexico City, Mexico

E-mail: aguinagamonica09@gmail.com

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**Mexicanos. Material y métodos:** Reclutamos 57 pacientes infériles con cuentas espermáticas anormales (26 con azoospermia y 31 con oligozoospermia) y 55 individuos con cuentas espermáticas normales. El análisis de las regiones se realizó mediante PCR. **Resultados:** 15.8% de los pacientes infériles presentó microdelecciones, no se encontraron microdelecciones en el grupo control. Las microdelecciones fueron observadas en todas las regiones excepto en AZFa. Adicionalmente, el modelo de red neuronal reveló una leve correlación genotipo-fenotipo entre microdelecciones de los marcadores sY1191, Sy1291 y sY254 con oligozoospermia, azoospermia y criptozoospermia, respectivamente. **Conclusiones:** Nuestros datos muestran que las microdelecciones en AZFb, AZFc, y gr/gr se asocian significativamente con infertilidad en la población Mexicana. Además, el modelo de red neuronal reveló una discreta correlación genotipo-genotipo entre microdelecciones específicas con una anormalidad en particular. Nuestros resultados refuerzan la importancia del análisis de las regiones AZF en el abordaje de la infertilidad masculina.

**Palabras clave:** Infertilidad masculina. Microdelecciones del Cromosoma Y. Región AZF. Azoospermia. Oligozoospermia.

## Introduction

Approximately 7% of men present fertility problems during their lives, resulting in a public health issue<sup>1,2</sup>. Male infertility is a complex pathology defined by the failure to achieve a clinical pregnancy after 12 months of regular unprotected sexual intercourse, according to international consensus<sup>3</sup>. Male contribution to infertility represents 45%–50% in childless couples<sup>4,5</sup>. Diagnosis is made based on abnormal semen analysis according to the WHO criteria. Based on sperm count, patients can be classified as azoospermic, defined as the absence of sperm in at least two different ejaculate samples (including the centrifuged sediment), or oligozoospermic when sperm account is <15 million/mL. In addition, severe oligozoospermia is considered with sperm concentration <5 million/mL and criptozoospermia when sperm is only visualized after centrifugation<sup>6</sup>. Azoospermia is classified into two groups: 1) obstructive, caused by obstructive factors along the seminal pathways, and 2) secretory or non-obstructive azoospermia (NOA), which is commonly related to gonadal dysfunction. NOA is explained by genetic factors in 21%–29% of cases, whereas in 12%–41% of cases, the cause is idiopathic and probably related to unknown genetic factors<sup>7–9</sup>. The main genetic cause involved in male infertility are abnormalities of the Y chromosome<sup>10</sup>, such as numerical and structural alterations. In addition, epigenetic modifications, such as decreased DNA methylation of the IGF2-H19 region, autosomal gene mutations, i.e. in the gene CFTR and in the X chromosome, the CAG polymorphism in the androgen receptor gene, have also been involved<sup>11–13</sup>. Of interest is the azoospermia factor region (AZF region) localized on Yq, which contains genes involved in the control of male meiosis<sup>14</sup>. Six AZF regions are known, AZFa, AZFb, AZFc, and their combinations<sup>15</sup>. Non allelic homologous recombination between

repetitive sequences can lead to chromosome deletions or duplications, this mechanism is believed to account for the random appearance of *de novo* AZF microdeletions<sup>16</sup>. AZF microdeletions have been proved to be in a clear cause-effect relationship with spermatogenic impairment<sup>14,17,18</sup>. Microdeletions are detected in 10%–15% of patients with NOA and 5%–10% of patients with severe oligozoospermia<sup>19,20</sup>. The most frequent deletion occurs in the AZFc region (~80%), followed by AZFb (1%–5%), AZFbc (1%–3%) and AZFa (0.5%–4%)<sup>21</sup>. Patients harboring deletion of AZFa can present hypospermatogenesis and inhibition of the production and maturation of germ cells<sup>22,23</sup>. The phenotype observed in patients with AZFb deletion is a pre-meiotic arrest with normal spermatogonia and primary spermatocytes. AZFb overlaps with the AZFc region<sup>24</sup>. The AZFc region contains critical transcripts for normal spermatogenesis. Spermatid or sperm maturation anomalies have been found in patients with AZFc microdeletions<sup>17</sup>.

While the analysis of AZF deletions have been introduced as a routine genetic test for infertile patients, the role of partial AZFc deletions, i.e., gr/gr deletion, b1/b3, and b2/b3, has been the focus of long-lasting debate. The risk associated with this genetic anomaly varies between populations, reaching the highest OR in Italians (OR 7.9, 95% CI 1.8–33.8)<sup>25</sup>. Current evidence suggest that the gr/gr deletion is a significant risk factor for impaired sperm production.

We designed the present study to analyze the frequency of microdeletions in the AZF region in a group of Mexican mestizo infertile men.

## Materials and Methods

### Patients

This study was performed at the Genetics and Genomics Department of the National Institute of Perinatology

in Mexico during a four years period, all procedures were approved by the institutional ethics committee. Patients with idiopathic infertility were referred from the Andrology Department. Participants were invited to the study and signed an informed consent form. A total of 57 patients were included, 26 had azoospermia and 31 had severe oligozoospermia (12 criptozoospermic and 19 oligozoospermic), all of them underwent to a GTG karyotype. The control group was composed by 55 males with normal spermatobioscopy.

### Molecular analysis

Genomic DNA was isolated from peripheral blood with the Wizard Genomic DNA Purification Kit (Promega) according to the manufacturer's instructions. A NanoDrop 2000 Spectrophotometer (Thermo Scientific) was used to determine DNA purity and concentration.

Two multiplex PCR reactions were performed to analyze the AZFa, AZFb, and AZFc regions and singleplex PCR reaction to analyze the gr/gr region, as described elsewhere<sup>18</sup>. The multiplex PCR reaction employed the primers ZFX/Y, sY86, sY127, sY254 and the singleplex used the primers sY14 (SRY), sY84, sY134, and sY255. We confirmed the deletions using a single PCR reaction. For amplification of the gr/gr region, we used the primers sY1291 and sY1191. The heterochromatic Yq region was analyzed with the sY160 marker. The list of primer sequences, and expected product sizes has been previously published<sup>18</sup>.

Each multiplex or singleplex PCR reaction contained 0.7–1 µg of DNA, 200 nM of each primer and 1.5 units of HotStarTaq Master Mix Kit. Cycling conditions were as previously described<sup>20</sup>. PCR products were size separated by electrophoresis in a 2.5% agarose gel (Invitrogen, Carlsbad, CA, USA).

### Statistical analysis

Descriptive statistics are presented for all variables. Kruskall Wallis test was performed to evaluate quantitative variables. Pearson's  $\chi^2$  test was used to compare proportions between study groups.

A multilayer perceptron neural network model was executed to determine whether the presence of a determined deletion could predict azoospermia, criptozoospermia, or oligozoospermia. A classification and regression tree (CRT) was later used to corroborate neural network predictions and as a predictive model for

**Table 1.** Percentage of patients and controls with and without microdeletions

Group	Without deletion n (%)	With deletion n (%)	Total	P*
Patients	48 (84.2%)	9 (15.8%)	57	0.002
Controls	55 (100%)	0	55	
Total	103 (92.0%)	9 (8.0%)	112	

\*Statistically significant difference between patients and controls by Pearson  $\chi^2$ .

azoospermia, criptozoospermia, or oligozoospermia, according to the presence of deletions in the different regions analyzed. Lastly, another CRT model was executed to determine whether the number of deletions in the evaluated regions could be related to any of the three diagnoses. Statistical analyses were performed using IBM SPSS Statistics (Armonk, NY, USA), version 22. The significance level was  $\alpha = 0.05$ .

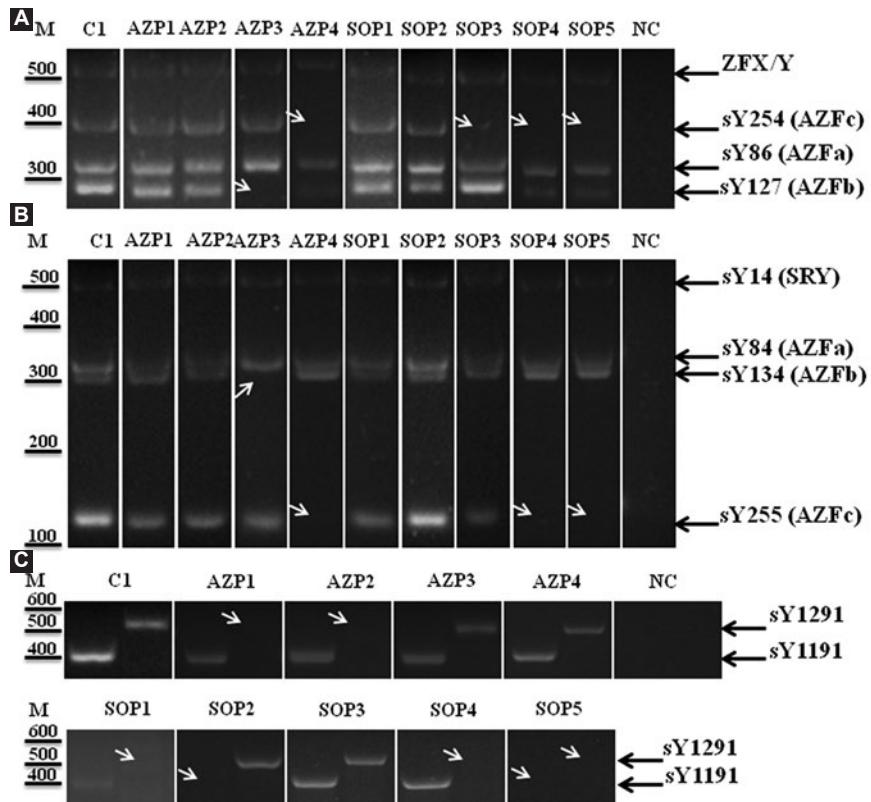
### Results

We analyzed 55 individuals with normal spermatobioscopy as controls and 57 diagnosed with infertility. All participants had a normal karyotype. Within the infertility group, 26 were azoospermic (45.6%) and 31 were severely oligozoospermic, from these, 12 (21.1%) were criptozoospermic and 19 (33.3%) oligozoospermic. The mean age of participants was 32.7 (SD 6.7) years and mean semen sample volume was 2.56 (SD 1.86) mL. Kruskall Wallis tests showed no significant difference in participants' age and semen sample volume among the different diagnoses (azoospermia, criptozoospermia, and oligozoospermia).

None of the controls presented microdeletions within the STSs analyzed. We found a microdeletion in 9 (15.8%) individuals from the infertility group. When we compared the proportion of individuals with microdeletions through a Pearson  $\chi^2$  test we observed a statistically significant difference ( $p=0.002$ ) (Table 1).

Table 2 shows the number of patients with microdeletions according to the clinical diagnoses within the infertility group. We did not find statistically significant differences when comparing individuals with azoospermia versus severe oligozoospermia (Pearson  $\chi^2$  test,  $p=0.615$ ).

Among azoospermic patients, one had a complete deletion of the AZFb region (absence of sY127 and sY134 markers; Figure 1A and B, patient AZP3). Another had a complete deletion of the AZFc region (absence of sY254 and sY255 markers, AZP4) (Fig. 1A and B). Two



**Figure 1.** AZFa, AZFb, AZFc, and gr/gr microdeletions in azoospermic or severe oligozoospermic Mexican patients. **A:** representative image of multiplex PCR reaction A to analyze the presence/absence of STS sY86 (AZFa), sY127 (AZFb) and sY254 (AZFc), and the positive control ZFX/Y. **B:** representative image of multiplex PCR reaction B to analyze the presence/absence of STS sY84 (AZFa), sY134 (AZFb) and sY255 (AZFc), and the positive control sY14 (SRY). **C:** representative image of singleplex PCR reactions to analyze the presence/absence of STS sY1291 and sY1191. White arrows show the presence of microdeletion. AZP: azoospermic patients, C: controls, NC: negative controls, SOP: severe oligozoospermic patients.

**Table 2. Proportion of azoospermic or severe oligozoospermic patients with microdeletions**

Diagnosis	Without deletion	With deletion	Total
Azoospermic	22 (84.6 %)	4 (15.4%)	26
Severe oligozoospermic			
Criptozoospermic	9 (75%)	3 (25%)	12
Oligozoospermic	17 (89.5%)	2 (10.5%)	19
Total	48 (84.2%)	9 (15.8%)	57

No statistically significant differences were observed between azoospermic and severe oligozoospermic patients by Pearson  $\chi^2$  ( $p = 0.615$ ).

of them had the gr/gr microdeletion (absence of sY1291 and presence of sY1191 markers, patients AZP1 and AZP2) (Fig. 1C). Within the severe oligozoospermic group, two patients had a complete deletion of the AZFc region (Fig. 1A and B) (patients SOP4 and SOP5). Patient SOP4 presented absence of the sY1291 gr/gr marker (Fig. 1C), while patient SOP5 had absence of

both gr/gr markers (Fig. 1C). One patient had a partial microdeletion of AZFc (absence of sY254 marker, SOP3) (Fig. 1A). Another had a complete gr/gr microdeletion (absence of sY1291 marker, SOP1) (Fig. 1C). Another patient presented a partial gr/gr microdeletion (absence of sY1191 marker, SOP2) (Fig. 1C). Table 3 summarize microdeletions findings.

A multilayer perceptron neural network model using the sigmoid activation function was performed to determine if the presence of deletions in the sY127, sY134, sY254, sY255, sY1291, or sY1191 regions were associated with azoospermia, cryptozoospermia, or oligozoospermia. The data were divided randomly into a training group (70%) and a holdout group (30%) with n1/n2 cross-validation to evaluate the accuracy of the network model. The model was re-run several times with different random starting seeds to ascertain that the results were consistent. The area under the curve for azoospermia, cryptozoospermia, and oligozoospermia in the training set were 0.640, 0.643, and

**Table 3. Summary of Y-chromosome microdeletions found in infertile patients**

Diagnosis	AZFb		AZFc		gr/gr	
	SY127	SY134	SY254	SY255	SY1291	SY1191
Azoospermic AZP1					X	
Azoospermic AZP2					X	
Azoospermic AZP3	X	X				
Azoospermic AZP4			X	X		
Severe oligozoospermic SOP1 (Criptozoospermic)			X			
Severe oligozoospermic SOP2 (Criptozoospermic)					X	
Severe oligozoospermic SOP3						X
Severe oligozoospermic SOP4 (Criptozoospermic)			X	X	X	
Severe oligozoospermic SOP5			X	X	X	X

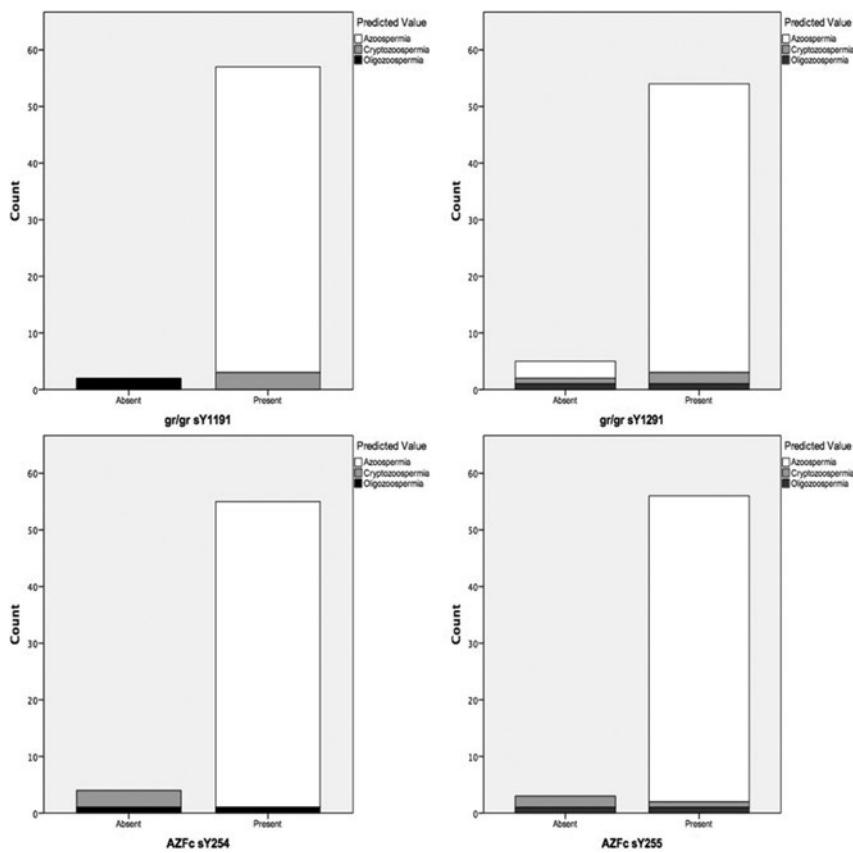
0.635, respectively. The model accurately predicted 54.3% of training cases. The regions with the highest importance to the model were sY254 (100%), sY1191 (99%), sY1291 (66.8%), and sY255 (65.2%). The predicted values for deletions in the regions with highest importance to the model according to diagnosis are presented in Figure 2. The model predicted that deletions in sY1191 were more likely related to oligozoospermia, while deletions in sY1291 were more related to azoospermia and deletions in sY254 were more related to cryptozoospermia. A follow-up CRT decision tree indicated that deletions in the sY1191 region were mainly associated with oligozoospermia ( $n = 2$ , 100%), whereas the absence of deletion in sY1191 and the presence of deletion in sY254 were mostly related to cryptozoospermia ( $n = 2$ , 66.7%) and to azoospermia ( $n = 1$ , 33.3%). On the other hand, neither deletion in sY1191 nor deletion in sY254, accompanied by a deletion in sY1291 was mainly related to azoospermia ( $n = 2$ , 66.7%) and to cryptozoospermia ( $n = 1$ , 33.3%) (data not shown). The most important predictive variables in the model were sY1191, sY254, and sY1291. It is noteworthy that none of the patients with azoospermia or cryptozoospermia had deletions in sY1191.

Finally, a CRT model was executed to determine if not only the presence of deletion for each region but the total number of deletions could predict any of the three diagnoses. The tree indicated that the most important independent variable predicting diagnosis was the total number of deletions (normalized importance of 100%), followed by sY1191. The model showed that patients with

deletions in the sY1191 region were more likely to have oligozoospermia, but patients with no deletion in the sY1191 and one or more deletions in any of the other regions were more likely to belong to the azoospermia or cryptozoospermia groups (57.1% and 42.9%, respectively). The decision tree is shown in figure 3.

## Discussion

We investigated Y-chromosome microdeletions in patients diagnosed with infertility. We screened microdeletions using STS markers for the AZFa, AZFb, AZFc, and gr/gr regions. Regardless of deletion type, the overall deletion frequency in azoo-/severe oligozoospermic men was higher than in normozoospermic (15.8% vs. 0). The statistical analysis showed that microdeletions are significantly associated with infertility in our population ( $p = 0.002$ ). This result suggests that such deletions could be a risk factor for impaired spermatogenesis in the Mexican population. There are few studies in Mexican populations analyzing the prevalence of Yq deletions in infertile men. Piña et al, studied the presence of Yq microdeletions in Mexican men from couples with recurrent pregnancy loss, they did not find microdeletions<sup>26</sup>. Martínez-Garza S.G, et al found that 12.2% of infertile males had microdeletions of AZFb or AZFc, however they did not analyze gr/gr microdeletions<sup>27</sup>. Our results, including gr/gr deletions, showed a higher percentage (15.8%), compared to their results. It is noteworthy that they used other STS markers, they found two patients with deletion of sY121 and/or sY128 in AZFb. However, the



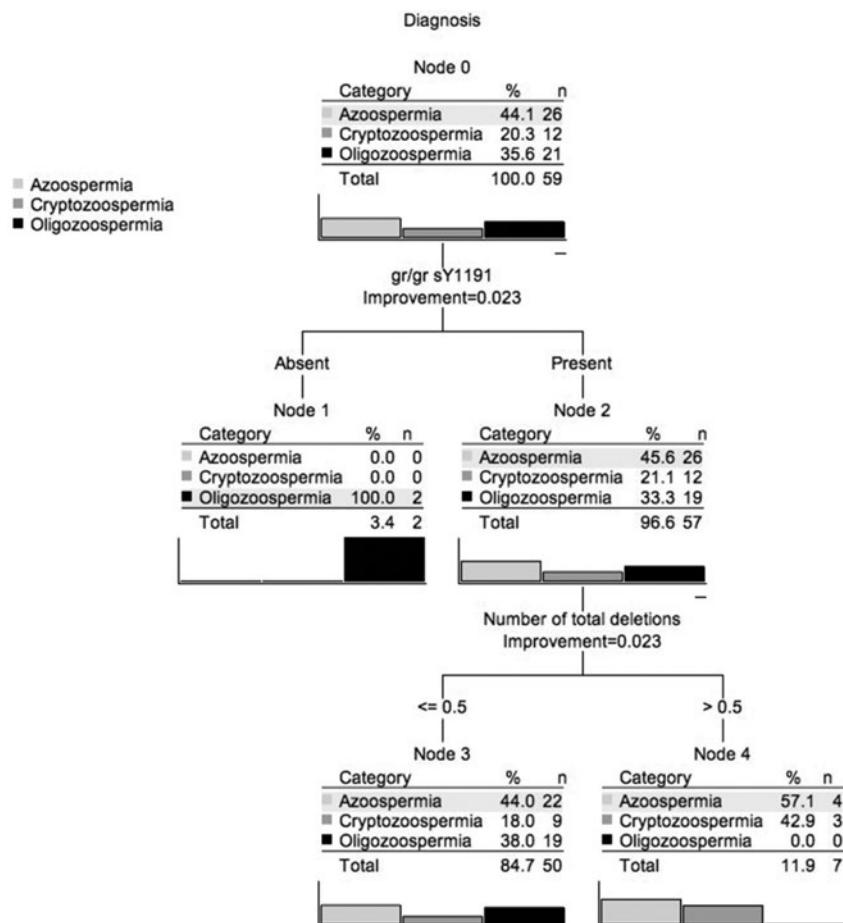
**Figure 2.** Stacked bar charts of the predicted values for azoospermia, oligozoospermia, and cryptozoospermia according to microdeletions obtained from a neural network model. The top left bar chart shows that the model predicted that patients with the sY1191 deletion were more likely to be oligozoospermic. The top right bar graph shows that the model predicted that patients with sY1291 deletions were more likely to be azoospermic. The bottom charts show that the model predicted that patients with sY255, and especially those with sY254, were more likely to be cryptozoospermic (cryptozoospermic and oligozoospermic).

aforementioned markers are not included in the EAA/EMQN Guidelines 2013<sup>20</sup>. These STS markers could be important in the analysis of Mexican populations and could be analyzed in future studies.

The impact of gr/gr deletions on male fertility is unclear. Gianchini et al, found that the frequency of gr/gr deletions was significantly higher in the infertile group compared to controls, suggesting a possible deleterious effect on spermatogenic efficiency. They reported an OR of 10.1, indicating that gr/gr deletions could be considered a risk factor for oligozoospermia<sup>28</sup>. However, other studies have not detected strong association. Hucklenbroich et al, did not find significant differences of gr/gr deletions in German population when compared men with NOA versus normospermic men<sup>29</sup>. A lack of association was also observed by Machev et al in Italian population<sup>30</sup>. They observed that 5.3% of infertile men (7/150) had gr/gr deletions compared to 0.5% of fertile individuals (1/189).

Although these data suggested a significant association, from these seven patients, four were defined as idiopathic, one had a history of cryptorchidism and two had varicocele<sup>31</sup>.

In our study, from the infertile men who only presented a complete deletion of the gr/gr region, 2/26 were azoospermic (7.7%) and 1/31 (3.2%) had severe oligozoospermia (cryptozoospermia). Whereas, none of the controls presented the deletion. There were significant differences in various parameters associated with semen quality in men with gr/gr subdeletions, mainly in the sperm concentration, which further reinforces the point that these mutations may be associated with spermatogenesis impairment. This observation has been described previously<sup>28</sup>. To further define the genotype-phenotype correlation, we found the role of partial gr/gr subdeletions to be more complicated than previously thought and probably is related to the study population<sup>32</sup>.



**Figure 3.** Classification and regression tree. The CRT indicates that the tree split first according to sY1191 deletions and that 100% of patients with this type of deletion had oligozoospermia. However, in those patients that did not have sY1191 deletions, the most important variable defining the infertility categories was the number of deletions per participant. The final nodes in the tree indicate that patients with one or more deletions were more likely to have azoospermia or cryptozoospermia.

The Pearson  $\chi^2$  test did not find differences in the STSs deleted between azoospermic and severely oligozoospermic patients. However, the neural network model showed that some STS deletions could be related to azoospermia, criptozoospermia, or oligozoospermia. The model showed that the sY1191 deletion could predict oligozoospermia, while the sY1291 deletion may predict azoospermia and the sY254 deletion could be related to criptozoospermia. These results were corroborated by a classification and regression tree (CRT). We also performed a CRT to determine if the number of deletions per patient could predict any of the diagnoses. Again, the CRT model showed that patients with deletions in the sY1191 region were more likely to have oligozoospermia, and patients without sY1191 deletion and one or more deletions in any of the other regions were more likely to be azoospermic or cryptozoospermic.

Although this study reports novel findings concerning the potential correlation between certain microdeletions with azoospermia, cryptozoospermia, and oligozoospermia, it has some limitations. Certainly, the sample size and the small number of microdeletions found may have influenced our results. A study with a larger sample size is necessary to confirm our results.

Future studies in larger groups should focus on the combined definition of the type and copy number of the AZFc genes deleted in men with partial deletions and the haplogroup of the Y chromosome. A detailed analysis of these and other yet unidentified genetic factors is necessary prior to offer assisted reproductive techniques.

## Conclusions

Our findings corroborate the importance of microdeletions of the AZF region in infertile patients.

Despite the controversy of the gr/gr deletion as a risk factor for male infertility, we did not observe this deletion in fertile controls. More studies with larger samples in ours and other populations are needed to define the gr/gr deletion as a factor compromising fertility. Nevertheless, the study of AZF microdeletions has to be included in the clinical approach of infertile males.

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## Conflict of interest

The authors report no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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# Selective radical resection for unresectable pancreatic cancer

## *Resección radical selectiva para el cáncer de páncreas irreseccable*

Changku Jia<sup>1</sup>, Ling Liu<sup>1</sup>, Hanzhang Zhu<sup>1</sup>, Weimin Shen<sup>1</sup>, and Chunfeng Yang<sup>2\*</sup>

<sup>1</sup>Department of Hepatopancreatobiliary Surgery, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine; <sup>2</sup>Department of Hepatopancreatobiliary Surgery, Xiaoshan Hospital, Zhejiang, China

### Abstract

**Objective:** The objective of the study was to evaluate safety and value of radical resection for unresectable pancreatic cancer (UPC). **Materials and methods:** Clinical data were analyzed retrospectively. In unresectable group, 360° resection of the involved artery sheath, resection and reconstruction of the involved artery, resection and reconstruction of the involved vein as well as resection and reconstruction of combined organs were, respectively, performed. Operation time, intraoperative blood loss, intensive care unit (ICU) transitional treatment, pancreatic fistula, bleeding, reoperation, and survival time were analyzed for two groups. **Results:** Operation time and intraoperative blood loss were greatly increased in the unresectable group. The incidence of intractable diarrhea and abdominal hemorrhage in the unresectable group was higher. However, the rate of ICU transitional therapy, delayed gastric emptying, and reoperation was lower. Grade C pancreatic fistula occurred in neither group. **Conclusions:** Surgical treatment through strict selection for patient with UPC is safe and their median survival time is similar to patient with resectable pancreatic cancer.

**Keywords:** Pancreatic cancer. Radical resection. Complications. Survival time. Prognosis.

### Resumen

**Objetivo:** evaluar la seguridad y el valor de la resección radical para el cáncer de páncreas irreseccable (CPU). **Material y métodos:** Los datos clínicos se analizaron de forma retrospectiva. En el grupo irresecable, se realizó resección de 360° de la vaina de la arteria afectada, resección y reconstrucción de la arteria afectada, resección y reconstrucción de la vena afectada, así como resección y reconstrucción de órganos combinados, respectivamente. Se analizaron el tiempo operatorio, la pérdida de sangre intraoperatoria, el tratamiento transitorio en la UCI, la fístula pancreática, el sangrado, la reintervención y el tiempo de supervivencia para dos grupos. **Resultados:** El tiempo de operación y la pérdida de sangre intraoperatoria aumentaron considerablemente en el grupo irresecable. La incidencia de diarrea intratable y hemorragia abdominal en el grupo irresecable fue mayor. Sin embargo, la tasa de terapia de transición en la UCI, el retraso del vaciamiento gástrico y la reintervención fueron menores. La fístula pancreática de grado C ocurrió en ninguno de los grupos. **Conclusiones:** el tratamiento quirúrgico mediante selección estricta del paciente con CP irresecable es seguro y su mediana de supervivencia es similar a la del paciente con CPR.

**Palabras clave:** Pancreatic cancer. Radical resection. Complications. Survival time. Prognosis.

### Correspondence:

\*Chunfeng Yang,  
No. 728, Yucaibei Road,  
Hangzhou 311202, Zhejiang, China  
Telephone: +860571-83865815  
E-mail: ycf087@outlook.com  
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## Introduction

Patients with pancreatic cancer have poor prognoses<sup>1,2</sup>. Because pancreas is closely related to blood vessel and pancreatic cancer infiltratively grows, it is prone to invade portal vein, superior mesenteric vein (SMV) and superior mesenteric artery (SMA) to make its operation more difficult. In domestic and foreign guidelines for diagnosis and treatment of pancreatic cancer, based on the relationship between tumor and blood vessel, pancreatic cancer is divided into three types: resectable, borderline resectable and unresectable. For pancreatic head carcinoma, if (1) SMA is encapsulated by the tumor more than 180° and the tumor is close to celiac artery trunk; or if (2) SMV or portal vein is involved to make resection or reconstruction impossible; for pancreatic carcinoma of body and tail, if (1) SMA or celiac artery trunk is encapsulated more than 180°; or if (2) SMV and portal vein is involved to make resection or reconstruction impossible, the tumor is considered to be unresectable<sup>3,4</sup>. However, in addition to pre-operative imaging evaluation, the resectability of pancreatic cancer is closely related to experience and ability of surgeons<sup>5,6</sup>. There is no identical standard for clinical application in unresectable pancreatic cancer (UPC)<sup>7,8</sup>. We selectively carried out radical surgery on some patients with UPC and explored its safety and significance compared with the surgery for resectable pancreatic cancer (RPC).

## Material and Methods

### **Patients**

Patients with pancreatic cancer who underwent radical resection from August 2010 to January 2018 in Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine and had complete follow-up data were selected. Inclusion criteria were the patients being diagnosed as pancreatic cancer before operation through enhanced CT and/or enhanced MRI, together with tumor markers; no distant metastasis; with resectable tumor according to pre-operative imaging and intraoperative judgment, vascular invasion and possible arterial sheath resection or vascular segmental resection and reconstruction. There were 77 patients with pancreatic cancer undergoing radical surgery during the above period, including 43 males and 34 females, aged 47-79 years, with a

median age of 63.5 years. There was no significant difference in gender and age between the two groups ( $p > 0.05$ ), which was comparable. According to the guideline<sup>3</sup>, 69 cases were resectable (to form a resectable group) and eight cases were unresectable (to form an unresectable group) for more than 180° of arterial encapsulation or vein invasion for neither resection nor reconstruction. There were 56 cases and six cases of pancreatic head carcinoma, respectively, in the resectable group and in the unresectable group, and 13 cases and two cases of pancreatic carcinoma of body and tail in the two groups. There were seven cases of tumor invading artery and one case of tumor invading vein for carrying out neither resection nor reconstruction in the unresectable group (Table 1).

### **Treatment and surgical procedures**

Radical resection with no pre-operative chemotherapy was performed on the patients in the resectable group. While pancreaticoduodenectomy (PD) with standard or extended lymphatic dissection was performed upon the patients with pancreatic head carcinoma, pancreatic splenectomy with standard or extended lymphatic dissection was performed on the patients with pancreatic carcinoma of body and tail. Chemotherapy was performed for three cases in the unresectable group before operation, of which, two cases were treated with gemcitabine and one case was treated with modified Folfirinox. The other five cases refused preoperative chemotherapy, so they were not treated with it. PD was performed on the patients with pancreatic head carcinoma in the unresectable group. According to preoperative imaging and intraoperative vascular exploration, we performed 360° arterial sheath resection or resection and reconstruction of the involved artery and the involved vein. Pancreatic splenectomy was performed on the patients with pancreatic carcinoma of body and tail in the unresectable group. According to pre-operative imaging examination, intraoperative vascular exploration and adjacent organ involvement, 360° arterial sheath resection or resection and reconstruction of the involved artery and combined organs were performed. 360° arterial sheath resection was performed (Figure 1) while SMA or celiac trunk artery sheath was encapsulated more than 180° but arterial sheath was not involved. Arterial resection and reconstruction were performed on the patients with arterial adventitia and intimal infiltration (Figure 2). Respective anastomosis of Y-type iliac

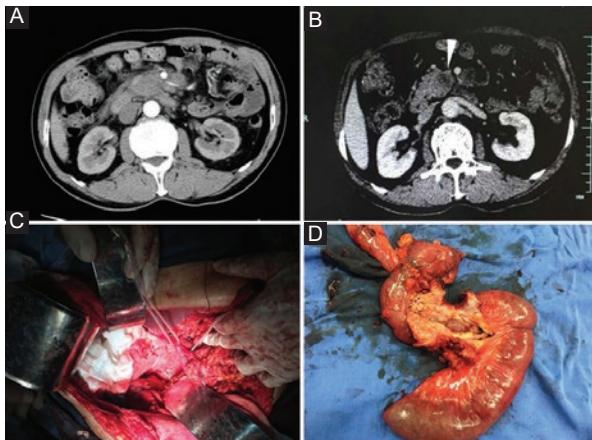
**Table 1. The data of the unresectable group**

	<b>Case 1</b>	<b>Case 2</b>	<b>Case 3</b>	<b>Case 4</b>	<b>Case 5</b>	<b>Case 6</b>	<b>Case 7</b>	<b>Case 8</b>
Age (years)	68	54	63	64	61	64	64	55
Gender	male	male	male	female	Male	male	male	female
Position	head of pancreas	head of pancreas	pancreatic body and tail	pancreatic body and tail	head of pancreas	head of pancreas	head of pancreas	head of pancreas
Tumor vascular invasion	more than 180° of SMA encapsulation	SMV was all involved with jejunal vein, ileum vein, and portal vein	more than 180° of celiac trunk encapsulation	more than 180° of celiac trunk, hepatic artery and splenic artery encapsulation	more than 180° of SMA encapsulation and splenic vein involvement	more than 180° of SMA encapsulation and SMV invasion	more than 180° of SMA encapsulation	more than 180° of SMA encapsulation
Pre-operative chemotherapy	No	No	Yes	Yes	No	Yes	No	No
Operation	PD+360° SMA sheath resection	PD+resection of affected segment vein+sheath reconstruction+of Y-type iliac artery and portal vein and jejunal ileovenous anastomosis	360° celiac trunk artery sheath resection+pancreas body tail splenectomy	resection of celiac trunk and common hepatic artery with end-to-end anastomosis+pancreas body tail splenectomy	PD+SMA root resection, left gastric artery anastomosis with SMA end-to-end and reconstruction, splenic vein resection in the invaded segment and other splenic vein exclusion	PD+360° SMA sheath resection+affected SMV resection and end-to-end anastomosis	PD+360° SMA sheath resection	PD+360° SMA sheath resection
Operation time (min)	340	450	300	360	630	600	330	350
Intraoperative blood loss (ml)	700	800	900	700	900	1000	500	600
ICU transitional treatment	No	No	No	No	No	No	No	No
Pancreatic fistula	No	No	No	Grade B	No	No	No	Grade A
Diarrhea	Yes	No	No	No	Yes	Yes	No	Yes
Delayed gastric emptying	No	No	No	No	No	No	No	No
Postoperative bleeding	No	No	No	Yes	No	No	No	No
Reoperation	No	No	No	No	No	No	No	No
Post-operative chemotherapy	No	Yes	No	Yes	Yes	No	No	Yes
Survival time (months)	8.1	12.5	26.3	13.1	13.2	10.3	16.6	15.4

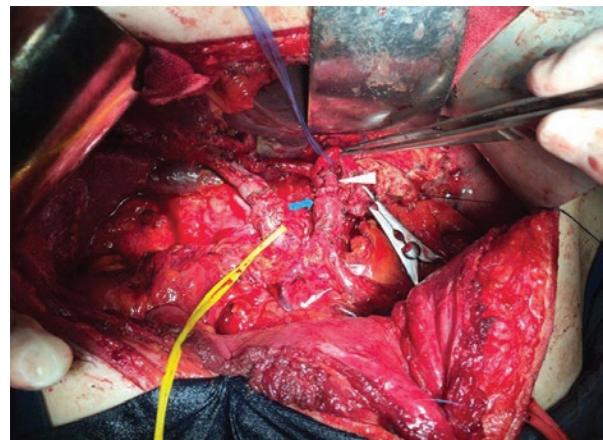
Survival time has been followed up until August 1, 2018.

artery allografts with portal vein and venae jejunales et ilei was performed on the patients whose SMV was all involved, with portal vein involvement at the

top and jejunal ileal vein below (Figure 3). Extended lymphatic dissection was performed on the patients in the unresectable group.



**Figure 1.** Case 6 in the unresectable group. **A:** pancreatic CT showed that superior mesenteric artery was encapsulated more than 270°. **B:** CT showed that the tumor completely invaded superior mesenteric vein and occluded it to about 1.5 cm long. The arrow points to the occluded superior mesenteric vein. **C:** SMA sheath has been removed by 360°. **D:** in the isolated specimen, superior mesenteric artery, and vein appeared to be encapsulated by the tumor more than 270°.



**Figure 2.** Case 5 in the unresectable group. Left gastric artery and superior mesenteric artery were anastomosed and reconstructed. Left gastric artery was obliquely cutoff to enlarge its lumen diameter. Distal left gastric artery was ligated and proximal left gastric artery was pulled down from splenic artery to anastomose with superior mesenteric artery. Triangular arrow points to left gastric artery and the arrow points to superior mesenteric artery.

### Intraoperative and post-operative observation indicators

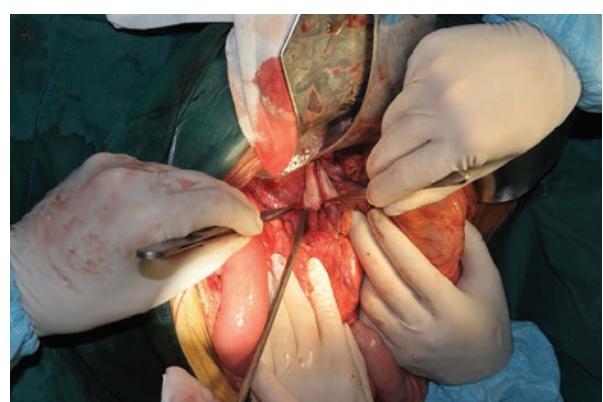
Operation time, intraoperative blood loss, post-operative intensive care unit (ICU) transitional treatment, post-operative pancreatic fistula, bleeding, reoperation, and survival time were recorded.

### Statistical method

SPSS 16 software was used for statistical analysis. Its measurement data were expressed by  $x \pm s$  and unpaired Student t-test or Welch's t test was adopted on the comparison between two groups, while counting data were expressed by rate and Pearson  $\chi^2$  or Fisher's exact test was adopted on the comparison between groups. Survival analysis was performed by Log rank test. The difference with  $p < 0.05$  was considered to be statistically significant.

### Results

In this research, no deaths occurred during perioperative period in any group. Compared with the resectable group, operation time and intraoperative blood loss in the unresectable group were greatly increased ( $p < 0.01$ ). For post-operative complications, the incidence of intractable diarrhea and abdominal hemorrhage in the unresectable group was obviously higher than those in the resectable group ( $p < 0.01$ ). The rate of ICU



**Figure 3.** Case 2 in the unresectable group. SMV was all involved, with portal vein involvement at the top and jejunal ileal vein below, respective anastomosis of Y-type iliac artery with portal vein, and jejunum ileum vein.

transitional therapy, delayed gastric emptying, and reoperation in the unresectable group was significantly lower than the resectable group ( $p < 0.01$ ). The patients in the unresectable group have a higher incidence of pancreatic fistula than the patients in the resectable group ( $p < 0.01$ ), but Grade C pancreatic fistula occurred in neither group. There were three cases (4.4%) in the resectable group of post-operative abdominal hemorrhage, of which, two cases received interventional embolization to stop bleeding and one case received reoperation to stop bleeding. In the unresectable group, one case (12.5%) of abdominal hemorrhage received interventional embolization to stop bleeding and no reoperation occurred. In

the unresectable group, reoperation rate was significantly lower than that in the resectable group. Post-operative survival time of 69 patients with RPC was 8.2-72.4 months and median survival time was 15.8 months. In the unresectable group, post-operative survival of 8 patients was 8.1-26.3 months and median survival time was 14.3 months. With the same median survival time of the two groups ( $p > 0.01$ ), there were three cases (4.4%) in the resectable group with survival time of longer than 5 years, but in the unresectable group, survival time of all the cases was < 3 years. Long-term survivors in the resectable group were significantly more than the unresectable group ( $p > 0.01$ ) (Table 2).

## Discussion

In domestic and foreign guidelines, surgical treatment is not recommended for the patients with UPC, but some scholars performed radical surgery on the patients with UPC after strict selection<sup>8,9</sup> and achieved a similar survival time with the patients with RPC<sup>7,10</sup>. Research shows that even if radical R0 resection is not achieved, the prognosis of locally advanced pancreatic cancer could be improved<sup>11,12</sup>.

In this research, after rigorous and systematic selection, 360° arterial sheath resection was performed on the patients with pancreatic cancer while arterial sheath was encapsulated more than 180° without arterial adventitia involved. Arterial resection and reconstruction with radical operations were performed on the patients with arterial adventitia and intimal infiltration. Reconstruction of Y-type iliac artery allografts to make portal vein and jejunal ileo-venous anastomosis was performed on the patients whose SMV was all involved, with portal vein involvement at the top and jejunal ileal vein below. These radical operations have all achieved good efficacy. In this study, death occurred during perioperative period in neither group. Although operation time and intraoperative blood loss in the unresectable group were significantly greater than those in the resectable group, the rate of post-operative ICU transitional therapy, delayed gastric emptying, and reoperation was significantly lower than the resectable group ( $p < 0.01$ ), and there was no Grade C pancreatic fistula. These indicate that it is safe to undergo surgical treatment for the patients with UPC by strict selection. In this research, median survival time was 15.8 months in the resectable group and 14.3 months in the unresectable group. There was no significant difference in median survival time between the two groups ( $p > 0.01$ ). The patients in the unresectable group had the same median survival time of 11-18 months reported in the previous literatures<sup>1,2</sup>.

Table 2. Intraoperative and post-operative comparison between the two groups (cases [%])

Group	Cases	In the operation		After the operation						median survival time (months)
		operation time (min, $x \pm s$ )	intraoperative blood loss (ml, $x \pm s$ )	ICU transitional treatment	pancreatic fistula	intractable diarrhea	delayed gastric emptying	intraperitoneal reoperation	perioperative hemorrhage	
Resectable	69	329.4 ± 45.0	478.3 ± 190.0	3/69 (4.4)	9/69 (13.0)	1/69 (1.4)	5/69 (7.2)	3/69 (4.4)	1/69 (1.4)	0
Unresectable	8	432.5 ± 124.0 <sup>a</sup>	762.5 ± 168.5 <sup>a</sup>	0/8(0) <sup>a</sup>	2/8(25.0) <sup>a</sup>	4/8 (50.0) <sup>a</sup>	0/8 (0) <sup>a</sup>	1/8(12.5) <sup>a</sup>	0/8(0) <sup>a</sup>	14.3

<sup>a</sup> $p < 0.01$ .

for the patients with RPC. This proves that surgical resection for UPC patients who are strictly selected is effective. However, long-term survival rate in the resectable group was significantly higher than that in the unresectable group ( $p > 0.01$ ). Three cases (4.4%) in the resectable group had a survival time of more than 5 years and no patients (0%) in the unresectable group had a survival time of more than 3 years. Even there were two patients in the unresectable group in this research with all negative lymph nodes (case 4, 0/16 and case 5, 0/27), their survival time was only 13 months. One died of Budd-Chiari syndrome with liver metastasis and the other died of consumption and malnutrition caused by refractory diarrhea. This indicated that even if arteriovenous invasion of pancreatic cancer was caused only by specific site of the tumor, it was also prone to early local recurrence and metastasis to result in poor long-term prognosis. Neoadjuvant chemotherapy is still the first choice for UPC. Operation should be performed after conversion therapy. Intractable diarrhea is the most common complication after extended radical resection of pancreatic cancer, especially SMA sheath resection and SMA reconstruction. About 50% of cases in the unresectable group presented with intractable diarrhea and one of them died of intractable diarrhea. Retaining artery sheath at the root of SMA as far as possible may reduce its incidence and severity.

At present, resectability assessment of pancreatic cancer is based on preoperative imaging, so there is the possibility of over-diagnosis and under-diagnosis<sup>6</sup>. Many guidelines consider  $> 180^\circ$  of main artery encapsulation as a criterion of UPC, but for many these patients, the tumor has been proven in surgery technically resectable and biological benefits have been achieved<sup>6</sup>.

The present study also has some limitations. First, the sample size is listed,

## Conclusions

In this research, radical operations including  $360^\circ$  arterial sheath resection and arterial resection and reconstruction were performed on the patients with main artery were encapsulated more than  $180^\circ$  or even  $270^\circ$  based on pre-operative assessment. There was no death during perioperative period and the patients even achieved the same survival time as the resectable group to suggest that radical resection for some patients with UPC is technically feasible. Therefore, the author believes that it could be regarded as an option to give active surgical treatment to UPC cases with rejection of neoadjuvant chemotherapy, unsatisfactory response or intolerance to chemotherapy, good general condition and no distant metastasis, which

can alleviate the symptoms and provide a good basis for follow-up combined treatment. Of course, both arterial resection and reconstruction and  $360^\circ$  arterial sheath resection are technically difficult, which require sophisticated surgical planning, elaborate surgical operation and experienced surgical, and anesthetic teams as the guarantee.

## Conflict of Interest

There are no any competing interests

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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# Predictors of anastomotic leak after total gastrectomy in patients with adenocarcinoma

*Predictores de fuga anastomótica después de gastrectomía total en pacientes con adenocarcinoma*

Jorge H. Rodríguez-Quintero\*, Jorge Aguilar-Frasco, Jesús Morales-Maza, Emilio Sánchez-García-Ramos, Heriberto Medina-Franco, and Ruben Cortes-Gonzalez

Department of Surgery, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico

## Abstract

**Background:** Esophagojejunal anastomotic leakage (EJAL) is among the most feared complications after gastric cancer surgery; they entail an uncertain prognosis and relate with increased morbidity and mortality. Factors associated with their development are not well determined, and their diagnosis and treatment vary between institutions. **Material and methods:** Retrospective case-control study of patients operated of total gastrectomy with Roux-en-Y esophagojejunostomy from January 2002 to December 2018. We divided our sample into two groups based on the presence of EJAL, and compared demographic, clinical, and histologic variables. We performed a logistic regression model to search risk factors associated with EJAL and described the management offered in our center. **Results:** We included 58 patients of which 8 (13.7%) presented clinically relevant EJAL. On the comparative analysis, albumin levels and diffuse histology presented a statistically significant difference between groups and presented association with EJAL in the logistic regression model. Regarding treatment of EJAL, ten patients (55.5%) required only conservative measures, whereas eight patients (44.4%) warranted an endoscopic or surgical intervention. **Conclusion:** Our retrospective analysis identified some factors that may be associated with the development of EJAL after gastric cancer surgery. High suspicion and prompt identification of this complication is essential to improve postoperative outcomes in this group.

**Keywords:** Total gastrectomy. Gastric cancer. Gastric adenocarcinoma. Esophagojejunal anastomotic leak. Postoperative leak.

## Resumen

**Introducción:** Las fugas de la anastomosis esófago-yejunal se encuentran entre las más temidas complicaciones de la cirugía para cáncer gástrico. Estas conllevan un mal pronóstico con una alta mortalidad y morbilidad. Los factores asociados a su desarrollo no están bien determinados y su diagnóstico, y tratamiento varían ampliamente entre instituciones. **Material y métodos:** Estudio retrospectivo de casos y controles en pacientes operados de gastrectomía total con esófago-yejuno anastomosis en Y de Roux en el periodo de enero 2002 a diciembre 2018. Nuestra muestra fue dividida en dos grupos con base al desarrollo de fuga de anastomosis en el postoperatorio. Se realizó un análisis comparativo de características demográficas, clínicas y histológicas. Se realizó además una regresión logística para identificar factores de riesgo asociados al desarrollo de fuga de anastomosis en nuestra serie. **Resultados:** Incluimos a 58 pacientes de los cuales 8 (13.7%)

### Correspondence:

\*Jorge H. Rodríguez-Quintero

Bainbridge Avenue 3400 Bronx,  
C.P. 10467, New York, Nueva York, United States  
E-mail: huroqu90@gmail.com

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presentaron fuga de anastomosis clínicamente relevante. En el estudio comparativo: Niveles disminuidos de albúmina e histología difusa fueron significativamente mayores en el grupo de fuga y se asociaron en el modelo de regresión logística. En cuanto al tratamiento, diez pacientes (55%) requirieron únicamente tratamiento conservador, mientras que ocho pacientes (44.4%) fueron sometidos a maniobras endoscópicas o quirúrgicas. **Conclusión:** Nuestro análisis retrospectivo identificó factores asociados al desarrollo de fuga de anastomosis posterior a cirugía de cáncer gástrico. Una alta sospecha diagnóstica es esencial para mejorar el pronóstico de estos pacientes.

**Palabras clave:** Gastrectomía Total. Cáncer Gástrico. Adenocarcinoma Gástrico. Fuga anastomótica. Fuga postoperatoria

## Introduction

According to GLOBOCAN 2018, gastric cancer is considered the sixth most common cause of cancer worldwide<sup>1</sup>. It is, currently, the fifth cause of cancer death and is considered one of the main contributors to the disability-adjusted life year burden among all types of malignancy<sup>2</sup>. Its incidence is especially high in Asia, Latin America, and the center and east of Europe<sup>3</sup>.

Several different classifications have been utilized for this entity<sup>4,5</sup>. However, the most used divides it in two main types depending on its histologic characteristics, diffuse, and intestinal<sup>6</sup>.

Nowadays, surgical resection remains the only curative approach in the treatment of gastric cancer. The objective of such operation is the complete excision of the tumor aiming for a free 5 cm margin and proper lymph node dissection (D1 + D2 with a goal of examining at least 15 lymph nodes) with subsequent gastrointestinal reconstruction, which is usually achieved with a Roux en Y esophagojejunostomy (EJ). An R0 resection is accomplished in 45-60% of the cases subjected to surgical treatment. Most of those cases usually require a total gastrectomy (TG) due to the characteristics of the tumor and its relation with adjacent structures. Those cases with pre-operative evidence of invasion to distant or adjacent structures are not considered surgical candidates on an initial basis and benefit from neoadjuvant chemoradiotherapy and subsequent re-staging of the disease to assess for the most convenient approach<sup>7,8</sup>.

Esophagojejunal anastomotic leakage (EJAL) is among the most feared complications after gastric cancer surgery; both subclinical and symptomatic cases entail an uncertain prognosis and relate with increased morbidity and mortality. The reported incidence of this complication is quite variable worldwide<sup>9</sup>; this has a strict correlation with the heterogeneity of their operative definition, which has further complicated the development of generalized algorithms for their treatment and early recognition. Studies have demonstrated that

the presence of EJAL is associated to prolonged hospitalization and a significant risk of death<sup>10</sup>. Furthermore, there is evidence suggesting that infectious complications after gastric cancer surgery are associated with increased rates of cancer recurrence<sup>11</sup>.

Factors associated with the development of EJAL after gastric cancer surgery are not well determined. A large retrospective study from Asia, suggest that older age (> 65 years), increased intraoperative blood loss and comorbidities may be related<sup>12</sup>. However, such findings have not been reproduced consistently by others<sup>13-15</sup>. EJAL can present in two different clinical scenarios. The first and most indolent, is in asymptomatic patients that undergo either routine imaging studies before starting oral feeding or an imaging study requested for another reason; and in symptomatic patients who frequently present with abdominal pain, fever, peritoneal irritation, and saliva or intestinal content in perianastomotic drains after the procedure or when the start of oral intake is attempted. The diagnostic approach and treatment varies depending on the particular case. However, there is marked diversity between institutions<sup>9,10</sup>.

The purpose of this study was to identify risk factors for the development of EJAL in patients subjected to TG in a third level university based oncologic center and describe the treatment algorithm utilized to manage this complication in our hospital.

## Materials and methods

We performed a retrospective analysis of our hospital registry to identify the subjects of this study. All patients over 18 years old with the diagnosis of gastric cancer, who were subjected to TG with Roux en Y EJ at our third level academic center between January 2002 and December 2018, were included in the study. Patients with incomplete data were excluded from the analysis. This study received approval of the local Institutional review board. All patients were approached by laparotomy and operated by a board-certified surgical oncologist.

EJAL was defined as any clinical or imaging evidence of luminal spillage adjacent to the EJ; Including evidence of intestinal contents or saliva in perianastomotic drains, evidence of extraluminal contrast material in imaging studies (esophagogram and contrast-enhanced Computed tomography [CT] scan) or fluid collections adjacent to the EJ in CT scan or ultrasound. All post-operative imaging studies of analyzed patients were reviewed for the purpose of this study to decrease risk of bias, some of which were requested for an alternate diagnostic suspicion.

The variables age, gender, comorbidities (Type 2 diabetes, high blood pressure, hypothyroidism, or dyslipidemia) perioperative chemotherapy, histologic type, and presence of signet ring cells were recorded. Relevant routine preoperative laboratory values, obtained at admission 1 day previous to the operation, were also registered, including hemoglobin, total leukocytes, total neutrophils, total lymphocytes, neutrophil to lymphocyte ratio platelets, and albumin levels. Variables related to the surgical procedure such as surgical technique (hand sewn vs. stapled anastomosis), operative time and operative bleeding were included in the study.

Our sample was divided in two groups for statistical analysis, based on the presence of EJAL during their post operatory period. Variables were compared between these two groups.

All patients were assessed by a multidisciplinary team, and were operated by a certified surgical oncologist. The pre-operative assessment and post-operative routine were according current international practice guidelines. The standard protocol was early feeding as tolerated, total parenteral nutrition (when required and progression of analgesia to achieve early discharge).

Patients with identified EJAL were defined as asymptomatic when no clinical symptoms suggestive of secondary abdominal sepsis (such as pain, oral intolerance, or peritonitis) were present during serial examinations and were treated with supportive treatment including nothing by mouth, intravenous hydration, analgesia, and antibiotics and fluid collection drainage with interventional approaches when appropriate. Such patients were followed closely with clinical examinations and serial imaging. None of these patients required invasive interventions.

Symptomatic patients were assessed and treated according their particular presentation. Our general approach included nothing by mouth, early nutritional support, intravenous antibiotics, drainage of fluid

collections, and depending on the nature of the case either endoscopic revision with fibrin glue, clip, or stent placement over defect or surgical management. All such procedures were considered emergency interventions.

We also included the variables hospital stay, perioperative mortality, and overall survival for descriptive purposes.

### **Statistical analysis**

Categorical variables were presented as total frequencies (n), proportions and percentages (%). Continuous variables were analyzed for normal distribution. Variables with normal distribution were presented as means and standard deviations ( $\pm$  SD) and those with non-normal distribution were presented as medians and ranges. Categorical variables were compared within groups using Chi-square test or Fischer's exact test, whereas continuous variables were compared using Student's t-test or Mann-Whitney U test. All tests were two sided and utilized an alpha of 0.05.

Univariate logistic regression analysis was performed utilizing the included variables. Odds ratios and 95% confidence intervals were calculated. All values were two tailed in this analysis and p <0.05 was considered to be statistically significant. The analysis was performed employing SPSS Version 22.0 (IBM Corporation, Armonk, New York, NY).

### **Results**

We included a total of 58 patients subjected to TG in our sample. No patients were excluded due to lack of available data after our review. All included patients were analyzed.

A total of 18 patients (31.03%) fulfilled our definition of EJAL during their post operatory period. All patients were diagnosed within 1 week of their operation and were still hospitalized when the EJAL was identified. Ten cases (55.5% of the anastomotic leaks) were classified as asymptomatic and were identified during the post-operative period through either routine imaging (contrast-enhanced esophagogram) requested before starting oral intake, or imaging studies pursuing alternate diagnostic suspicion.

The remaining eight patients with EJAL, were considered symptomatic and presented with fever (100%), diffuse abdominal pain (25%), peritonitis (25%), oral intolerance (75%), leukocytosis  $> 12.500 \times 10^9/L$ , 75%), elevated acute phase reactants (CRP  $>1.5$  mg/dl,

**Table 1. Clinical and histologic variables**

	All Patients (n = 58)	EJAL (n = 18)	No EJAL (n = 40)	p < 0.05
Age (years)	61.5	63.8	60.5	0.21
Gender				
Male	22 (37.9%)	12 (66.6%)	20 (50%)	0.268
Female	26. (44.8%)	6 (33.3%)	20 (50%)	
Comorbidities				
With	33 (56.89%)	10 (55.5%)	23 (57.5%)	1.0
Type 2 diabetes	17 (29.3%)	8 (44%)	9 (22.5%)	
Dyslipidemia	7 (12%)	3 (16.6%)	4 (10%)	
High blood pressure	19 (32.7%)	6 (33.3%)	13 (32.5%)	
Hypothyroidism	2 (0.1%)	2 (11.1%)	0 (0%)	
Others	10 (17.4%)	4 (22.2%)	6 (15%)	
Without	25 (43.10%)	8 (44.4%)	17 (42.5%)	
Perioperative Chemotherapy				
No	19 (32.7%)	6 (33.3%)	13 (32.5%)	0.17
Neoadjuvant	11 (18.9%)	6 (33.3%)	5 (12.5%)	
Adjuvant	10 (17.24%)	1 (5.55%)	9 (22.5%)	
Perioperative	18 (31.03%)	5 (27.77%)	13 (32.5%)	
Histologic Type				
Intestinal	19 (32.7%)	4 (22.2%)	15 (37.5%)	0.05
Diffuse	29 (50%)	9 (50%)	20 (50%)	
Mixed	10 (12%)	5 (27.7%)	5 (12.5%)	
Presence of Signet ring cells				
With	35 (60.3%)	9 (50%)	26 (65%)	0.385
Without	23 (39.6%)	9 (50%)	14 (35%)	

100%), or intestinal content on the perianastomotic drain (50%).

The mean age of our patients was 61.5 years with no statistically significant difference found between groups. In the initial comparative analysis, we found no significant difference in the clinical variables gender, comorbidities, perioperative chemotherapy, and presence of signet ring cells in histology. With the variable histologic type reaching p = 0.5 (Table 1).

Variables related to the surgical procedure and laboratory values were similar between groups with exception of serum albumin levels, which were significantly lower in the EJAL group (mean 3.9 mg/dl vs. 3.5 mg/dl p = 0.02) (Table 2).

On univariate analysis (Table 3), patients were more likely to develop EJAL if they presented diffuse gastric adenocarcinoma, according to the post-operative pathology report. The rest of the variables included in the analysis did not present a significant association with the development of EJAL in our sample.

**Table 2. Laboratory and procedure related variables**

	EJAL (n = 18)	No EJAL (n = 40)	p < 0.05
Hemoglobin (g/dl)	12.4 (10.03-14.81)	12 (9.38-14.64)	0.56
Total Leukocyte count (cells/microL)~	7.5 (3.6-8.5)	6.7 (6.0-13.7)	0.14
Total Neutrophil count (cells/microL)~	4.9 (2.05-6.35)	4.0 (3.5-11.8)	0.31
T. Lymphocyte count (cells/microL)~	1.9 (0.78-2.7)	1.6 (0.18-8.54)	0.19
Total Neutrophil/Lymphocyte ratio~	2.3 (0.91-21.5)	2.3 (0.83-14.8)	0.65
Platelets ( $\times 10^9/L$ )	260.2 (126.9-393.4)	275.3 (211.2-339.2)	0.77
Serum albumin (mg/dl)	3.5 (2.66-4.34)	3.9 (3.38-4.44)	0.02
Operative time (min)	268.3 (223-313.6)	275.3 (211.2-339.2)	0.64
Operative Blood loss (ML)	498.9 (258.5-739.2)	530.5 (257.1-803.3)	0.66
Type of Anastomosis			
Mechanic (Stapled)	16 (88.8%)	29 (72.5%)	0.30
Manual (Hand Sewn)	2 (11.1%)	11 (27.5%)	

Variables with normal distribution were expressed as means±STD. Non-normal variables (~) were expressed as median±ranges.

Mean hospital stay was 29.5 days in the EJAL group and 12 days in the control. The mean overall survival in our entire sample was 26.97 months with no difference between groups.

Regarding treatment of the symptomatic EJAL, six patients required percutaneous drainage of fluid collections (10.3%). Four patients with symptomatic EJAL (6.8%) required an endoscopic intervention, involving application of fibrin glue in three patients and endoscopic clip in one patient. Two patients (3.4%) were treated with a primary operative intervention due to sepsis. Both were approached through laparotomy and were subjected to remodeling of the EJ and closed drain placement. One of such patients died in the post operative period secondary to severe sepsis and multiorgan failure. The rest of the EJAL identified were treated conservatively.

## Discussion

This study aimed to identify the incidence of EJAL after gastric cancer surgery, as well as risk factors that were associated with their development in western population.

**Table 3. Univariate logistic regression analysis of factors associated with EJAL**

Risk Factor for EJAL	Unadjusted OR (95% CI)	p < 0.05
Gender	0.50 (0.15-1.59)	0.241
Comorbidities	0.92 (0.30-2.83)	0.89
(+) Signet ring cells	0.53 (0.17-1.66)	0.28
Manual anastomosis vs. Mechanic	3.03 (0.59-15.41)	0.18
Chemotherapy	0.28 (0.02-2.90)	0.29
Histologic type		
Diffuse/Intestinal	9.32 (1.29-67.64)	0.02
Mixed/Intestinal	5.55 (0.90-34.24)	0.06
Hemoglobin (g/dl)	0.93 (1.29-67.64)	0.56
Leukocyte count (cells/microL)	1.13 (0.94-1.37)	0.17
Total Neutrophil count (cells/microL)	1.18 (0.9-1.37)	0.23
T. Lymphocyte count (cells/microL)	1.15 (0.91-1.46)	0.21
Total Neutrophil/Lymphocyte ratio	1.05 (0.89-1.23)	0.55
Platelets ( $\times 10^9/L$ )	0.99 (0.99-1.004)	0.76
Serum albumin (mg/dl)	0.82 (0.72-1.37)	0.07
Operative time (min)	0.99 (0.98-1.008)	0.67
Operative Blood loss (ML)	1 (0.99-1.002)	0.66

We realized that there is a very limited amount of research papers studying this complication in the context of gastric cancer, and that most of the studies are based on retrospective data, and focused mainly on Asian population<sup>11-14</sup>. This is concerning because of the well-known differences in the perioperative approach paradigms and patient characteristics between western and eastern institutions<sup>15</sup>. The prevalence of EJAL following open gastrectomy for gastric cancer has been reported to range from 2.1 to 14.6%<sup>16,17</sup>, with mortality associated with EJAL ranging from 0 to 50%<sup>17,18</sup>. The differences in the literature may be explained by variations in study design, study cohort size, country, and study periods<sup>19</sup>. The EJAL incidence and mortality tend to be lower in Asian countries (including Japan) than in Western countries. The incidence of EJAL following open TG was 4.4% in a prospective cohort study from a Japanese nationwide registry<sup>20</sup>, whereas the incidence ranged from 4 to 26% in phase III studies conducted in Western countries<sup>21,22</sup>. This difference may be attributed to the higher incidence of cardiopulmonary comorbidities and intra-abdominal complications in patients with gastric

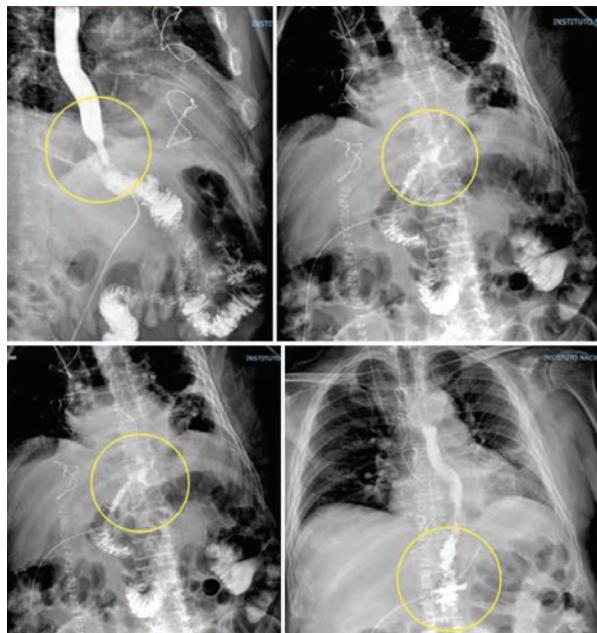
cancer from Western countries as well as the higher incidence of gastric cancer in Asian patients<sup>23,24</sup>.

Identification of the risk factors of EJAL helps to decrease its incidence. The reported risk factors include patient and tumor characteristics and intraoperative factors. The impact of a challenging anastomosis on the occurrence of EJAL indicates that prevention is crucial to reduce this complication. Migita et al.<sup>25</sup> found that blood loss was significantly greater in gastrectomy with a complicated anastomosis (783 vs. 423 g, p < 0.05). Furthermore, gastrectomy with anastomotic complications tended to have a longer median duration of operation in comparison to that without it (351 vs. 290 min, p = 0.0682). These results indicate that more complicated gastrectomy is associated with higher incidence of the anastomotic complications. In our study, variables related to the surgical procedure were similar between groups.

On the other hand, anemia and malnutrition may result in insufficient blood and energy supplies to the anastomosis, which might affect the healing of the anastomosis and reduce the levels of inflammatory cells, inflammatory factors, and administered antibiotics, thereby increasing the risks of infection and of anastomotic leakage<sup>26-28</sup>. In our series, we demonstrated significantly lower albumin levels in patients who present EJAL, which is widely known as a predictor of EJAL, but has merely been described in this specific context<sup>29,30</sup>. Furthermore, to the best of our knowledge, no previous study had determined diffuse histologic type to be related to EJAL; this could relate to a more increased local inflammatory reaction elicited by this aggressive type of neoplasm but again, more studies are needed to better understand this concept on a molecular basis.

Furthermore, we are aware that our series demonstrate a higher incidence of EJAL than other contemporary literature. However, we believe that this is due to the marked heterogeneity in the diagnostic approach and definition of EJAL. Most studies include only clinically significant EJAL and exclude perianastomotic fluid collections from their operative definition and thus describe higher rates of invasive interventions.

In comparison most of our EJAL were subclinical. The percentage of patients which required an intervention (either endoscopic or surgical) was 13.7%, which is similar to that reported in other series<sup>31,32</sup>. We still decided to include all the patients with any evidence of contrast extravasation either clinical or sub-clinical for the comparison as even asymptomatic



**Figure 1.** Contrast-enhanced esophagogram performed 4 days after total gastrectomy showing evidence of EJAL (yellow circle).

leaks resulted in a deviation from the conventional post operative management in our institution either because of increased hospital stay, medication regime and serial follow-up studies and allocation of resources.

Concerning the diagnostic approach of EJAL, some authors have proposed the performance of contrast-enhanced esophagogram previous to start oral feedings in their patients<sup>33,34</sup> (Fig. 1).

However, further evidence has demonstrated that this practice has a low diagnostic yield and should not be done on a regular basis<sup>35</sup>. On a study performed in our center, routine contrast enhanced esophagogram revealed to have a sensitivity of 86%, specificity 100%, positive predictive value 100%, and negative predictive value of 86% for detection of EJAL<sup>36</sup>.

In our institution, perioperative practices have evolved through the years, showing a tendency to perform more imaging studies to our patients, attempting to identify complications earlier and improve prognosis.

As described earlier, all our patients received multidisciplinary expert care but still, the criteria to subject the patients to post operatory imaging for different reasons, varied depending on the physician in charge; this variable criteria for the performance of imaging studies it is the main limitation of this retrospective review, in conjunction with its limited power.

Regarding the treatment of patients with EJAL, we usually perform a step up approach depending on the clinical presentation; our approach starts with nothing per mouth, naso-jejunum tube placement, intravenous hydration, early nutritional support, analgesia and antibiotics, followed by multidisciplinary consensus for the most appropriate invasive intervention which usually includes percutaneous treatment, endoscopic placement of sealants, clips or stents and surgical remodeling of the EJ, which is usually reserved for patients with large dehiscence of the anastomosis. This approach is similar to other current practices described in the literature.

## Conclusions

EJAL is among the most feared complications after gastric cancer surgery; they entail an uncertain prognosis and relate with increased morbidity and mortality. Our retrospective analysis identified some factors that may be associated with the development of EJAL after gastric cancer surgery. High suspicion and prompt identification of this complication are essential to improve postoperative outcomes in this group.

## Conflicts of interest

The authors have no conflicts of interest to disclose.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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# Sensibilidad y especificidad del índice neutrófilo/linfocito en pacientes pediátricos con apendicitis aguda complicada

*Sensitivity and specificity of neutrophil-to-lymphocyte ratio in pediatric patients with acute complicated appendicitis*

Manuel Gil-Vargas<sup>1\*</sup>, Ivonne Cruz-Peña<sup>2</sup> y Mary S. Saavedra-Pacheco<sup>3</sup>

<sup>1</sup>Servicio de Cirugía Pediátrica, Hospital General de Puebla "Eduardo Vazquez Navarro"; <sup>2</sup>Servicio de Pediatría, Hospital General de Puebla "Eduardo Vazquez Navarro; <sup>3</sup>Facultad de Medicina, Benemérita Universidad Autónoma de Puebla. Puebla, México

## Resumen

**Objetivo:** Determinar la sensibilidad y la especificidad del índice neutrófilo/linfocito (INL) en pacientes pediátricos con apendicitis aguda complicada. **Método:** Estudio transversal, observacional, descriptivo y retrospectivo. Se seleccionaron pacientes de 4 a 16 años con diagnóstico de apendicitis aguda a quienes se realizó appendicectomía de enero 2017 a diciembre 2019. Se calculó el INL de cada paciente. Para analizar las variables se utilizó la prueba de Mann-Whitney y se valoraron la sensibilidad y la especificidad del INL. **Resultados:** Se estudiaron 245 pacientes, 81 con apendicitis simple y 144 con apendicitis complicada. Se realizaron 27 appendicectomías laparoscópicas. El INL tuvo una media de 10.48 en la apendicitis simple y de 13.03 en la complicada ( $p = 0.02$ ). Con un área bajo la curva de 0.622 se estimó un punto de corte para el INL de 8.2 en los pacientes con apendicitis complicada. **Conclusiones:** El INL ha sido poco estudiado en pacientes pediátricos con apendicitis aguda. En el presente estudio, el INL resultó con valor significativo en los casos de apendicitis aguda complicada en pacientes pediátricos, con sensibilidad intermedia y especificidad relativamente baja.

**Palabras clave:** Índice neutrófilo/linfocito. Apendicitis. Niños. Appendectomy.

## Abstract

**Objective:** Establish the sensibility and specificity of the neutrophil-lymphocyte rate (NLR) in pediatric patients with acute complicated appendicitis. **Method:** Transversal, observational, descriptive, and retrospective study of pediatric patients between 4 to 16 years old with diagnosis of acute appendicitis, who had appendectomy, from December 2017 to January 2019. We calculated the NLR in every patient. To analyze the variables, we used the test of Mann-Whitney and we value the sensibility and specificity of the NLR. **Results:** There were 245 patients, 81 with simple appendicitis and 144 with complicated appendicitis. Just 27 of them were laparoscopic appendectomy. The NLR had a media of 10.48 in simple appendicitis, and 13.03 in complicated ones, with a  $p$  value of 0.02. the area under the curve was 0.622. There was a rate of 8.2 in complicated appendicitis to the NLR. **Conclusions:** The NLR has been poorly studied in pediatric patients with acute appendicitis. In this study the NLR had a significant value in the patients with acute complicated appendicitis, with medium sensibility and a relatively low specificity.

**Keywords:** Neutrophil-lymphocyte rate. Acute appendicitis. Children. Appendectomy.

## Correspondencia:

\*Manuel Gil-Vargas

E-mail: gilvm@yahoo.com

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## Introducción

La apendicitis aguda es la emergencia quirúrgica más frecuente en la infancia<sup>1</sup>. En la mayoría de los casos su diagnóstico depende de la clínica del paciente, pero en los pacientes pediátricos es difícil distinguir la apendicitis de otros padecimientos. Solo del 10 al 36% de los pacientes pediátricos presentarán la sintomatología clásica de un cuadro apendicular, a diferencia de los adultos, que la presentan en un 60-70%<sup>2,3</sup>. De aquí la importancia del uso de auxiliares diagnósticos para un tratamiento oportuno.

Se ha reportado el índice de neutrófilos/linfocitos (INL) como un complemento útil en la predicción de la gravedad de la apendicitis, las complicaciones posoperatorias y la duración de la estancia. Es un marcador de inflamación, que resulta de dividir la cifra absoluta de neutrófilos entre la cifra absoluta de linfocitos. El INL puede ser útil como diagnóstico y pronóstico en diversas patologías inflamatorias<sup>4</sup>. Algunas publicaciones informan que el INL se relaciona con la infección bacteriana grave y con la respuesta inflamatoria sistémica<sup>5</sup>. Hay escasos estudios en población pediátrica que analizan la utilidad del INL en el diagnóstico de apendicitis aguda<sup>6</sup>.

La apendicitis aguda constituye la primera causa de abdomen agudo quirúrgico en la edad pediátrica. Detectar oportunamente un cuadro apendicular lleva a la disminución de numerosas complicaciones, como infección del sitio quirúrgico, perforación apendicular, absceso apendicular, peritonitis generalizada, adherencias y sepsis; además, disminuye la mortalidad y la estancia hospitalaria, y por tanto evita altos costos hospitalarios.

El objetivo principal de este estudio fue determinar la sensibilidad y la especificidad del INL en pacientes pediátricos con apendicitis aguda complicada.

## Método

Se realizó un estudio transversal, observacional, descriptivo y retrospectivo. Se recolectaron los datos de los pacientes pediátricos operados de apendicectomía de enero de 2017 a diciembre de 2019. Se incluyeron los expedientes clínicos de pacientes entre 4 y 16 años tratados en el Hospital General Zona Sur de Puebla Eduardo Vázquez Navarro con diagnóstico principal de apendicitis aguda. Se excluyeron expedientes clínicos incompletos, pacientes con intervención quirúrgica en otra unidad y pacientes con

apendicectomía profiláctica. Se eliminaron los expedientes clínicos de los pacientes operados de apendicectomía que en el posoperatorio fueron trasladados a otra unidad.

Se registraron las siguientes variables: edad, sexo, cuenta de leucocitos, cifra absoluta de neutrófilos, cifra absoluta de linfocitos, INL, abordaje quirúrgico para la apendicectomía, tipo de apendicitis y días de estancia hospitalaria. Se tomó como referencia la biometría hemática al ingreso del paciente y se calculó el INL dividiendo la cifra absoluta de neutrófilos entre la cifra absoluta de linfocitos en cada paciente.

La apendicitis no complicada es aquella que no tiene datos de perforación. Se consideraron complicadas aquellas apendicitis agudas perforadas, con o sin absceso localizado, o con peritonitis purulenta.

La muestra fue convencional, siendo el número de casos que se presentaron en esta unidad hospitalaria durante el periodo de estudio.

Se elaboró una hoja de recolección de datos, la información se concentró en el software Microsoft Excel versión 2013 y los datos se analizaron con el software IBM SPSS Statistic, versión 25.

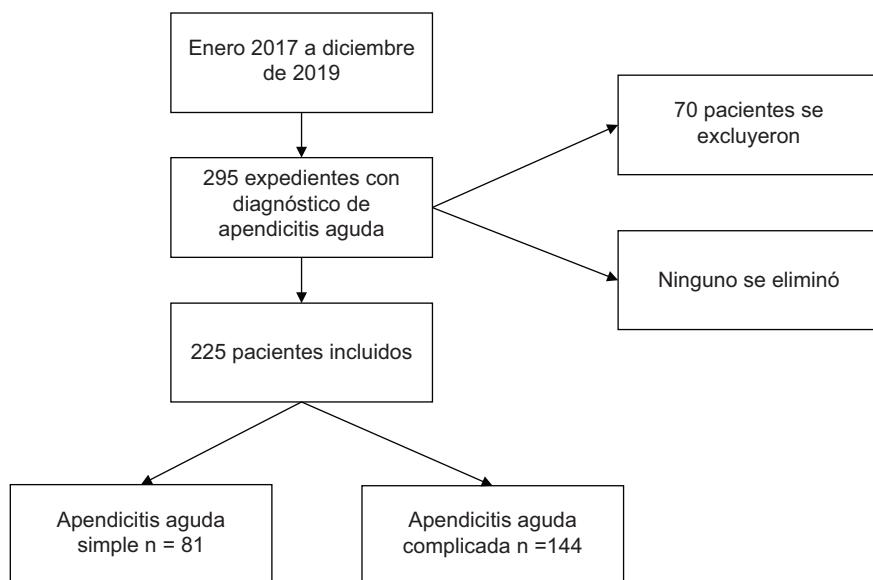
En el análisis estadístico, las variables continuas se expresaron como media y desviación estándar. Para las variables continuas distribuidas normalmente se utilizó la prueba t de Student de muestras independientes, y para analizar los datos continuos no distribuidos normalmente se utilizó la prueba de Mann-Whitney. La significancia estadística se estableció en  $p < 0.05$ .

La sensibilidad y la especificidad para el diagnóstico de apendicitis aguda complicada se determinaron mediante curvas ROC (*Receiver Operating Characteristic*). También se calculó el punto de corte de máxima precisión diagnóstica para cada parámetro analítico mediante el índice de Youden.

Este estudio fue aprobado por el comité de ética de investigación del Hospital General Eduardo Vázquez Navarro.

## Resultados

Se analizaron 295 expedientes clínicos de pacientes pediátricos con diagnóstico de apendicitis aguda y se excluyeron 70 por datos incompletos, resultando una muestra de 225 expedientes clínicos: 81 con diagnóstico transoperatorio de apendicitis aguda simple y 144 con diagnóstico de apendicitis aguda complicada (Fig. 1). De los expedientes clínicos de

**Figura 1.** Diagrama de flujo de los pacientes incluidos en el estudio.**Tabla 1.** Variables analíticas estudiadas

Apendicitis simple (n = 81)				Apendicitis complicada (n = 144)			
Variable	Media	DE	Rango	Media	DE	Rango	p
Leucocitos	14636	5406	1344-1583	16886	5.117	1604-1772	0.02*
Neutrófilos	12066	5010	1095-1317	14118	4.604	1336-1487	0.02*
Linfocitos	1638	863	1447-1829	1442	818	1307-1577	0.062†
Bandas	2.23	2.55	1.67-2.80	3.77	4.11	3.09-4.45	0.07†
Estancia hospitalaria	2.36	1.34	2.06-2.66	4.31	2.25	3.94-4.68	0†

DE: desviación estándar.

\*Prueba t de Student para muestras independientes.

†Prueba U de Mann-Whitney.

pacientes con apendicitis aguda simple, 51 fueron de sexo masculino y 30 de sexo femenino, con una edad promedio de 11 años (desviación estándar [DE]:  $\pm 3$ ). De los expedientes de pacientes con apendicitis aguda complicada, 94 fueron de sexo masculino y 50 de sexo femenino, con una edad promedio de 10 años (DE:  $\pm 4$ ).

En cuanto al abordaje quirúrgico de la apendicectomía, la técnica fue abierta en 198 pacientes (71 con apendicitis aguda simple y 127 con apendicitis aguda complicada) y laparoscópica en 27 pacientes (10 con apendicitis aguda simple y 17 con apendicitis aguda complicada).

En los pacientes con apendicitis simple, el INL resultó con una media de 10.48 (DE:  $\pm 8.4$ ) y un rango de 8.6-12.36, mientras que en los pacientes con apendicitis

complicada la media fue de 13.03 (DE:  $\pm 10.24$ ) y el rango fue de 11.34-14.72 ( $p=0.02$ ). En la tabla 1 se muestran las otras variables estudiadas.

El INL en los pacientes con apendicitis complicada tuvo un área bajo la curva (AUC) de 0.622 y un intervalo de confianza del 95% (IC95%) de 0.542-0.702, considerándose su punto de corte en 8.2, con una sensibilidad del 70% y una especificidad del 46% ( $p = 0.02$ ). Para los neutrófilos se encontró un AUC de 0.621 (IC95%: 0.545-0.697), con un punto de corte de 17.390, con una sensibilidad del 25% y una especificidad del 99% ( $p = 0.03$ ). Para los leucocitos se obtuvo un AUC de 0.12 (IC95%: 0.536-0.688), con un punto de corte de 19.785, con una sensibilidad del 27% y una especificidad del 99% ( $p = 0.05$ ) (Tabla 2 y Fig. 2).

Tabla 2. Área bajo la curva ROC para el diagnóstico de apendicitis complicada

Apendicitis complicada	AUC	IC95%	Punto de corte	Sensibilidad (%)	Especificidad (%)	p
Índice neutrófilo-linfocito	0.622	0.542-0.702	8.2	70	46	0.02
Neutrófilos	0.621	0.545-0.697	17.390	25	99	0.03
Leucocitos	0.12	0.536-0.688	19.785	27	99	0.05

AUC: área bajo la curva; IC95%: intervalo de confianza del 95%.

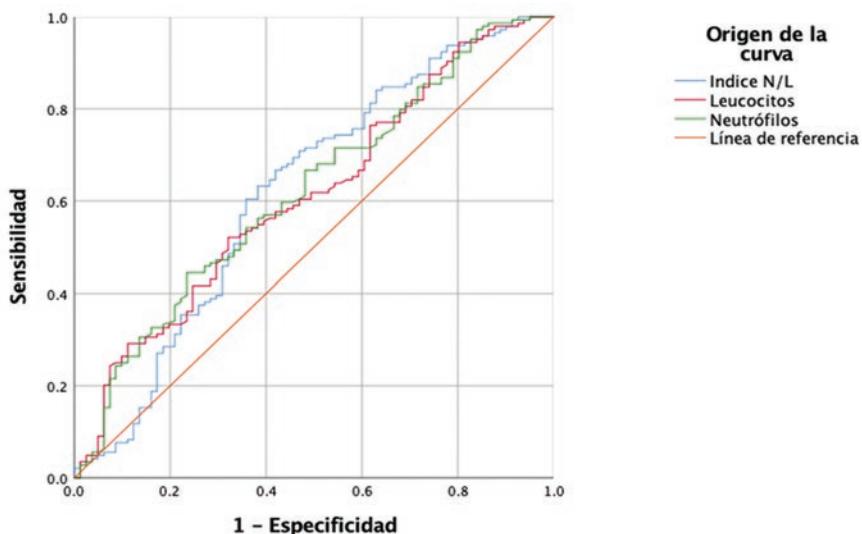


Figura 2. Curva ROC para el diagnóstico de apendicitis aguda complicada.

## Discusión

El INL es un marcador de inflamación sistémica que puede ser adecuado para pronosticar la gravedad de las enfermedades cardiovasculares, oncológicas e infecciosas. Este índice también es valioso al momento del diagnóstico de apendicitis aguda.

El objetivo fue alcanzado al determinar la sensibilidad y la especificidad del INL en pacientes pediátricos con apendicitis aguda complicada. De nuestra muestra, más del 50% de los pacientes presentaron este diagnóstico y es importante destacar que su INL tuvo un punto de corte alto y con sensibilidad diagnóstica intermedia.

Hay informes de que el INL es un marcador prometedor que puede predecir tanto el diagnóstico como la gravedad de la apendicitis, con sensibilidad y especificidad aceptables, lo que potencialmente facilita la toma de decisiones, al tener pacientes pediátricos con el diagnóstico de apendicitis aguda, dándoles

prioridad para realizar su tratamiento quirúrgico de emergencia<sup>7</sup>.

Yazici et al.<sup>8</sup> publicaron un estudio con 240 pacientes con edades de 3 a 16 años, que dividieron en dos grupos: el primero, 183 pacientes con diagnóstico de apendicitis aguda, y el segundo, 57 pacientes con dolor abdominal no específico. Encontraron un INL de 3.5 como punto de corte para los pacientes con apendicitis aguda, con una especificidad del 88% y una sensibilidad del 90%. En este estudio no se analizó la asociación con apendicitis complicada.

Tuncer et al.<sup>9</sup> reportaron en su estudio la gran utilidad del INL para diferenciar a pacientes pediátricos con apendicitis aguda de pacientes con fiebre mediterránea familiar o con linfadenitis mesentérica. Sin embargo, tampoco asocian específicamente las apendicitis complicadas.

Yilmaz et al.<sup>10</sup> informaron datos similares en un estudio descriptivo y retrospectivo, en pacientes menores de 18 años, con una edad promedio de 11.35

años, que investigaron en dos grupos: uno de 628 pacientes con apendicitis aguda y tratados con apendicectomía, y otro con otras patologías abdominales. En el primer grupo, los resultados del AUC fueron de 0.694 para el INL, con un valor de corte de 3.5, con una sensibilidad del 84.2% y una especificidad del 56.7% ( $p = 0.008$ ). También evaluaron el INL como predictor en el diagnóstico de apendicitis aguda en población pediátrica.

Delgado et al.<sup>6</sup> evaluaron los parámetros analíticos de la biometría hemática en niños entre 5 y 16 años con diagnóstico de peritonitis secundaria a apendicitis aguda complicada, y encontraron al INL con un AUC de 0.783, un punto de corte de 8.3, una sensibilidad del 75% y una especificidad del 72.2%. El INL no tiene valores fijos, sino que dependen de la patología en estudio y la evolución clínica del paciente, y por lo tanto modifican la sensibilidad y la especificidad, encontrándose este valor más elevado en pacientes con apendicitis aguda complicada.

Nazik et al.<sup>11</sup> realizaron un estudio en el que valoraron la relación entre apendicitis y distintos marcadores, uno de ellos el INL. Incluyeron 63 pacientes pediátricos: 30 con apendicitis y 33 controles. Reportaron que el grupo de pacientes con apendicitis obtuvo un INL significativamente mayor que los pacientes sanos.

Godinez et al.<sup>5</sup> publicaron un estudio retrospectivo en pacientes adultos jóvenes, con una edad promedio de 36.4 años, en el que compararon el INL con otros biomarcadores, así como con escalas de gravedad. Se determinó la gravedad de la patología relacionada con apendicitis aguda complicada, con un punto de corte del INL de 12, relacionado con peritonitis generalizada y apendicitis perforada, con una sensibilidad del 86%, una especificidad del 68% y un AUC de 0.756 ( $p = 0.023$ ). Este estudio concluye que el INL puede emplearse para identificar aquellos pacientes con mayor riesgo de complicaciones y, por lo tanto, los casos que requieren una vigilancia posoperatoria más estrecha.

Özaydin et al.<sup>12</sup> señalan que el INL es un marcador relativamente nuevo que se asocia con una escasa supervivencia en muchas enfermedades. Los autores evaluaron a 154 pacientes entre 18 y 65 años (media: 34.2 años) en dos grupos: con apendicitis aguda complicada y con apendicitis no complicada. Obtuvieron en el primer grupo un AUC del INL de 0.856, con un valor de corte de 7.3, una sensibilidad del 75.8% y una especificidad del 81.8%. Por otro lado, Çelik et al.<sup>13</sup> analizaron pacientes pediátricos en dos grupos,

con apendicitis aguda complicada y no complicada, y obtuvieron un AUC de 0.717, una sensibilidad del 61.1% y una especificidad del 73.2% para diferenciar las apendicitis complicadas.

Los resultados de los estudios previamente mencionados son similares a los obtenidos en el nuestro; sin embargo, la mayoría no han evaluado pacientes pediátricos con apendicitis aguda complicada y en México no encontramos estudios realizados en población pediátrica. Invitamos a otros investigadores a realizar más estudios relacionados con este enfoque para incrementar la evidencia, y proponemos que se aplique en la práctica clínica.

## Conclusiones

En algunos casos no es suficiente la clínica del paciente para establecer el diagnóstico de apendicitis y es necesario recurrir a otras herramientas diagnósticas. En el presente estudio, el INL resultó con valor significativo en los casos de apendicitis aguda complicada en pacientes pediátricos, con sensibilidad intermedia y especificidad relativamente baja. Aplicar este índice en la práctica clínica puede apoyar tempranamente el diagnóstico en pacientes con apendicitis y proporcionar el tratamiento quirúrgico oportuno.

Proponemos que el punto de corte obtenido para el INL sea tomado en consideración, pues aunado a una alta sospecha clínica de apendicitis aguda puede ayudar a reducir exploraciones quirúrgicas con apendicitis negativas, días de estancia intrahospitalaria y complicaciones en pacientes pediátricos con cuadro apendicular.

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## Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

## Responsabilidades éticas

**Protección de personas y animales.** Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

**Confidencialidad de los datos.** Los autores declaran que en este artículo no aparecen datos de pacientes.

**Derecho a la privacidad y consentimiento informado.** Los autores declaran que en este artículo no aparecen datos de pacientes.

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# Precisión de la calculadora de riesgo quirúrgico ACS NSQIP para predecir morbilidad y mortalidad en pacientes mexicanos

*Accuracy of the ACS NSQIP surgical risk calculator to predict morbidity and mortality in Mexican patients*

José J. Macías-Cervantes\*, Rafael S. Vázquez-Rentería, Sandra C. López-Romero y  
Noé I. Gracida-Mancilla

Servicio de Cirugía General, Clínica de Patología Quirúrgica Aguda, Hospital General de México "Dr. Eduardo Liceaga", Ciudad de México, México

## Resumen

**Antecedentes:** El American College of Surgeons (ACS) desarrolló la calculadora de riesgo quirúrgico ACS NSQIP que predice los resultados de las cirugías electivas y de urgencia. Dicha herramienta ha sido útil para mejorar las cifras de morbilidad y mortalidad en hospitales de los Estados Unidos y Canadá. **Objetivo:** Evaluar la utilidad de la calculadora de riesgo ACS NSQIP para predecir complicaciones posquirúrgicas en pacientes mexicanos. **Método:** Estudio prospectivo, observacional y analítico. Se registraron los pacientes sometidos a cirugía abdominal, se capturaron 21 variables preoperatorias y se ingresaron en la calculadora. Se vigilaron hasta cumplir 30 días de posoperatorio y se identificaron 14 tipos de complicaciones posoperatorias. **Resultados:** Se registraron 109 pacientes y se hizo una comparación entre las probabilidades de complicaciones calculadas y observadas, obteniendo una buena correlación en las complicaciones de paro cardiaco, infección de sitio quirúrgico, reintervención quirúrgica, sepsis y mortalidad ( $p < 0.05$ ). **Conclusiones:** La calculadora de riesgo ACS NSQIP es útil en la población mexicana, ya que el puntaje obtenido predice la mayoría de las complicaciones posoperatorias, incluida la mortalidad. El uso de esta herramienta ofrece una oportunidad para mejorar la toma de decisiones en la atención del paciente quirúrgico.

**Palabras clave:** Morbilidad. Mortalidad. México.

## Abstract

**Background:** American College of Surgeons (ACS) developed the ACS NSQIP surgical risk calculator that predicts the results of elective and emergency surgical procedures. This tool has been useful improving the morbidity and mortality in hospitals in the United States and Canada. **Objective:** To evaluate the usefulness of the ACS NSQIP risk calculator for predicting post-operative complications in Mexican population. **Method:** Prospective, observational, analytical study. Patients undergoing abdominal surgery were recorded, 21 preoperative variables were captured and entered into the calculator. They were followed up to 30 days postoperatively, identifying 14 types of postoperative complications. **Results:** 109 patients were registered. A comparison was made between the calculated and observed complications, obtaining a good correlation in the complications of cardiac arrest, surgical site infection, reoperation, sepsis and mortality ( $p < 0.05$ ). **Conclusions:** ACS NSQIP risk calculator is useful in the Mexican population, since the score obtained predicts most postoperative complications including mortality. The use of this tool offers an opportunity to improve decision-making in the care of the surgical patient.

**Keywords:** Morbidity. Mortality. Mexico.

## Correspondencia:

\*José J. Macías-Cervantes

Dr. Balmis 148

Col. Doctores, Cuauhtémoc

C.P. 06726, Ciudad de México, México

E-mail: jesusmaciascerv@gmail.com

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## Introducción

El American College of Surgeons (ACS) desarrolla desde el año 2005 el *National Surgical Quality Improvement Program* (NSQIP). Este programa recolectó información de alta calidad que incluía factores de riesgo preoperatorio y complicaciones posoperatorias de 1,414,006 pacientes provenientes de 393 hospitales pertenecientes al NSQIP<sup>1,2</sup>. La información fue utilizada por el ACS para desarrollar la calculadora de riesgo quirúrgico ACS NSQIP (<http://riskcalculator.facs.org>)<sup>2</sup>. La calculadora universal utiliza 21 variables predictoras (demográficas y comorbilidad) y el procedimiento planeado, e informa sobre ocho resultados posoperatorios a 30 días<sup>2</sup>. Cabe mencionar que esta herramienta se encuentra en constante mejora, siendo calibrada y actualizada con frecuencia para ofrecer resultados más precisos y confiables<sup>2,3</sup>.

Algunos estudios han comprobado que la precisión de la calculadora ACS NSQIP en cirugía electiva es bastante buena<sup>4-7</sup>; sin embargo, la precisión en cirugía de urgencia no ha sido ampliamente evaluada. En este escenario de urgencias, algunas series demuestran una adecuada precisión de la herramienta<sup>8,9</sup>, pero otros estudios reportan cifras subestimadas de morbilidad y mortalidad<sup>10-13</sup>. Existen pocos estudios sobre la efectividad de la calculadora ACS NSQIP en cirugía tanto electiva como de urgencia en la población mexicana<sup>14</sup>.

El objetivo de este estudio es evaluar la utilidad de la calculadora de riesgo para predecir complicaciones posquirúrgicas en pacientes operados en el escenario de urgencia por el servicio de cirugía general.

## Método

### Tipo de estudio

Se realizó un estudio prospectivo, observacional, analítico y unicéntrico.

### Población y muestra

Se registraron los datos de los pacientes sometidos a cirugía abdominal de urgencia por el servicio de patología quirúrgica aguda de cirugía general del Hospital General de México, de mayo a julio de 2019, y se vigiló la evolución clínica hasta cumplir 30 días de posoperatorio. Se obtuvo una muestra por conveniencia no probabilística con los pacientes atendidos, mismos que se registraron en la base de datos de la

clínica como población de estudio. Se excluyeron pacientes sometidos a cirugía electiva, aquellos en los que no se completó el periodo de vigilancia de 30 días de posoperatorio, los sometidos a cirugía por otro servicio quirúrgico y los que no quisieron formar parte del protocolo de estudio.

### Procedimiento y análisis estadístico

Se utilizó la calculadora de riesgo quirúrgico ACS NSQIP, que se encuentra disponible en internet (<http://riskcalculator.facs.org/RiskCalculator/index.jsp>). Dicha calculadora se utilizó para predecir las probabilidades de complicaciones posoperatorias, y se registraron el porcentaje de probabilidad y la estancia hospitalaria calculada. Se emplearon estadísticos descriptivos para la presentación de los datos analizados. Las variables ordinales se presentaron como media, mediana, rangos y varianzas, en tablas de contingencia, y para la comparación entre grupos se presentaron en gráficos de cajas. En cuanto a las variables cuantitativas, se utilizaron medias, desviaciones estándar y prueba de varianzas empleando la prueba de Levene. Se dividieron los grupos de acuerdo con los resultados obtenidos: los que no presentaron la complicación y los que sí la presentaron. Se compararon ambas poblaciones mediante la prueba t de Student y posteriormente se realizó la prueba de hipótesis utilizando la prueba no paramétrica de muestras independientes U de Mann-Whitney en todos los resultados posoperatorios posibles. Se consideró un valor de  $p < 0.05$  como criterio para rechazar la hipótesis nula de diferencias entre grupos.

### Aspectos éticos y de bioseguridad

El protocolo fue aprobado por el comité de ética del Hospital General de México, en mayo de 2019, con la clave de registro DI/19/305/03/033. La información recolectada se utilizó exclusivamente para fines académicos y de investigación. La información se manejó de tal forma que se garantizaron la protección de los derechos individuales y la confidencialidad. Se solicitó la firma del consentimiento informado a todos los pacientes para la inclusión dentro del protocolo de estudio.

## Resultados

Del periodo comprendido de mayo a julio de 2019 se logró integrar una muestra de 109 pacientes operados

por el servicio de cirugía general que cumplían los criterios de inclusión. En la tabla 1 se resumen los datos demográficos de la población de estudio, así como las variables clínicas preoperatorias predictoras que son utilizadas por la calculadora ACS NSQIP para predecir el riesgo quirúrgico para morbilidad y mortalidad.

## Resultados posoperatorios

Una vez realizadas la valoración preoperatoria y la predicción de riesgos, se sometió a los pacientes a los procedimientos quirúrgicos, siendo la apendicectomía el procedimiento más frecuente, con 53 (48.7%) intervenciones, de las cuales 38 (34.9%) fueron abiertas y 15 (13.8%) laparoscópicas. El resto de los procedimientos fueron 26 (23.9%) laparotomías exploradoras, 16 (14.7%) colecistectomías laparoscópicas y 4 (3.7%) colecistectomías abiertas, 4 (3.7%) plastias femorales, 4 (3.7%) plastias inguinales y 2 (2.7%) plastias de pared.

Los diagnósticos posoperatorios se muestran en la tabla 2.

## Frecuencia de complicaciones

Las complicaciones posoperatorias observadas se detallan en la tabla 3. Es necesario mencionar que ningún paciente presentó tromboembolia venosa o pulmonar ni evento vascular cerebral posquirúrgico.

## Comparación de resultados

Se realizó la comparación entre los resultados calculados y los observados en las variables de morbilidad y mortalidad de los pacientes operados durante el periodo de estudio. En la tabla 4 se muestra un resumen del análisis multivariado de los resultados calculados y observados, así como la comparación mediante la prueba de hipótesis mediante el test U de Mann-Whitney. Las variables de complicaciones graves, total de complicaciones, paro cardiorrespiratorio, infección de sitio quirúrgico, reintervención quirúrgica no programada, sepsis posoperatoria y mortalidad obtuvieron un valor de  $p < 0.05$ , por lo que consideramos que la calculadora de riesgo estimó adecuadamente los pacientes con probabilidad de tener dichas complicaciones. En contraste, con las variables de neumonía, infección de vías urinarias y reingreso hospitalario no fue precisa para determinar

**Tabla 1. Datos demográficos y variables clínicas preoperatorias**

	Frecuencia (n = 109)	Porcentaje (%)
Edad media, años	43 (18-88)	
Sexo		
Masculino	57	52
Femenino	52	48
Índice de masa corporal		
Normal	46	42.2
Sobrepeso	40	36.7
Obesidad	23	21.1
Estatus funcional		
Independiente	100	91.7
Parcialmente dependiente	7	6.4
Totalmente dependiente	2	1.8
Clasificación ASA		
1	17	15.6
2	57	52.3
3	31	28.4
4	3	2.8
5	1	0.9
Uso de esteroides		
No	109	100
Ascitis		
No	109	100
Sepsis preoperatoria		
No	39	35.8
SIRS	25	22.9
Sepsis	44	40.4
Choque séptico	1	0.9
Ventilación mecánica preoperatoria		
No	108	99.1
Sí	1	0.9
Cáncer diseminado		
No	107	98.2
Sí	2	1.8
Historia de EPOC grave		
No	109	100
Diabetes		
No	98	89.9
Tratamiento oral	6	5.5
Insulina	5	4.6
Hipertensión arterial sistémica		
No	93	85.3
Sí	16	14.7
Insuficiencia cardiaca preoperatoria		
No	108	99.1
Sí	1	0.9
Disnea preoperatoria		
No	109	100

(continua)

**Tabla 1. Datos demográficos y variables clínicas preoperatorias (continuación)**

	Frecuencia (n = 109)	Porcentaje (%)
Paciente fumador		
No	91	83.5
Sí	18	16.5
Uso de diálisis		
No	109	100
Falla renal preoperatoria		
No	96	88.1
Sí	13	11.9
Ajuste de cirujano		
Sin ajuste	98	89.9
Riesgo alto de complicaciones	10	9.2
Riesgo muy alto de complicaciones	1	0.9

ASA: American Society of Anesthesiologists; EPOC: enfermedad pulmonar obstructiva crónica; SIRS: síndrome de respuesta inflamatoria sistémica.

**Tabla 2. Diagnósticos posoperatorios**

	Frecuencia	Porcentaje
Apendicitis		
No complicada	25	23
Complicada	30	27
Colecistitis aguda	20	18
Hernias		
Inguinal	5	4.6
Femoral	5	4.6
Ventral	4	3.7
Cáncer	4	3.7
Perforación intestinal	3	2.8
Enfermedad diverticular complicada	2	1.8
Oclusión intestinal por adherencias	2	1.8
Enfermedad inflamatoria pélvica	2	1.8
Hernia interna	2	1.8
Íleo biliar	2	1.8
Trauma penetrante	2	1.8
Laparotomía no terapéutica	1	0.9

quiénes las presentarían, obteniendo un valor de  $p$  de 0.118, 0.256 y 0.311, respectivamente. No se incluyen la tromboembolia venosa ni la lesión renal aguda, ya que no se cuenta con muestra suficiente para realizar un análisis comparativo.

**Tabla 3. Frecuencia de complicaciones observadas**

	Frecuencia (n = 109)	Porcentaje
Mortalidad	5	4.5
Neumonía	3	2.75
Paro cardiorrespiratorio	3	2.75
Infección de sitio quirúrgico		
Superficial	5	4.6
Profunda	2	1.8
Órgano-espacio	9	8.3
Infección de vías urinarias	5	4.59
Falla renal posoperatoria	1	1.05
Reintervención quirúrgica no programada	9	8.26
Sepsis posoperatoria	11	10
Readmisión hospitalaria	3	2.75
Dehiscencia de herida quirúrgica	3	2.75

Mediante la calculadora de riesgo ACS NSQIP se estimaron los días de estancia hospitalaria ( $\bar{x}$ : 4.87 días) y se compararon con los días de estancia hospitalaria reales de los pacientes ( $\bar{x}$ : 5.37 días). Se utilizó la prueba  $t$  de Student para comparar las poblaciones, obteniendo un valor de  $p < 0.001$ .

## Discusión

En nuestro estudio se incluyeron 109 pacientes, una muestra representativa de la población general, ya que está conformada por un 47.7% de mujeres y un 52.3% de hombres, con una edad promedio de 43 años (desviación estándar:  $\pm 18.6$ ). El índice de masa corporal coincide con el de la población general, siendo ligeramente menor en cuanto a los índices de sobrepeso y obesidad, ya que obtuvimos una prevalencia combinada del 57.8%, la cual contrasta con la prevalencia combinada de sobrepeso y obesidad del 72.5% en la población mexicana adulta<sup>15</sup>.

La calculadora de riesgo ACS NSQIP es una herramienta efectiva para estimar la probabilidad de complicaciones posoperatorias en un paciente quirúrgico individual<sup>3,5</sup>. El propósito de este estudio fue determinar si la calculadora es capaz de predecir complicaciones posoperatorias en población mexicana y en escenario de urgencia. En cirugía de urgencia, el paciente tiene un riesgo más alto de complicaciones debido a la naturaleza de su enfermedad y a la incapacidad de optimizar la comorbilidad<sup>16</sup>.

Los resultados de nuestro estudio indican que el puntaje obtenido con la calculadora ACS NSQIP

**Tabla 4. Comparación de complicaciones calculadas frente a observadas**

Variables observadas	n	Riesgo calculado (%)		p
		Media	DE	
Complicaciones graves				< 0.001
No	90	8.48	6.92	
Sí	19	20.95	11.04	
Cualquier complicación				< 0.001
No	85	11.05	8.18	
Sí	24	25.03	12.40	
Neumonía posoperatoria				0.118
No	106	2.01	2.51	
Sí	3	4.26	3.05	
Paro cardiorrespiratorio				0.007
No	106	1.18	2.25	
Sí	3	6.86	5.20	
Infección de sitio quirúrgico				0.026
No	93	3.40	2.31	
Sí	16	4.41	1.27	
Infección de vías urinarias				0.250
No	104	0.79	0.98	
Sí	5	1.32	0.97	
Reingreso hospitalario				0.311
No	106	7.44	4.44	
Sí	3	10.46	6.08	
Reintervención quirúrgica no programada				0.003
No	100	2.74	2.05	
Sí	9	4.78	1.80	
Sepsis				0.011
No	98	0.49	1.15	
Sí	11	1.48	1.38	
Mortalidad				0.002
No	104	2.93	6.89	
Sí	5	25.08	20.79	

DE: desviación estándar.

predice la mayoría de las complicaciones posoperatorias, incluyendo paro cardíaco, infección de sitio quirúrgico, reoperación no programada, sepsis y mortalidad. Sin embargo, la calculadora no fue precisa para predecir la probabilidad de neumonía, infección de vías urinarias y readmisión hospitalaria, de modo similar a lo reportado en otro estudio mexicano<sup>17</sup>. En el caso de la tromboembolia pulmonar y la falla renal

aguda, la muestra fue insuficiente para determinar la precisión de la calculadora.

De manera global se compararon las poblaciones que presentaron complicaciones graves y aquellas que no lo hicieron, y mediante la prueba U de Mann-Whitney se observó que la calculadora es precisa para diferenciar los pacientes con complicaciones graves (8.48% vs. 20.95%; p < 0.001) y para predecir la presentación de cualquier complicación, incluyendo infección de sitio quirúrgico superficial, apoyo ventilatorio y Enfermedad Vascular Cerebral (EVC) (11.05% vs. 25.03%; p < 0.001).

La mortalidad global de nuestra población fue del 4.5%, siendo un total de cinco pacientes: tres por choque séptico debido a peritonitis secundaria que ameritaron manejo en la unidad de cuidados intensivos, uno que presentó broncoaspiración con diagnóstico de oclusión intestinal por adherencias, y otro que presentó falla renal aguda en el posoperatorio y no aceptó terapia de sustitución renal (de lo contrario, tenía posibilidad de mejoría). La calculadora fue capaz de predecir mortalidad posoperatoria comparando los puntajes de ambas poblaciones (2.93% vs. 25.08%; p = 0.002). Estos resultados coinciden con lo publicado en la literatura médica internacional<sup>8,9,11,16</sup>, aunque un estudio mexicano reporta una baja precisión de la calculadora en la variable de mortalidad<sup>17</sup>.

En el escenario de infección del sitio quirúrgico observamos una prevalencia del 14.68%, con una distribución del 4.6% superficial, el 1.8% profunda y el 8.3% de órgano-espacio. La prevalencia general de la infección de sitio quirúrgico es similar a la reportada en otros estudios<sup>6,8</sup>. Sin embargo, se observó una prevalencia alta de infección de órgano-espacio (8.3%) en comparación con los otros tipos de infección, lo cual puede deberse a varios factores: nuestra alta incidencia de apendicitis aguda complicada con perforación o peritonitis, el inconstante uso de antibióticos de manera preoperatoria, que puede retrasar el diagnóstico y enmascarar la patología de base, o el incremento en las resistencias bacterianas por uso de los mismos. Es necesario realizar más estudios para definir los principales factores de riesgo para la infección de sitio quirúrgico en nuestro hospital. Aunque de manera preoperatoria la calculadora de riesgo ACS NSQIP no permite incluir más de un procedimiento quirúrgico ni considera el diagnóstico de ingreso, sí pudo predecir la infección de sitio quirúrgico en nuestro estudio (3.4% vs. 4.41%; p = 0.026).

Las cirugías realizadas durante el periodo de estudio fueron, por orden de frecuencia, apendicectomía,

laparotomía y colecistectomía; estas se reportan de manera similar en la literatura, así como en los registros anuales de nuestro hospital<sup>16</sup>. Sin embargo, una parte de los pacientes requirieron más procedimientos adicionales a la cirugía planeada, como resección intestinal, anastomosis intestinal, formación de estomas, drenaje de colecciones y enterotomías, entre otros. Consideramos un defecto de la calculadora que únicamente se puede introducir un solo procedimiento planeado (Código CPT); es evidente que, si se llevan a cabo varios procedimientos de manera simultánea, se pueden alterar los resultados posoperatorios. Algunos autores han reportado que los procedimientos concurrentes impactan en la estimación de complicaciones graves en la reparación de hernia ventral<sup>6</sup>, la cistectomía radical<sup>12</sup> y la cirugía hepatobiliar<sup>13</sup>. Consideramos que la inclusión de más procedimientos adicionales en la calculadora de riesgo quirúrgico puede mejorar su precisión para predecir complicaciones.

En cuanto al tiempo de estancia hospitalaria, la calculadora estimó de manera precisa los días de estancia hospitalaria: 4.8 días calculados frente a 5.3 días observados ( $p < 0.001$ ). En algunos estudios se considera que la calculadora subestima el tiempo de estancia<sup>5,6,8,17</sup>. Vélez-Pérez et al.<sup>17</sup>, en su estudio realizado en un hospital privado de la Ciudad de México, reportan una baja precisión de la calculadora para estimar la estancia hospitalaria; sin embargo, en nuestro estudio la calculadora fue precisa.

## Limitantes del estudio

Podemos considerar que es un estudio prospectivo de un único centro hospitalario de la Ciudad de México, por lo que nuestros resultados pueden ser diferentes de los de otros hospitales mexicanos<sup>17</sup>. También consideramos que la muestra poblacional, tanto por su tamaño como por la obtención por conveniencia no probabilística, aunque es suficiente para realizar el estudio, limita el poder realizar inferencias sobre todos los resultados predichos por la calculadora de riesgo ACS NSQIP, lo cual es motivo para continuar con nuestra investigación a mayor escala.

## Conclusiones

La calculadora de riesgo ACS NSQIP es útil en la población mexicana, ya que el puntaje obtenido predice la mayoría de las complicaciones posoperatorias (paro cardíaco, infección de sitio quirúrgico, reoperación no programada, sepsis y mortalidad), y también

permite estimar los días de estancia hospitalaria de los pacientes operados en el escenario de urgencia. No obstante, es necesario realizar un estudio a mayor escala para poder definir su precisión en la población mexicana.

El uso de esta herramienta ofrece una oportunidad para mejorar la toma de decisiones en la atención del paciente quirúrgico, y así mismo plantea de manera objetiva y realista las expectativas de la cirugía y la recuperación del paciente. El NSQIP ha demostrado mejores resultados en la atención quirúrgica, con disminución en morbilidad y mortalidad, e incluso en gastos de atención en salud. Consideramos que es una buena herramienta para utilizarla en otros hospitales de nuestro país.

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Los autores declaran carecer de fuente de financiamiento.

## Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

## Responsabilidades éticas

**Protección de personas y animales.** Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

**Confidencialidad de los datos.** Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

**Derecho a la privacidad y consentimiento informado.** Los autores declaran que en este artículo no aparecen datos de pacientes.

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# Relación entre la medición por tomografía y ecografía del diámetro de la vaina del nervio óptico como estimador no invasivo de la presión intracranal

*Relationship between the measurement by tomography and ultrasound of the diameter of the optic nerve sheath as a non-invasive estimator of intracranial pressure*

Tania Rojas-Murillo\* y Natael Olvera-González

Servicio de Anestesiología, Centro Médico Naval, Ciudad de México, México

## Resumen

**Objetivo:** Comparar el diámetro de la vaina del nervio óptico (DVNO) medido por ultrasonografía (USG) y tomografía computarizada (TC) en pacientes con diagnóstico de hipertensión intracranal. **Método:** Estudio prospectivo, transversal, observacional y analítico. Se incluyeron 105 pacientes divididos en dos grupos: sanos (grupo control) y pacientes que presentaran datos clínicos de hipertensión intracranal (grupo de estudio). Se midió el DVNO por USG y TC. Para comparar el DVNO entre los pacientes se utilizó la prueba de Kruskal-Wallis, y para evaluar la correlación entre USG y TC se utilizó la prueba de Spearman. Un valor de  $p < 0.05$  fue considerado estadísticamente significativo. **Resultados:** De los 105 pacientes, el 58.1% eran hombres y el 41.9% mujeres. El grupo de estudio incluyó 14 pacientes con traumatismo craneoencefálico (TCE), evento vascular cerebral (EVC), neoplasia intracranal o neuroinfección. La mayor mediana de DVNO por USG la tuvo el grupo de EVC, seguido de los pacientes con TCE, neoplasia y neuroinfección, y la menor la tuvo el grupo control (7.5, 7.0, 6.8, 6.8 y 5.2 mm, respectivamente), siendo estas diferencias estadísticamente significativas ( $p < 0.001$ ). En el análisis de correlación entre USG y TC se encontró una buena correlación positiva estadísticamente significativa ( $\rho = 0.893$ ,  $p < 0.001$ ). **Conclusiones:** La evaluación por USG del DVNO ha demostrado ser una prueba confiable para el diagnóstico y el monitoreo no invasivo de la hipertensión intracranal.

**Palabras clave:** Neuromonitoreo. Nervio óptico. Presión intracranal.

## Abstract

**Objective:** To compare the ONSD measured by ultrasound and tomography in patients with a diagnosis of intracranial hypertension. **Method:** Prospective, transversal, observational, analytical study. 105 patients were included, divided into two groups: healthy (control group) and patients presenting clinical data of intracranial hypertension (study group). ONSD was measured by ultrasound and tomography. The Kruskal-Wallis test was used to compare the ONSD between the patients, and the Spearman test was used to assess the correlation between USG and CT. A value of  $p < 0.05$  was considered statistically significant.

## Correspondencia:

\*Tania Rojas-Murillo

Avda. H. Escuela Naval Militar 745

Coapa, Presidentes Ejidales 1ra Secc

Del. Coyoacán

C.P. 04470, Ciudad de México, México

E-mail: tatisromu7@gmail.com

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**Results:** Of the 105 patients, 58.1% were men and 41.9% women. The study group included 14 patients with TBI, CVD, intracranial neoplasia, or neuroinfection. The highest median of ONSD by Ultrasound was in the CVD group, followed by TBI, neoplasia and neuroinfection and the lowest was in the control group (7.5, 7.0, 6.8, 6.8 and 5.2 mm respectively); these differences being statistically significant ( $p < 0.001$ ). In the correlation analysis between Ultrasound and CT, a good statistically significant positive correlation was found ( $\rho = 0.893$ ,  $p < 0.001$ ). **Conclusions:** The ultrasound evaluation of ONSD has proven to be a reliable test for the diagnosis and non-invasive monitoring of intracranial hypertension.

**Keywords:** Neuromonitoring. Optic nerve. Intracranial pressure.

## Introducción

El uso de la ecografía se ha convertido en parte integral de la atención crítica en los últimos años. Proporciona una evaluación rápida, repetible y multisistémica para guiar el diagnóstico y el tratamiento de pacientes, sin requerir que estos sean transportados fuera de su entorno clínico para la obtención de imágenes<sup>1,2</sup>.

En comparación con los métodos convencionales de neuroimagen (como la tomografía computarizada [TC] o la resonancia magnética), la ultrasonografía (USG) ofrece, además, un sistema de monitorización neurológica continua<sup>3,4</sup>. El uso combinado de múltiples herramientas o «monitoreo multimodal» es frecuente en las áreas de atención de pacientes en estado crítico. Su aplicación se basa en complementar el examen neurológico y evaluar la progresión de la enfermedad en pacientes cuyas características clínicas del padecimiento se ven confundidas por los efectos de la sedación, la analgesia o el bloqueo neuromuscular, entre otros, y en pacientes comatosos (p. ej., edema cerebral grave, convulsiones e isquemia cerebral) en los que las respuestas neurológicas se acercan al mínimo y se vuelven insensibles a la evaluación clínica<sup>5</sup>.

La presión intracraneal (PIC) elevada, o hipertensión intracraneal, es un problema frecuente en los pacientes después de una lesión cerebral. No solo es un problema neurológico agudo, sino que también contribuye a malos resultados, pues se relaciona directamente con el incremento de la mortalidad, o bien puede conducir a secuelas neurológicas permanentes<sup>6,7</sup>. El incremento de la PIC puede surgir de una lesión traumática, hemorragias, lesiones ocupativas (neoplásicas), alteración de la circulación del líquido cefalorraquídeo, obstrucción de los senos venosos mayores u ocasionalmente ser idiopática. La hipertensión intracraneal prácticamente reduce el calibre de la vasculatura cerebral y, por lo tanto, reduce el flujo sanguíneo y las presiones de perfusión cerebral<sup>8,9</sup>.

El objetivo principal de la monitorización de la PIC es guiar las terapias que limitan la hipertensión intracraneal y optimizar la perfusión cerebral<sup>9</sup>. El método de referencia actual para monitorizar los cambios en la PIC es el transductor de presión intraventricular o intraparenquimatoso, colocado en el parénquima cerebral. Sin embargo, muchos pacientes pueden no recibir este monitoreo debido a los riesgos asociados, como infecciones y hemorragia, así como por la poca disponibilidad del recurso<sup>8,9</sup>.

Como resultado, se ha tratado de desarrollar métodos no invasivos, ampliamente disponibles y fáciles de usar para monitorear los cambios en la PIC de pacientes con lesiones cerebrales<sup>9,10</sup>.

El uso de la USG en el campo de la neurología fue descrito por primera vez por Karl Dussik en 1942, en la Universidad de Viena, para el diagnóstico de tumores cerebrales. A pesar de la naturaleza ecográfica impenetrable del hueso, existen dos áreas en la cabeza (de un adulto) para obtener una ventana acústica: la ventana ocular y las ventanas transcraneales en el perímetro del cráneo<sup>11</sup>.

Actualmente se puede incluir, entre muchas otras aplicaciones, la identificación de un aumento de la PIC a través de imágenes del diámetro de la vaina del nervio óptico (DVNO). En un reciente metaanálisis, Robba et al.<sup>12</sup> concluyeron que el DVNO puede ser útil para el monitoreo de la PIC, como un indicador de hipertensión intracraneal, cuando los monitores invasivos estándar no están disponibles o no están indicados<sup>12</sup>.

El nervio óptico está rodeado por las capas meníngeas y el líquido cefalorraquídeo fluye libremente entre el espacio subaracnoidal intracraneal e intraorbitario, los cuales experimentan los mismos cambios de presión. En 1968, Hayreh estableció la presencia de una comunicación constante entre el espacio subaracnoidal de la vaina del nervio óptico y la cavidad intracraneal<sup>13,14</sup>. El nervio óptico se encuentra envuelto en esta vaina que contiene líquido cefalorraquídeo, por lo que en condiciones de incremento de la PIC aumenta el diámetro de la vaina<sup>13</sup>.

Por lo tanto, el ancho (o diámetro) de la vaina del nervio óptico visto por USG es útil como medio no invasivo para evaluar los cambios de PIC, principalmente la hipertensión intracraneal<sup>14</sup>.

Se ha demostrado que las mediciones por USG de más de 5.0 mm de DVNO se correlacionan con un incremento de la PIC, y en un ensayo prospectivo mostraron una sensibilidad del 100% y una especificidad del 63% para identificar la elevación de la PIC por este método<sup>15</sup>.

El DVNO tiene utilidad para la medición de la PIC en la hemorragia intracraneal y el accidente cerebro-vascular isquémico, la meningitis y la encefalitis, y la hipertensión intracraneal idiopática<sup>16,17</sup>.

La técnica de medición del nervio óptico para estimar la PIC, basada en el concepto de que el nervio óptico es una extensión del sistema nervioso central, fue descrita por primera vez por Helmke y Hansen en 1997<sup>18</sup>.

Un DVNO «normal» en la ecografía se considera < 5.0 mm para adultos; los valores por arriba del indicado se consideran anormales<sup>2,11</sup>. Comparando modelos de regresión lineal, el DVNO es un predictor mucho más fuerte de hipertensión intracraneal en comparación con otras características de la TC<sup>18,19</sup>.

La medición por USG del DVNO se propone como una herramienta no invasiva, rápida y accesible para identificar la hipertensión intracraneal. El objetivo principal del presente estudio fue comparar y correlacionar el DVNO obtenido mediante TC y USG en pacientes con diagnóstico clínico de hipertensión intracraneal, con alguna lesión del sistema nervioso central asociada.

## Método

Se realizó un estudio prospectivo, transversal, observacional y analítico, con 105 pacientes adultos (mayores de 18 años) divididos en dos grupos: sanos (grupo control) y pacientes con alguna lesión del sistema nervioso central que presentaran datos clínicos de hipertensión intracraneal (grupo de estudio).

El grupo de estudio incluyó 14 pacientes con datos clínicos de hipertensión intracraneal y con alguna de las siguientes lesiones: traumatismo craneoencefálico, evento vascular cerebral, algún tipo de neoplasia intracraneal o diagnóstico de neuroinfección. Además de la lesión del sistema nervioso central, en la TC se evaluó la presencia de desplazamiento de la línea media, borramiento de las cisuras o edema cerebral grave sugestivo de hipertensión intracraneal. Los

datos clínicos considerados fueron la hipertensión, la bradicardia y las alteraciones en el patrón respiratorio (tríada clásica), además de alteraciones de la conciencia (somanolencia, estupor o coma), cefalea persistente progresiva, vómito expulsivo (en proyectil), papiledema, visión borrosa o tinnitus; se incluyeron aquellos pacientes con cuatro o más de estos síntomas.

Se midió el DVNO por USG en el grupo control, y por USG y TC en el grupo de estudio. Para realizar las mediciones por USG se utilizó un equipo marca Philips, modelo Affiniti 70, con transductor lineal de 7.5 MHz, en modo bidimensional a 3 mm detrás del globo ocular. La evaluación por TC se realizó con un equipo marca Siemens, Somatom Sensation 64. Se utilizaron siempre los mismos equipos en todos pacientes.

Se realizó un análisis estadístico descriptivo de la información. Las variables cualitativas se expresaron mediante frecuencias simples y porcentajes, mientras que las variables numéricas (edad, DVNO) se expresaron con mediana y rango intercuartilar (diferencia entre los percentiles 75 y 25), debido a su distribución no normal.

Los pacientes fueron agrupados en sanos y enfermos, y para comparar la distribución de las variables entre estos grupos se utilizaron las pruebas  $\chi^2$  y U de Mann-Whitney. Para comparar el DVNO entre los pacientes (sanos, traumatismo craneoencefálico, neoplasia intracraneal, evento vascular cerebral y neuroinfección) se utilizó la prueba de Kruskal-Wallis. Finalmente, para evaluar la correlación entre el DVNO por USG y TC se construyó una gráfica de dispersión de puntos y se utilizó la prueba de Spearman. Un valor de  $p < 0.05$  fue considerado como estadísticamente significativo. Este estudio se realizó bajo las condiciones éticas de la unidad.

## Resultados

Se incluyeron en el estudio 105 sujetos, de los cuales el 58.1% eran hombres y el 41.9% eran mujeres. La mediana de edad fue de 30 años y el 91.4% tenían entre 20 y 39 años (Tabla 1).

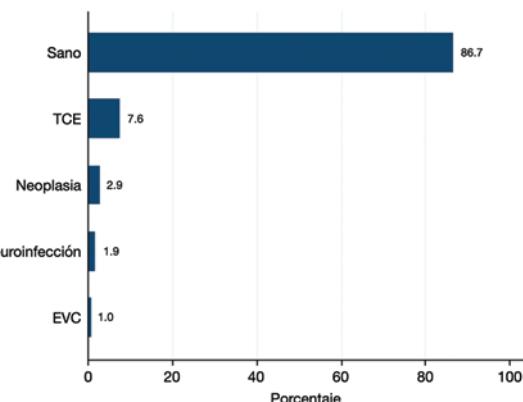
Pertenecieron al grupo control (sanos) 91 pacientes (86.7%) y en el grupo de estudio se incluyeron 14 pacientes: ocho con traumatismo craneoencefálico, tres con neoplasia intracraneal, dos con neuroinfección y uno con evento vascular cerebral (Fig. 1).

Al comparar los sujetos sanos y enfermos, se encontró que la mediana de edad fue mayor en el grupo

**Tabla 1. Características generales de los pacientes**

Características	n = 105
Sexo	
Masculino	61 (58.1%)
Femenino	44 (41.9%)
Edad, años	30 ± 4
20-39	96 (91.4%)
40-59	7 (6.7%)
60 y más	2 (1.9%)
Grupos de pacientes	
Sanos	91 (86.7%)
Trauma craneoencefálico	8 (7.6%)
Neoplasia intracranial	3 (2.9%)
Neuroinfección	2 (1.9%)
Evento vascular cerebral	1 (1%)

Los datos se muestran como número (%) o mediana ± rango intercuartil.



**Figura 1.** Gráfica que muestra la distribución de los pacientes. EVC: evento vascular cerebral; TCE: trauma craneoencefálico.

**Tabla 2. Características en los sujetos enfermos y sanos**

Características	Enfermos	Sanos	Ambos grupos	p*
n	14	91	105	
Sexo				
Masculino	7 (50%)	54 (59.3%)	61 (58.1%)	
Femenino	7 (50%)	37 (40.7%)	44 (41.9%)	0.510
Edad, años	45 ± 16	30 ± 4	30 ± 4	< 0.001
20-39	6 (42.9%)	90 (98.9%)	96 (91.4%)	
40-59	6 (42.9%)	1 (1.1%)	7 (6.7%)	
60 y más	2 (14.3%)	0 (0%)	2 (1.9%)	< 0.001
DVNO por USG, mm	6.9 ± 0.5	4.2 ± 0.4	5.2 ± 0.5	< 0.001
DVNO por TC, mm	6.8 ± 0.4	ND	6.8 ± 0.4	ND

DVNO: diámetro de la vaina del nervio óptico; ND: no disponible; TC: tomografía computarizada; USG: ultrasonografía.

Los datos se muestran como número (%) o mediana ± rango intercuartil.

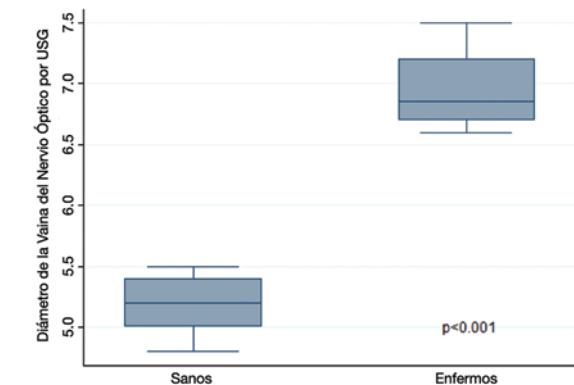
\*Valor de p mediante prueba  $\chi^2$  o U de Mann-Whitney.

de enfermos (45 vs. 30 años;  $p < 0.001$ ), con diferencias en la distribución por grupos de edad. En la distribución por sexo no se encontraron diferencias entre los grupos (Tabla 2).

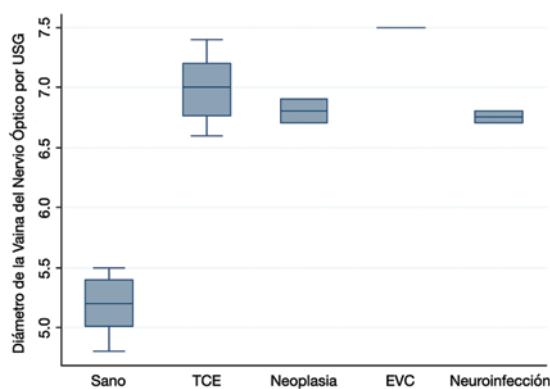
La mediana del DVNO por USG fue notoriamente superior en el grupo de enfermos (6.9 mm) que en el de sanos (4.2 mm;  $p < 0.001$ ) (Fig. 2).

La mayor mediana del DVNO por USG la tuvo el grupo con evento vascular cerebral, seguido de los pacientes con traumatismo craneoencefálico, neoplasia y neuroinfección, y la menor la tuvo el grupo control (7.5, 7.0, 6.8, 6.8 y 5.2 mm, respectivamente), siendo estas diferencias estadísticamente significativas ( $p < 0.001$ ) (Fig. 3).

Además de la medición por USG, se realizó estudio de TC de cráneo al grupo de estudio y se midió el DVNO también por este método (Tabla 3).



**Figura 2.** Diámetro medido de la vaina del nervio óptico por USG en sanos y enfermos. USG: ultrasonografía.



**Figura 3.** Diámetro de la vaina del nervio óptico medido por USG de acuerdo con el tipo de paciente. EVC: evento vascular cerebral; TCE: trauma craneoencefálico; USG: ultrasonografía.

Con relación a las mediciones de DVNO por TC realizadas en los pacientes enfermos, estas fueron muy similares entre los grupos ( $p = 0.406$ ) (Fig. 4).

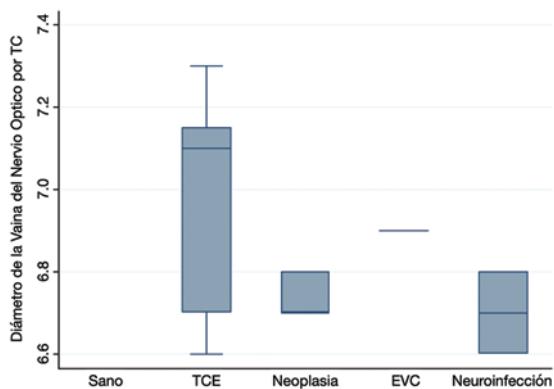
**Tabla 3.** Diámetro de la vaina del nervio óptico según el grupo de pacientes

Grupos	DVNO por USG	DVNO por TC
Sanos	5.2 ± 0.4	ND
Trauma craneoencefálico	7.0 ± 0.5	7.1 ± 0.5
Neoplasia intracranal	6.8 ± 0.2	6.7 ± 0.1
Neuroinfección	6.8 ± 0.1	6.7 ± 0.2
Evento vascular cerebral	7.5 ± 0	6.9 ± 0
p*	< 0.001	0.406

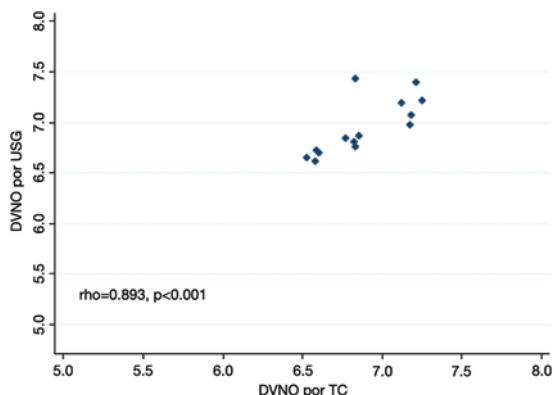
DVNO: diámetro de la vaina del nervio óptico; ND: no disponible; TC: tomografía computarizada; USG: ultrasonografía.

Los datos se muestran como número (%) o mediana ± rango intercuartílico.

\*Valor de p mediante prueba  $\chi^2$  o U de Mann-Whitney.



**Figura 4.** Diámetro de la vaina del nervio óptico medido por TC de acuerdo con el tipo de paciente. EVC: evento vascular cerebral; TC: tomografía; TCE: trauma craneoencefálico.



**Figura 5.** Correlación entre el diámetro de la vaina del nervio óptico (DVNO) por ultrasonografía (USG) y tomografía computarizada (TC) en pacientes enfermos. DVNO: diámetro de la vaina del nervio óptico; TC: tomografía; USG: ultrasonografía.

En el análisis de correlación entre el DVNO por USG y TC en el grupo de estudio, se encontró una buena correlación positiva estadísticamente significativa ( $\rho = 0.893$ ;  $p < 0.001$ ) (Fig. 5).

## Discusión

Las imágenes son indispensables en el diagnóstico y el manejo del paciente con enfermedad neurológica, quizás más que en otra área de la medicina<sup>18,19</sup>.

Los cambios del DVNO y la medición por USG parecen relacionarse de manera más lineal con el aumento de la PIC; esta relación y la alta sensibilidad demostrada proporcionan una herramienta útil para descartar la hipertensión intracraneal como causa del estado mental alterado en un paciente crítico<sup>19</sup>.

Se estima que la curva de aprendizaje para los médicos experimentados en el uso de la USG puede incluir tan solo 10 pacientes para realizar el estudio con precisión, mientras que los médicos que no están familiarizados con la USG pueden necesitar cerca de 25 escaneos para obtener la destreza necesaria y evaluar con precisión el DVNO<sup>20</sup>.

Son múltiples las causas de elevación de la PIC, por lo que se consideró incluir en este estudio distintas patologías que afectan al sistema nervioso central. La finalidad en este trabajo fue evaluar a los pacientes con datos clínicos de hipertensión intracraneal, independientemente del factor desencadenante, pero que de acuerdo con los resultados pudiera encontrarse una relación directa con la causa específica.

El grupo control fue útil para adquirir una mayor habilidad en la evaluación por USG del nervio óptico y su medición en sujetos sanos. La muestra obtenida del grupo de estudio fue uniforme en cuanto al sexo de los pacientes evaluados (50% hombres y 50% mujeres), y más del 75% se encontraban en un rango de edad de 28 a 49 años, con una media de 45.4 años y una mediana de 45, mostrando una distribución normal o similar en el grupo de pacientes con datos de hipertensión intracraneal.

Se observó que el 100% de los pacientes con diagnóstico clínico de hipertensión intracraneal y con una lesión neurológica asociada presentaron un aumento del DVNO, medido con USG y corroborado por TC, y de acuerdo con nuestros resultados existe una fuerte correlación positiva entre ambos métodos, la cual se consideró estadísticamente significativa ( $p < 0.001$ ).

El presente estudio demuestra que la medición del DVNO por USG es un método no invasivo, de bajo costo, fácil de operar y que puede realizarse a la cabecera del paciente, y que debe considerarse en el abordaje inicial del paciente neurocrítico y para el monitoreo estrecho de su evolución.

## Conclusiones

La PIC elevada es una condición común con malos resultados clínicos y altas tasas de mortalidad. El objetivo principal de la monitorización de la PIC es guiar las terapias que limitan la hipertensión intracranal, optimizar la perfusión cerebral e implementar y evaluar la respuesta a las intervenciones realizadas.

Actualmente, la ecografía enfocada es utilizada por varias especialidades en diversas situaciones de monitoreo, diagnóstico y de intervención. Las mediciones del DVNO se correlacionan con mediciones no invasivas e invasivas de la PIC y con los hallazgos tomográficos de las diferentes lesiones cerebrales que pueden ser la causa de la elevación de la PIC. La evaluación por USG del DVNO ha demostrado ser una prueba confiable para el diagnóstico no invasivo de PIC elevada en pacientes neurocríticos.

Debe reconocerse que ningún monitor al final cambiará el resultado. En cambio, cómo se integra e interpreta esa información en la toma de decisiones es lo que influirá en la evolución del paciente.

## Financiamiento

Los autores declaran no haber recibido financiamiento.

## Conflicto de intereses

Los autores declaran no tener conflictos de intereses.

## Responsabilidades éticas

**Protección de personas y animales.** Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

**Confidencialidad de los datos.** Los autores declaran que en este artículo no aparecen datos de pacientes.

**Derecho a la privacidad y consentimiento informado.** Los autores declaran que en este artículo no aparecen datos de pacientes.

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# Heridas por asta de toro, análisis de 138 casos

*Bull horn injuries, analysis of 138 cases*

Aníbal A. Medina-Velasco<sup>1\*</sup>, Vladimir Arteaga-Peralta<sup>1</sup>, Roberto De la Plaza-Llamas<sup>1</sup>, Miguel Torralba-González de Suso<sup>2</sup>, Aylhin López-Marcano<sup>1</sup>, Daniel A. Díaz-Candelas<sup>1</sup>, M. Dolores Picardo-Gomendio<sup>1</sup>, Raquel Latorre-Fragua<sup>1</sup> y José M. Ramia-Ángel<sup>1</sup>

<sup>1</sup>Servicio de Cirugía General y del Aparato Digestivo; <sup>2</sup>Servicio de Medicina Interna, Unidad de Investigación. Hospital Universitario de Guadalajara, Guadalajara, España

## Resumen

**Objetivo:** Las heridas por asta de toro (HAT) poseen características únicas y existe literatura escasa en esta área. Presentamos un análisis de 11 años de pacientes con HAT. **Método:** Estudio retrospectivo y analítico de 138 casos durante un periodo de 11 años, de pacientes ingresados durante más de 24 horas por HAT. Clasificamos a los pacientes en dos grupos: grupo A, sometidos a procedimientos bajo anestesia general, y grupo B, sometidos a procedimientos bajo anestesia local. Variables recogidas: edad, sexo, mes del suceso, hospitalización (días), región afectada, Comprehensive Complication Index (CCI), Injury Severity Score (ISS), ingreso y estancia en la unidad de cuidados intensivos (UCI) y mortalidad. **Análisis estadístico:** t de Student, ANOVA,  $\chi^2$ , regresión lineal y logística. **Resultados y conclusiones:** El ISS se relaciona directamente con la estancia hospitalaria, el CCI, el ingreso en UCI y el tratamiento recibido. Entre ambos grupos se evidenció una diferencia significativa en edad, ISS y estancia hospitalaria, siendo mayores en el grupo A. Existe un mayor riesgo de necesitar cirugía conforme aumentan la edad, el ISS y las heridas en tórax, abdomen o pelvis. El CCI puede ser un buen método para cuantificar la morbilidad posoperatoria en pacientes politraumatizados o con lesiones en otras áreas distintas del abdomen.

**Palabras clave:** Ganado. Lesiones. Heridas penetrantes. Trauma. Heridas.

## Abstract

**Objective:** Bull-horn injuries (BHI) are unique and there is reduced published literature about it. We present an analysis of a 11-year BHI case series. **Method:** Study of 138 cases developed during a 11-year period with hospitalization admission greater than 24 hours with diagnosis of BHI/contusion. We classified patients in two groups: group A, patients undergoing procedures under general anaesthesia and group B undergoing procedures under local anaesthesia. Variables: age, sex, date, hospitalization length, main region affected, Comprehensive complication index (CCI), ISS, intensive care unit (ICU) admission, stay and mortality. Statistical analysis: t-Student test, ANOVA,  $\chi^2$  and linear or logistic regression. **Results and conclusions:** ISS was related to hospital stay, CCI, ICU admission and type of treatment applied. The comparative statistical analysis of variables between both groups determined a significant difference in age, ISS and hospitalization length, being greater in those belonging to group A. There is a more risk of undergoing surgery by increasing age, ISS and presenting the wounds in thorax-abdomen-pelvis area. CCI may be a good method of quantifying postoperative morbidity in polytraumatized patients or in other areas besides the abdomen.

**Keywords:** Cattle. Injuries. Penetrating wounds. Trauma. Wounds.

### Correspondencia:

\*Aníbal A. Medina-Velasco

Calle Valencia, 1

Algete C.P. 28110, Madrid, España

E-mail: animedv90@gmail.com

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## Introducción

Las heridas por asta de toro (HAT) ocurren con frecuencia en zonas donde los festejos taurinos son práctica habitual, especialmente en Iberoamérica<sup>1-3</sup>. La *tauromaquia*, de ταῦπος, *taūros* (toro), y μάχομαι, *máchomai* (luchar), se define como el espectáculo en el que el toro y el peleador (a pie o a caballo) se enfrentan<sup>3</sup>. Las HAT suelen producir daños tan graves que toda persona que las sufre debe ser considerada como un paciente politraumatizado. Los avances en la cirugía en estos pacientes han permitido reducir hasta el 5% la mortalidad en HAT que en otros tiempos eran mortales<sup>2</sup>.

La provincia de Guadalajara, en España, con una población aproximada de 253,000 habitantes en el año 2017, celebra entre 500 y 600 festejos taurinos al año<sup>4,5</sup>. Las HAT tienen unas características propias dentro de los pacientes politraumatizados, tales como desgarros tisulares amplios, múltiples trayectos de lesión, presencia de cuerpos extraños e inoculación masiva de gérmenes, pudiendo comprometer la vida<sup>1</sup>. La mortalidad, generalmente secundaria a shock hipovolémico y sepsis, suele ser menor del 5%<sup>1,3</sup>. En la actualidad existe literatura escasa y heterogénea, siendo objeto de investigación en las zonas de elevada incidencia. Como objetivo de este estudio, presentamos un análisis estadístico basado en la morbilidad de 138 casos de HAT en los últimos 11 años en nuestro hospital.

## Método

Estudio de serie de casos consecutivos, retrospectivo, analítico y observacional, desarrollado en el Hospital General Universitario de Guadalajara (hospital de segundo nivel) durante el periodo de enero de 2006 a diciembre de 2016. Se revisaron las historias clínicas electrónicas (Mambrino XXI®) de ese periodo de pacientes atendidos por el servicio de urgencias, según manejo ATLS (*Advanced Trauma Life Support*) e ingresados durante más de 24 horas con el diagnóstico de «herida/traumatismo por asta de toro». La disponibilidad de la atención por parte del servicio de urgencias fue de 24 horas durante los 7 días de la semana, con posibilidad de recursos para reanimación, cirugía y cuidados intensivos de la mayoría de los pacientes politraumatizados (nivel III de trauma según la clasificación americana). Además del tratamiento específico en función del órgano afectado, el

tratamiento quirúrgico bajo anestesia general consistió en el lavado de la herida con solución antiséptica, Friedrich y sutura de piel sobre drenajes no aspirativos. En la mayoría de los casos se utilizó para el cierre de la herida material de sutura no reabsorbible, utilizando el reabsorbible en ocasiones para sitios de mayor profundidad a la piel. En los procedimientos de cirugía bajo anestesia local se utilizó mepivacaína al 1%, con posterior limpieza de la herida con solución antiséptica y sutura de la piel con colocación de drenajes no aspirativos. La terapia antimicrobiana fue de amplio espectro, con pauta empírica de amoxicilina-ácido clavulánico o gentamicina más metronidazol en caso de alergia a los betalactámicos, modificándose en función de la antibioticoterapia específica en casos de infección de las heridas. El tipo de traumatismo atendido en este ámbito fue variable, desde una simple contusión o laceración por asta de toro hasta desgarros musculares amplios, con penetración a la cavidad abdominal/torácica, pudiendo estar acompañados de lesiones viscerales o vasculares.

Clasificamos a los pacientes en dos grupos según el tipo de tratamiento empleado: el grupo A incluyó aque-lllos sometidos a procedimientos bajo anestesia general y el grupo B aquellos con procedimientos bajo anestesia local. Se excluyeron del análisis por grupos los pacientes que no fueron intervenidos quirúrgicamente (10 pacientes). Las variables estudiadas en ambos grupos fueron edad, sexo, mes del suceso, días de hospitalización, región principal afectada, *Comprehensive Complication Index* (CCI) (solo el grupo A), complicación y número de complicaciones (solo el grupo B), *Injury Severity Score* (ISS), ingreso y estancia en la unidad de cuidados intensivos (UCI), y mortalidad.

El análisis estadístico fue realizado mediante el software SPSS v.20. Para la descripción de las variables categóricas y cuantitativas se utilizaron las frecuencias y medianas y el rango intercuartil (RI), respectivamente. Para la comparación de medias de las variables entre ambos grupos se utilizó la prueba t student o ANOVA para las variables cuantitativas, y la prueba de  $\chi^2$  para las cualitativas. Para el análisis multivariable se realizó regresión lineal o logística en función de que la variable dependiente fuese lineal o binaria. Todos los contrastes fueron en dos colas y se consideró significación estadística un valor de  $p < 0.05$ .

## Resultados

Se analizaron 138 casos, con una mediana de edad de 34.7 años, de los cuales 10 fueron mujeres (7%)

y 128 fueron hombres (93%). Los meses de mayor incidencia fueron agosto y septiembre (35% y 38%, respectivamente). La mediana de hospitalización fue de 5 días (RI: 4-9). La región principal afectada fueron los miembros inferiores, con 83 casos (60%), seguidos del tronco (tórax, abdomen y pelvis) con 45 casos (33%), los miembros superiores con 6 casos (4%), y cabeza y el cuello con 4 casos (3%) (Fig. 1). El ISS tuvo una mediana de 1 punto (RI: 1-9). El ingreso en UCI fue necesario en 12 pacientes (9%), con una mediana de estancia de 8,5 días (RI: 2-21). En nuestra serie no hubo fallecimientos (Tabla 1). El análisis descriptivo por grupos resultó según lo reflejado en la tabla 2.

La intervención quirúrgica más frecuente fue Friedrich (50%), seguida de la laparotomía exploradora (10%); el resto de las intervenciones se detallan en la tabla 3.

El análisis estadístico comparativo de variables entre ambos grupos determinó una diferencia significativa con respecto a edad, ISS y días de hospitalización, siendo mayor en los pertenecientes al grupo A. Por otra parte, en dicho grupo hubo una predominancia de localización de HAT en el tórax, el abdomen y la pelvis (50.7%), a diferencia del grupo B (15.4%), en el que predominaron en los miembros inferiores o superiores (*odds ratio [OR]*: 5.66; intervalo de confianza del 95% [IC95%]: 2.5-12.9;  $p < 0.001$ ). El resto de las variables no arrojaron diferencias significativas (Tabla 4).

El análisis estadístico multivariante (ajustado por edad y sexo) en la población total mostró que el ISS se relaciona con la estancia hospitalaria, la morbilidad posoperatoria (CCI), el ingreso en UCI y el tipo de tratamiento aplicado (grupo A o grupo B). Si el ISS se incrementa en una unidad, la estancia media hospitalaria se prolonga 0.39 días (IC95%: 0.19-5.59;  $p < 0.001$ ). Por cada incremento en una unidad de ISS aumenta en 1.04 puntos el CCI (IC95%: 0.50-1.59;  $p < 0.001$ ). Además, los pacientes con mayor ISS incrementan su probabilidad de ingreso en UCI (*OR*: 1.23; IC95%: 1.11-1.37;  $p < 0.001$ ). De igual modo, por cada incremento en 1 unidad de ISS, la probabilidad de presentar un tratamiento del grupo A se incrementa en un 14% (*OR*: 1.14; IC95%: 1.07-1.22;  $p < 0.001$ ). Por último, a su vez, por cada incremento en 1 unidad del ISS, la frecuencia de las HAT en las regiones expuestas a traumatismos viscerales (tórax, abdomen y pelvis) se incrementa en un 20% (*OR*: 1.20; IC95%: 1.12-1.29;  $p < 0.001$ ) (Tabla 5).

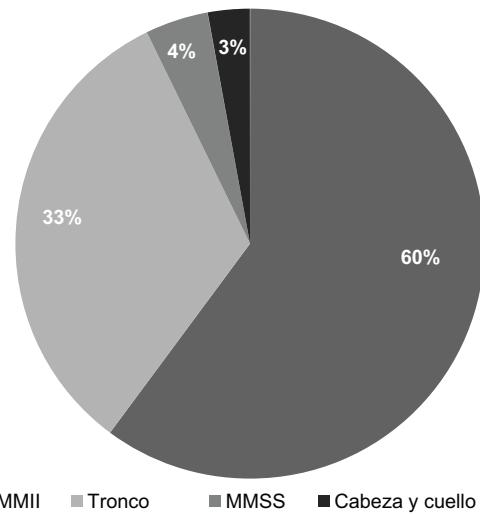


Figura 1. Distribución de las heridas por asta de toro, región principal afectada. MMII: miembros inferiores; MMSS: miembros superiores.

Tabla 1. Características principales de los pacientes con heridas por asta de toro

Edad, mediana (RI)	34 (26-50)
Hombre	128 (93%)
Mujer	10 (7%)
Mes del evento	Agosto (35%) y septiembre (38%)
Tiempo de hospitalización, mediana (RI)	5 (4-9) días
Grupo A, casos	72 (52%)
Grupo B, casos	66 (48%)
ISS, mediana (RI)	1 (1-9) puntos
Ingreso en UCI	12 casos (9%)
Estancia en UCI, mediana (RI)	9 días (2-21)
Fallecimientos	0%

ISS: Injury Severity Score; RI: rango intercuartil; UCI: unidad de cuidados intensivos.

## Discusión

Las HAT son lesiones con elevada incidencia en países donde la práctica recreativa del toreo es frecuente<sup>1</sup>. Nuestra serie coincide demográficamente con las principales publicadas en la literatura, siendo más frecuente la afectación del sexo masculino y con una media de edad entre la segunda y la tercera décadas de la vida<sup>1,2,6-8</sup>. Shukla et al.<sup>8</sup> han descrito otro subgrupo de pacientes en zonas rurales de la India en los que predomina el sexo femenino. Esto podría

**Tabla 2. Descripción por grupos de los pacientes con heridas por asta de toro**

Variables	Grupo A	Grupo B
Casos	72 (52%)	66 (48%)
Edad en años, mediana (RI)	39 (29-52)	31 (23-42)
Hombres	67 (93%)	61 (92%)
Mujeres	5 (7%)	5 (8%)
Tiempo de hospitalización, mediana (RI)	6 (4-9) días	4 (4-7) días
ISS, mediana (RI)	7 (1-16) puntos	1 (1-1) puntos
Ingreso en UCI	9 (13%) casos	3 (5%) casos
Estancia en UCI, mediana (RI)	15 (5-26) días	2 (1-2) días

ISS: Injury Severity Score; RI: rango intercuartil; UCI: unidad de cuidados intensivos.

explicarse porque la interacción con estos animales es con finalidad laboral y no recreativa, pudiendo haber predominio del sexo femenino en este ámbito.

El periodo anual más frecuente son los meses de agosto y septiembre, verano en España, fechas en las que son más frecuentes las fiestas locales. Para disminuir la morbilidad y la mortalidad es necesaria la disposición de un servicio médico-quirúrgico permanente o temporal en cercanía a las instalaciones donde se celebren espectáculos taurinos<sup>2</sup>. También se podría plantear la dotación con más personal sanitario a los centros hospitalarios de referencia en los meses en que prevalecen los festejos, especialmente en provincias con mayor cantidad de festejos taurinos al año, considerando nuestra provincia como perteneciente a este grupo.

La mediana de estancia hospitalaria en nuestro centro fue casi un 50% menor que en la mayoría de las series (5 días), encontrándose en estas una media de 10-15 días<sup>1,3,7,9</sup>.

Las características de las HAT dependen del mecanismo de lesión, ligada al contexto de convivencia con el animal (festividad, crianza). Las cornadas no están condicionadas solo por la forma del asta, sino principalmente por la clase de toro y el sentido o la disposición de este durante la cornada. Por leyes de balística y de agresiones por arma blanca, en estas existe una relación directa entre la posición del agredido y el arma, pero en las HAT este principio no se cumple del todo, pudiendo encontrar trayectos y lesiones graves a distancia de la puerta de entrada de la cornada. Sin embargo, lo que sí está relacionado es la disposición del agredido, ya que difiere si está

**Tabla 3. Procedimientos quirúrgicos en pacientes con heridas por asta de toro**

Tipo	Frecuencia	Porcentaje
Friedrich	58	50
Laparotomía exploradora	11	10
Sutura diafragmática	4	4
By-pass femoropoplíteo	4	4
Sutura intestinal	3	3
Toracostomía: tubo de tórax Argyll	3	3
Reducción y osteosíntesis	3	3
Reparación parietal abdominal	3	3
Artrodesis	2	2
Clavo intramedular	2	2
Hepatectomía	2	2
Resección intestinal	2	2
Packing abdominal	2	2
Colostomía	2	2
Reconstrucción auricular	1	1
Procedimiento endovascular	1	1
Colgajo cutáneo	1	1
Esfinteroplastia	1	1
Reconstrucción peneana	1	1
Sutura pulmonar	1	1
Reconstrucción de mucosa anal	1	1
Cistostomía	1	1
Nefrectomía	1	1
Colectomía	1	1
Sutura de párpado	1	1
Resección clavicular (parcial)	1	1
Stent endovascular	1	1
Anastomosis venosa poplítea	1	1
Total	115	100

en sedestación o en decúbito. Al encontrarse con los músculos tensos durante el movimiento o de pie, el desgarro muscular puede ser de mayor profundidad y, por ende, de mayor gravedad<sup>10</sup>.

Nuestro sitio de lesión más frecuente en ambos grupos fueron los miembros inferiores, similar a lo encontrado en la literatura<sup>1-3,11</sup>. Sin embargo, esta frecuencia

**Tabla 4. Análisis comparativo de variables entre ambos grupos**

Variables	Grupo A	Grupo B	p	Diferencias de media	IC95%
Edad. años	41.3	35.1	0.024	6.2	0.84-11.52
ISS	8.8	3.1	< 0.001	5.69	3.25-8.12
Días hospitalización, mediana	9.3	5.5	0.01	3.8	0.95-6.66

IC95%: intervalo de confianza del 95%; ISS: *Injury Severity Score*.**Tabla 5. Análisis multivariable ajustado por edad y sexo**

Variables	Coeficiente/ OR*	p	IC95%
			Coeficiente/OR*
Días de hospitalización	0.39	< 0.001	0.19-5.59
CCI (puntuación)	1.04	< 0.001	0.50-1.59
Ingreso en UCI*	1.23	< 0.001	1.11-1.33
Tipo de tratamiento (grupo A)*	1.14	< 0.001	1.07-1.22
Heridas viscerales vs. miembros superiores e inferiores*	1.2	< 0.001	1.12-1.29

\*Análisis mediante OR. CCI: *Comprehensive Complication Index*; IC95%: intervalo de confianza del 95%; OR: *odds ratio*; UCI: unidad de cuidados intensivos.

cambia en el análisis por grupos, ya que en los intervenidos quirúrgicamente la región afectada con mayor frecuencia fue el tórax-abdomen-pelvis, probablemente secundario a una mayor gravedad del politraumatismo, al estar propensos a lesiones viscerales en estas regiones, que a su vez coincidió con un mayor puntaje de ISS en este grupo. Por otra parte, en una serie de 101 casos relacionados con el ámbito laboral predominaron las lesiones perineales y toracoabdominales<sup>7,9</sup>. Posiblemente se deba a que los pacientes en ese momento no se encontrasen en estado de alerta, o en disposiciones en el área laboral distintas a las de huida, como suelen encontrarse en los festejos taurinos. En la mayoría de las series, como en la nuestra, el tratamiento predominante fue quirúrgico<sup>1-3,7-9,11</sup>.

El CCI es una herramienta cuantitativa (0-100) para calcular la morbilidad posoperatoria, englobando todos los datos recolectados mediante la clasificación de Clavien-Dindo en los pacientes intervenidos quirúrgicamente, evitando señalar solo la complicación mayor, lo cual puede ser un sesgo<sup>12,13</sup>. Cabe destacar que esta última está diseñada para procedimientos en el ámbito de la cirugía general, sin incluir la cirugía en extremidades<sup>12</sup>. La región afectada con mayor frecuencia en nuestro estudio fueron los miembros

inferiores, realizando como tratamiento quirúrgico procedimientos de partes blandas en su mayoría (p. ej., Friedrich), pudiendo extrapolarse a procedimientos de cirugía general (p. ej., hernioplastias, linfadenectomías). Los estudios en el área de la cirugía ortopédica están comenzando a aplicar el CCI en la cirugía de miembros<sup>14</sup>. Debido a esto, hemos decidido emplearlo como herramienta de recolección de la morbilidad, siendo el primer estudio en la literatura de HAT que lo utiliza, englobando complicaciones que pudieran pasar desapercibidas en otras series.

Las complicaciones más frecuentes publicadas en otras series fueron infección de herida/absceso y necrosis cutánea<sup>1-3,7,11</sup>. En nuestra serie, en los pacientes que no se realizaron procedimientos en el quirófano de forma inicial, la complicación más frecuente fue el hematoma, seguido de infección de herida/absceso que necesitó drenaje, remarcando la importancia de la adecuada exploración quirúrgica, Friedrich y cura de la herida.

Al ser considerados como pacientes politraumatizados, cuantificamos el grado de afectación mediante el ISS, siendo realizado previamente solo por García-Marín et al.<sup>3</sup>; sin embargo, estos autores utilizan una medida de tendencia central (media) no adecuada para el análisis del mismo. En nuestro estudio, al correlacionar el ISS con la morbilidad posoperatoria (CCI), el tipo de tratamiento, la estancia hospitalaria y la necesidad de UCI, conseguimos una relación directa entre la magnitud/gravedad del traumatismo y el pronóstico del paciente, siendo el primer estudio analítico de la literatura de HAT.

## Conclusiones

Existe un mayor riesgo de ser intervenido quirúrgicamente conforme aumentan la edad, el ISS y las zonas de riesgo de lesión visceral (tórax, abdomen y pelvis). El ISS se relaciona directamente con la estancia hospitalaria, la morbilidad posoperatoria (CCI) y el ingreso en UCI, así como también el tipo de tratamiento a recibir, apuntando más hacia el quirúrgico

cuanto mayores sean el ISS y la edad de los pacientes con HAT. Consideramos que el CCI puede ser un buen método de cuantificación de la morbilidad posoperatoria en los pacientes politraumatizados o con lesiones en otras zonas además del abdomen. Con respecto a los parámetros descriptivos, el resto de los resultados fueron similares a los de otras series: la mayoría de los pacientes con HAT son de sexo masculino, predominan los miembros inferiores como sitio de lesión principal y ocurren en la época del año en que son más frecuentes los festejos taurinos.

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## Conflicto de intereses

Los autores declaran no tener conflicto de intereses con la realización de este estudio.

## Responsabilidades éticas

**Protección de personas y animales.** Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

**Confidencialidad de los datos.** Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

**Derecho a la privacidad y consentimiento informado.** Los autores declaran que en este artículo no aparecen datos de pacientes.

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# Infarto cerebral embólico como complicación perioperatoria de un mixoma auricular

*Embolic stroke as a perioperative complication of atrial myxoma*

Yuri Medrano-Plana<sup>1\*</sup>, Carlos E. Hernández-Borrotto<sup>2</sup>, Ramón González-Chinea<sup>3</sup>, Gustavo de Jesús Bermúdez-Yera<sup>4</sup>, Ernesto Chaljub-Bravo<sup>4</sup> y Yoandy López-De la Cruz<sup>4</sup>

<sup>1</sup>Facultad de Ciencias Médicas, Universidad Laica Eloy Alfaro de Manabí, Manta, Ecuador; <sup>2</sup>Servicio de Salud Metropolitano Norte, Santiago de Chile, Chile; <sup>3</sup>Servicio de Imagenología, Hospital Básico del Instituto Ecuatoriano de Seguridad Social, Esmeralda, Ecuador; <sup>4</sup>Servicio de Cirugía Cardiovascular, Cardiocentro Ernesto Che Guevara, Villa Clara, Cuba

## Resumen

*El accidente cerebrovascular perioperatorio es una de las complicaciones que pueden presentarse durante el proceder quirúrgico y hasta los 30 días posteriores al mismo. Se presenta el caso de una mujer de 52 años, sin síntomas neurológicos y con diagnóstico de masa intracardiaca. Se le realizó cirugía cardiaca con resección del tumor, que resultó compatible con mixoma auricular. En el posoperatorio inmediato presentó sintomatología neurológica y se diagnosticó infarto de ganglios basales de etiología embólica. El accidente cerebrovascular perioperatorio aparece con mayor frecuencia en las cirugías cardiovasculares, pero rara vez es reportado en cirugías de exéresis de tumores cardíacos.*

**Palabras clave:** Accidente cerebrovascular. Cirugía torácica. Mixoma.

## Abstract

*Perioperative stroke is one of the complications that can occur during the surgical procedure and up to 30 days after it. A 52-year-old woman with no neurological symptoms and a diagnosis of intracardiac mass. She underwent cardiac surgery with resection of the tumor that was compatible with atrial myxoma. In the immediate postoperative, she presented neurological symptoms and was diagnosed with basal ganglia infarction of embolic etiology. Perioperative stroke appears most frequently in cardiovascular surgery but is rarely reported in heart tumor resection surgery.*

**Keywords:** Stroke. Thoracic surgery. Myxoma.

## Introducción

La cirugía es considerada uno de los pilares terapéuticos de importancia en todo el mundo, ya que existen diversas enfermedades que requieren de ella como método de tratamiento. Esta puede ser

realizada de manera electiva o urgente, y está asociada a la aparición de complicaciones, que ocurren no solo durante el proceder quirúrgico, sino hasta en los 30 días posteriores. El riesgo de complicaciones producto de la cirugía depende tanto de la enfermedad del paciente como de la existencia de

### Correspondencia:

\*Yuri Medrano-Plana

Calle, 314

Conjunto habitacional RANIA,  
C.P. 130802 Manta, Manabí, Ecuador

E-mail: yuri.medrano@uleam.edu.ec  
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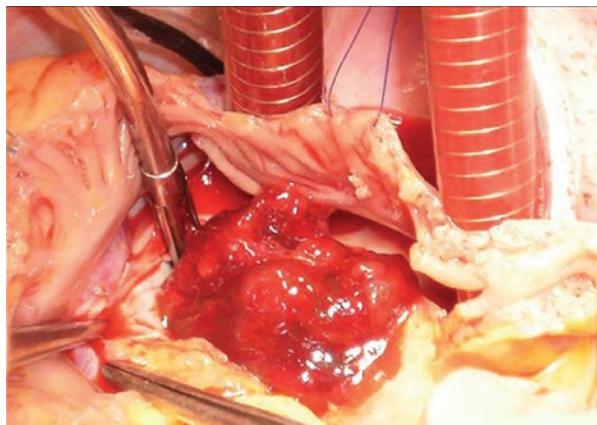
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**Figura 1.** Mixoma auricular. Se aprecian las características macroscópicas de su superficie.

comorbilidad, el tipo de cirugía y la magnitud y la duración del procedimiento. El accidente cerebrovascular perioperatorio puede aparecer como una de estas complicaciones, asociándose a diferentes grados de morbilidad. La mayoría ocurren dentro del primer día posoperatorio, siendo el accidente cerebrovascular isquémico el que con más frecuencia se reporta en relación con el hemorrágico<sup>1</sup>.

## Caso clínico

Mujer de 52 años, con antecedentes de asma bronquial y episodios de disnea de esfuerzo de más de 6 meses de evolución. Fue evaluada en su área de salud, donde clínicamente y con estudios complementarios se constata la presencia de una masa intracardiaca, siendo derivada al servicio de cirugía cardiovascular. En este, en un ecocardiograma transotorácico se corroboró la presencia de una masa, de superficie irregular, que ocupaba gran parte de la aurícula izquierda, definiéndose su tratamiento quirúrgico. Por el tamaño de la lesión, se decidió el abordaje auricular mediante la técnica de Guiraudon, que logra un mejor campo quirúrgico. En el transoperatorio se constató un tumor de aproximadamente 8 cm de diámetro, bilobulado, con aspecto gelatinoso y friable, de color verdoso y rojizo, adosado a la pared lateral y el techo de la aurícula izquierda (Fig. 1). Se realizó su exérésis completa, con un tiempo de paro anóxico de 20 minutos y un tiempo total de circulación extracorpórea de 65 minutos. El estudio anatomopatológico de la pieza informó tumor auricular de aproximadamente 8 x 3 cm, contornos irregulares, color pardo grisáceo, que al corte presentaba color pardo

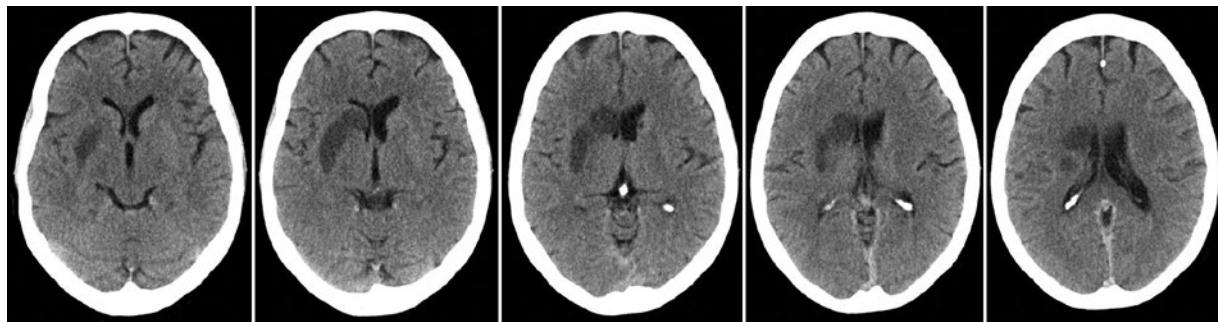
y zonas blanquecinas, histológicamente compatible con mixoma auricular.

La paciente evolucionó con una hemodinamia favorable en el posoperatorio inmediato, pero con una disfunción neurológica inicial caracterizada por períodos de agitación que no permitieron su extubación temprana. Posteriormente presentó una hemiparesia izquierda que evolucionó a una hemiplejia izquierda a predominio crural. Se realizó tomografía computada simple de cráneo (Fig. 2), que concretó el diagnóstico de infarto de ganglios basales del lado derecho de etiología embólica, decidiéndose comenzar con su rehabilitación cerebrovascular. Fue egresada a los 15 días de posoperatorio y en la actualidad se encuentra en clase funcional II de la New York Heart Association; neurológicamente mantiene una hemiparesia izquierda residual.

## Discusión

El accidente cerebrovascular perioperatorio varía según el tipo de procedimiento quirúrgico realizado, apareciendo con más frecuencia en las cirugías cardiovasculares, como cirugía de revascularización miocárdica con colocación de puentes aortocoronarios, cirugías valvulares y cirugías carotídeas, en comparación con las cirugías no cardiovasculares. En los pacientes sometidos específicamente a cirugías cardíacas, la presencia de una lesión neurológica perioperatoria constituye un factor de mal pronóstico en la evolución, reportándose con una mayor incidencia en aquellos pacientes a quienes se realizan cirugías de revascularización miocárdica con colocación de puentes aortocoronarios con necesidad de circulación extracorpórea. Se han propuesto varios mecanismos para explicar el desarrollo de los eventos isquémicos asociados con la cirugía cardíaca, entre los cuales aparecen hipoperfusión, respuesta inflamatoria sistémica, desorden metabólico y embolia, siendo esta última la más comúnmente reportada<sup>1,2</sup>.

A pesar de que los tumores cardíacos son considerados de rara aparición, el mixoma cardíaco es uno de los tumores cardíacos primarios de etiología benigna que con mayor frecuencia se reporta, con una incidencia aproximada de 0,5-1% por millón de habitantes. La sintomatología de estos pacientes varía en dependencia de las características que presente el tumor: tamaño, morfología, movilidad y localización; sin embargo, un 3.2-46.4% de los casos pueden ser asintomáticos. Entre las manifestaciones clínicas neurológicas asociadas a una alta morbilidad están las embolizaciones periféricas, que pueden aparecer



**Figura 2.** Tomografía computada simple de cráneo. Se aprecia una imagen hipodensa que ocupa la cabeza del n úcleo caudado y los n úcleos grises basales derechos, sin efecto de masa sobre las estructuras de la l ínea media, en relaci ón con lesi ón isquémica a este nivel de probable etiología embólica por los antecedentes de la paciente.

aproximadamente en un 20-50% de los casos. El grado de embolización se asocia en general a las características del tumor, antes mencionadas, sobre todo a las particularidades de su superficie. Seg n su aspecto, durante el estudio ecocardiogr áfico o macroscópicamente durante la cirugía o el estudio anatopatológico del tumor, se evidencian dos tipos de superficie: lisa con aspecto polipoide y consistencia compacta, o irregular con múltiples extensiones vellosas y consistencia suave. Esta última es la que habitualmente se asocia a fenómenos embólicos, pues contribuye a la fragmentación tumoral<sup>3</sup>.

La exérésis quirúrgica es una t écnica que reporta una baja incidencia de complicaciones, siendo considerada como el tratamiento m ás efectivo y la intervención preventiva de elecci ón en pacientes asintomáticos con diagn óstico de mixoma cardiaco, sobre todo de aquellos con superficie irregular. El accidente cerebrovascular perioperatorio es una complicaci ón de rara aparici ón en este tipo de cirugía. En el presente caso se considera que ocurrió como producto de un accidente transoperatorio, debido a las caracter ísticas propias del tumor y a su manipulaci ón durante la extracci ón, que conllevaron el desprendimiento de alg n fragmento tumoral que posteriormente embolizó y causó el infarto cerebral en los ganglios basales derechos. Existen otras tras alteraciones que tambi én pueden estar vinculadas al accidente cerebrovascular perioperatorio, pero que no fueron reportadas en la paciente, como ateromatosis en la zona seleccionada para la colocaci ón de la pinza de clampaje a órtico, embolia gaseosa durante el proceso de canulaci ón o descanulaci ón, cambios hemodinámicos con hipotensi ón e hipoperfusi ón cerebral, enfermedad carotídea previa y alteraciones de la coagulaci ón<sup>4-6</sup>.

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## Conflicto de intereses

Los autores declaran no tener ning n conflicto de intereses.

## Responsabilidades éticas

**Protecci ón de personas y animales.** Los autores declaran que para esta investigaci ón no se han realizado experimentos en seres humanos ni en animales.

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**Derecho a la privacidad y consentimiento informado.** Los autores han obtenido el consentimiento informado de los pacientes y/o sujetos referidos en el art ículo. Este documento obra en poder del autor de correspondencia.

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# Diagnóstico de un quiste duodeno-colónico con contenido inflamatorio derivado de la metástasis de adenocarcinoma de vesícula biliar: reporte de caso

*Diagnosis of a duodenal-colonic cyst with inflammatory content derived of a metastatic gallbladder adenocarcinoma: a case report*

Elsa K. Vargas-García<sup>1\*</sup>, José L. García-Saravia<sup>1</sup>, Augusto R. Fernández-Aristi<sup>2</sup> y María A. Cáceres-Bedoya<sup>3</sup>

<sup>1</sup>School of Medicine, Universidad Peruana de Ciencias Aplicadas; <sup>2</sup>Faculty of Health Sciences, Universidad Peruana de Ciencias Aplicadas; <sup>3</sup>Service of Hepatobiliary Surgery, Hospital Nacional Dos de Mayo. Lima, Peru

## Resumen

La existencia de un quiste cuyas paredes se originaron de una metástasis de adenocarcinoma de vesícula biliar es infrecuente. Varón de 68 años con distensión abdominal, hiporexia e ictericia. En la laparotomía exploratoria se evidencia un quiste duodeno-colónico de paredes conformadas por células metastásicas producto de un adenocarcinoma de vesícula biliar. La metástasis del adenocarcinoma de vesícula biliar hacia colon transverso y duodeno formaron adherencias entre ambos órganos, conduciendo a la formación de una masa quística. Las células cancerígenas pueden adaptarse de muchas maneras para sobrevivir en entornos adversos.

**Palabras clave:** Adenocarcinoma. Vesícula biliar. Masa quística. Reporte de caso.

## Abstract

The existence of a cystic mass which walls originated from a metastatic gallbladder adenocarcinoma is infrequent. We present the case of 68-year-old male that present to the emergency department with abdominal distention, hyporexia and jaundice. Upon exploratory laparotomy, a duodeno-colonic cyst with walls formed by metastatic cells derived from a Gallbladder Adenocarcinoma. Metastatic disease from a gallbladder adenocarcinoma to transverse colon and duodenum formed adherences between both organs, leading to the formation of cystic mass. Cancer cells have multiple adaptation mechanisms in order to survive harsh environments.

**Keywords:** Adenocarcinoma. Gallbladder. Cystic Mass. Case Report

## Correspondencia:

\*Elsa K. Vargas-García.

Corzo 138,

Vista Alegre Santiago de Surco,

C.P. 15039, Lima, Peru

E-mail: elsa\_vargas11@hotmail.com

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## Introducción

El adenocarcinoma de vesícula biliar (ACVB) es la neoplasia de vesícula biliar más frecuente; tiene un pronóstico desfavorable con un rango de supervivencia de menos del 5% en 5 años, usualmente a causa de su presentación asintomática en la mayoría de los casos<sup>1,2</sup>.

Las manifestaciones clínicas usualmente son difíciles de diferenciar de una enfermedad benigna, a causa de su presentación inespecífica. Por este motivo, aproximadamente de 40 a 75% de los casos, usualmente presentan síntomas que son diagnosticados en estadios avanzados de la enfermedad.<sup>2</sup> Los síntomas observados en la enfermedad metastásica son producto de la invasión local del ACVB a las estructuras cercanas como el hígado y los nódulos linfáticos y se manifiestan como dolor abdominal, ictericia, pérdida de peso y malestar general. De forma menos frecuente, la diseminación local de ACVB se podría propagar al duodeno, manifestándose con cambios en el ritmo defecatorio.<sup>3</sup> Este es el caso de un paciente con una presentación atípica de ACVB con metástasis al duodeno y al colon, cuyas células formaron un quiste.

## Reporte de caso

Un hombre de 68 años, ganadero de oficio, se presentó al departamento de emergencia con una historia de enfermedad de 6 semanas caracterizada por distensión abdominal, malestar y vómitos. Dentro de la evolución, también se presentó intolerancia oral asociada a hiporexia, astenia y leve pérdida de peso inintencionada. Al momento del diagnóstico, el paciente padecía, también, de diarrea intermitente y constipación. En la última semana antes del ingreso, se evidenció una ictericia lentamente progresiva con sensación de plenitud abdominal a predominio del cuadrante superior derecho. Al examen físico en admisión, se encontraba con ictericia mucocutánea generalizada. Además, se evidenció distensión abdominal a nivel de hipocondrio derecho con una matidez focal a la percusión de dicha zona. Al ingreso, se planteó como diagnóstico un quiste hidatídico con compromiso hepático, por lo que se le solicitó bioquímica sanguínea, dando como resultados PCR y VSG elevados, marcadores tumorales negativos, bilirrubina total elevada, a predominio directo (8 mg/dl), y un patrón obstructivo colestásico.

La TAC abdominal contrastada reveló una colección hipodensa a nivel de la segunda porción del duodeno y la presencia de una masa quística de 12 x 14cm de contenido hipodenso, que comprometía las paredes del duodeno y del colon transverso (FIG. 1). Por este motivo, fue admitido al servicio de cirugía hepatobiliar. El primer día después de la admisión, se le realizó una endoscopía, la cual mostró una disminución del lumen en la segunda porción del duodeno con una masa exofítica y una reacción de mucosa (FIG. 2). Se tomaron biopsias del tejido comprometido. Tres días después de la admisión, las muestras revelaron Duodenitis Histiocitaria Crónica Granulomatosa sin signos de infiltración maligna. Al cuarto día después de admisión, se le realizó una ecografía guiada para drenaje del quiste intraabdominal, obteniendo casi 1500 cc de fluido de tipo exudativo, alinfocítico con un gram y cultivo positivo a Enterococco Durans, alejando de esta forma el diagnóstico de quiste hidatídico planteado al inicio, orientando hacia un absceso intraabdominal. Debido a esto, se inició terapia antibiótica durante el quinto día de hospitalización, con Gentamicina 420 mg dividida cada 8 horas y Vancomicina EV 2 gr dividida cada 12 horas por 5 días. Durante el curso del tratamiento antibiótico, se solicitaron exámenes de función renal que no mostraron elevación significativa de creatinina o urea. A pesar de la terapia antibiótica durante cinco días, no se evidenció una remisión clínica, por lo que el paciente fue programado a cirugía con el fin de observar el tamaño de la masa quística y las estructuras circundantes comprometidas. Durante la intervención, se evidenciaron adherencias abdominales extendidas en la zona superior además de una vesícula engrosada, hemorrágica y atrófica de 1 x 2 cm con un diámetro de 2 cm y micro abscesos dentro de la pared. También, se evidenció, una masa quística bifásica de 10 x 8 cm, con un grosor de pared de 3cm, dependiente de la segunda porción de duodeno, localizada a 3cm de la ampolla de Vater, comprimiéndola. Macroscópicamente, el hígado no mostró ningún signo de extensión local de enfermedad. Esta masa, también, se extendió al colon ascendente y al transverso, infiltrando la capa serosa en ambas porciones del órgano (FIG. 3); la masa reveló contenido seroviscoso amarillento, levemente hemático. Por este motivo, se procedió a removerla del abdomen con escisión de las paredes de duodeno y colon comprometidas. Luego, se llevó a cabo la anastomosis de las terminaciones libres; no hubo complicaciones. Se tomaron biopsias y muestras apropiadas del procedimiento.



Figura 1. TAC abdominal contrastada: engrosamiento de paredes de Vesícula Biliar y presencia de una masa quística dependiente de duodeno y de colon.

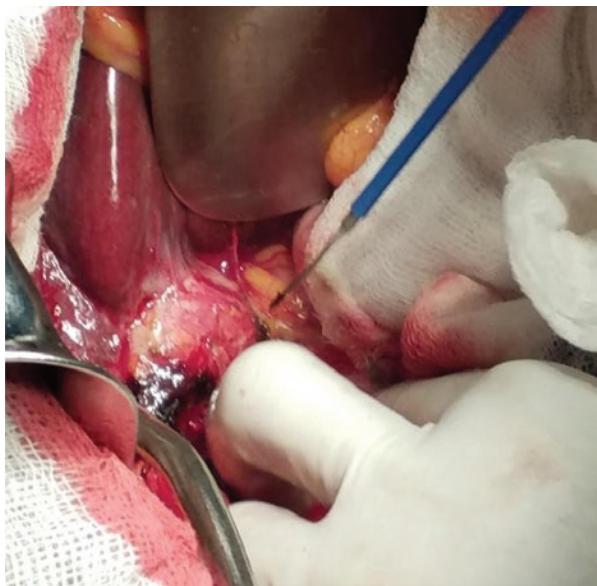


Figura 3. Escisión intraoperatoria de la masa quística duodeno-colónica.

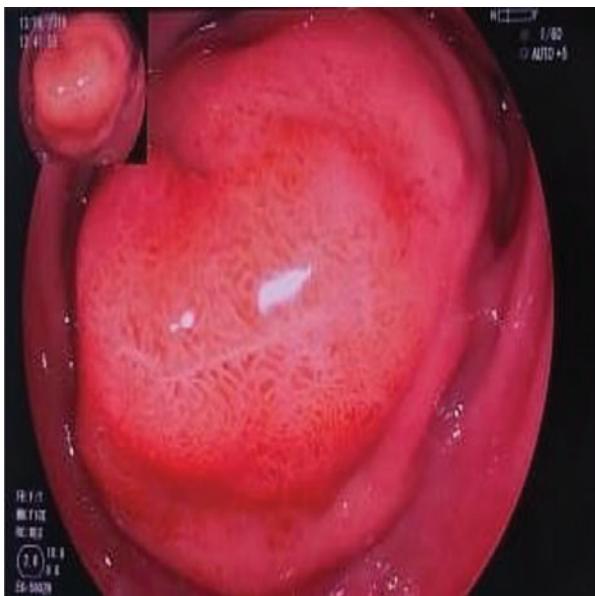


Figura 2. Endoscopia: presencia de una masa exofítica, de la segunda porción duodeno, que demuestra la reactividad de la mucosa frente a la respuesta crónica inflamatoria.

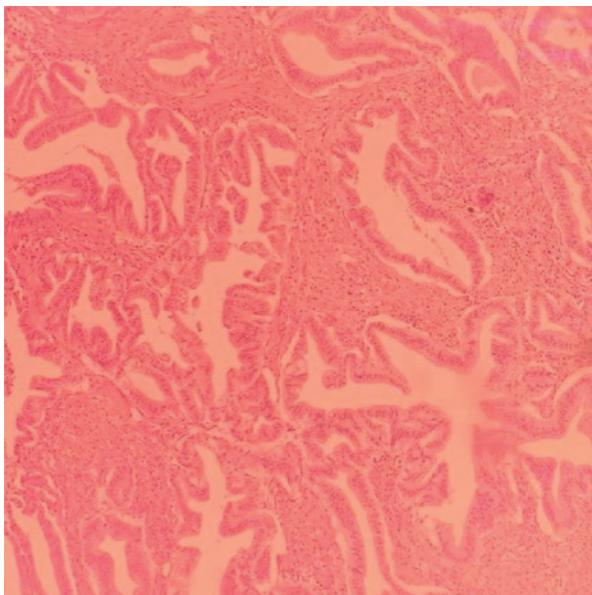
El diagnóstico post operatorio fue una masa quística dependiente de colon transverso y de duodeno además de un engrosamiento patológico de vesícula biliar a descartar neoplasia maligna. El examen histopatológico de las muestras remitidas, reveló un adenocarcinoma moderadamente diferenciado, ulcerado e infiltrante de vesícula biliar, de extensión predominantemente superficial con necrosis extensa

coagulativa de las paredes (FIG 4). El quiste duodenocolónico poseía paredes compuestas de células metastásicas provenientes de la neoplasia primaria. Las muestras de biopsias hepáticas no mostraron signos de diseminación local. Después de quince días de hospitalización, se concluyó que la gradación del tumor fue de T4N4M1 y el paciente empezó cuidados paliativos. A pesar del tratamiento adecuado, el paciente falleció a causa de la enfermedad metastásica.

## Discusión

El presente reporte, describe la formación atípica de un quiste dependiente de colon y duodeno, cuyas paredes están formadas por células metastásicas producto de un ACVB. El ACVB representa la forma de proliferación neoplásica más frecuente de la vesícula biliar, sin embargo, es la neoplasia de tracto biliar maligna menos común. Dentro de los factores de riesgo asociados al origen de ACVB, están usualmente, el sexo femenino, la edad avanzada y el antecedente de colecistitis crónica calculosa.<sup>3</sup>

Las manifestaciones clínicas del ACVB son inespecíficas; generalmente, la pared de la vesícula biliar presenta una calcificación distrófica, lo cual no se observó en el paciente. En adición a esto, el diagnóstico pre quirúrgico es usualmente infrecuente y, a veces, conlleva a la necesidad de realizar biopsias



**Figura 4.** Hallazgos histopatológicos: Diseminación metastásica de un Adenocarcinoma de Vesícula Biliar moderadamente diferenciado

intraoperatorias para alcanzar el diagnóstico, lo cual está demostrado apropiadamente en este caso.

La metástasis del ACVB puede ser local o diseminada. Cuando es de extensión local, por contigüidad, afecta principalmente al hígado (86%) y a los ganglios linfáticos (60%) adyacentes. Por otro lado, la metástasis extrahepática, es decir, al colon y al duodeno, es muy infrecuente y manifiesta, desde ya, una enfermedad avanzada.<sup>4, 5, 6</sup> En el presente caso, tanto las paredes del duodeno como las del colon, estaban adheridas una a la otra a causa de la enfermedad metastásica del ACVB. Además, se evidenció un claro compromiso de la serosa de dichos órganos, mas no de la mucosa como es común observar. Todo esto permitió la creación de un ambiente óptimo para el crecimiento bacteriano de *Enterococco Durans*. Este hecho conllevó al crecimiento de la masa quística no dependiente del hígado, como se muestra en las biopsias tomadas, comprimiendo la ampolla de Vater y con ello originando el cuadro icterico en el paciente, además de cambios en el ritmo defecatorio por la compresión del duodeno y colon transverso. Debido a la presentación atípica del cuadro del paciente y, a sus antecedentes, se procedió a realizar una laparotomía exploratoria para determinar el diagnóstico. En el presente caso, no hubo momento en la historia de la enfermedad, en el que el hígado mostrara signos de expansión local de enfermedad primaria. Además, la formación quística, producto de la enfermedad metastásica, pudo haber sido un mecanismo celular adaptativo al nuevo medio ambiente, lo cual

les permitió proliferar y sobrevivir en su nueva locación.<sup>7</sup> Por otro lado, la formación quística y el fluido producido por las glándulas del adenocarcinoma, presentes en las paredes, pudo haber facilitado la translocación bacteriana de *Enterococco Durans*, quienes están particularmente, presentes en esta porción del tracto, como se dijo anteriormente. Estos microorganismos usualmente sobreviven en ciertos ambientes dentro del tracto colónico, lo cual les permite ser un reservorio con capacidad de diseminación. En este caso, la presentación inespecífica de este tipo de quiste, conllevó a realizar una punción guiada por ecografía para el drenaje y el estudio de la masa quística abdominal.

Por último, la presencia de necrosis coagulativa en la pared del quiste, sugiere que la resolución espontánea de la ictericia fue producto de la atrofia transitoria del quiste por muerte celular en la pared de la lesión.

## Conclusión

En conclusión, las células neoplásicas pueden adaptarse a sobrevivir en ambientes difíciles y pueden simular otra enfermedad con sintomatología inespecífica asociada, demorando así el proceso diagnóstico ó desviándolo de la enfermedad subyacente. Tal como en el caso presentado, pueden simular un quiste inflamatorio o, por los antecedentes del paciente, un quiste hidatídico, desviando así el diagnóstico final. Por este motivo, debe realizarse una historia médica apropiada, resaltando los antecedentes del paciente, y un plan de trabajo adecuado.

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## Conflicto de intereses

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## Responsabilidades éticas

**Protección de personas y animales.** Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

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# Ruptura hepática espontánea en paciente con síndrome HELLP

*Spontaneous hepatic rupture in a patient with HELLP syndrome*

José V. Caballero-Cuevas\* y Linda C. Jiménez-Ibáñez

Servicio de Ginecología y Obstetricia, Hospital de Alta Especialidad Dr. Gustavo A. Rovirosa Pérez, Villahermosa, Tabasco, México

## Resumen

*La hemorragia por ruptura hepática es una rara y letal complicación, de etiología desconocida. Obliga al equipo multidisciplinario a la interrupción del embarazo, al tratamiento agresivo y al manejo de la paciente en una unidad de cuidado intensivo (UCI). Se presentan dos pacientes con embarazo de término con ruptura de hematoma hepático subcapsular asociado a síndrome HELLP (hemolysis, elevated liver enzymes, low platelet count), asintomáticas, durante operación cesárea, con manejo en UCI, ambas con evolución tórpida; una fallece y la otra se egresa. La ruptura hepática requiere una alta sospecha y un manejo multidisciplinario oportuno, agresivo en todos los casos y de intervención quirúrgica en quienes desarrollen ruptura hepática, para mejorar la supervivencia.*

**Palabras clave:** Hematoma hepático. Ruptura hepática. Síndrome HELLP. Preeclampsia. Eclampsia.

## Abstract

*Hemorrhagic liver rupture is a rare and deadly complication. The pathogenesis is unknown. This situation forces the multidisciplinary team, the immediate termination of pregnancy, the treatment and management of the patient in an intensive care unit (ICU). We report the results of two patients with spontaneous rupture of the liver during pregnancy and HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, asymptomatic, during cesarean section, with management in ICU, poor evolution without adequate response; one died and the other leaves hospital. Liver rupture requires high suspicion and timely, aggressive multidisciplinary management in all cases and surgical intervention in those who develop liver rupture, to improve survival.*

**Keywords:** Liver hematoma. Hepatic rupture. HELLP syndrome. Preeclampsia. Eclampsia.

## Introducción

El síndrome HELLP (*hemolysis, elevated liver enzymes, low platelet count*) fue descrito por Weinstein, en 1982, como un cuadro clínico incluido dentro del amplio espectro de las alteraciones que complican la

preeclampsia-eclampsia, caracterizado por hemólisis (microangiopatía hemolítica), elevación de las enzimas hepáticas (aminotransferasa de dos a diez veces los valores normales) y trombocitopenia (<100,000/mm<sup>3</sup>)<sup>1</sup>. La etiopatogenia se desconoce con exactitud. Se ha señalado que probablemente esté relacionada con el

### Correspondencia:

\*José V. Caballero-Cuevas

Calle 3, s/n

Col. El Recreo

C.P. 86020, Villahermosa, Tab., México

E-mail: valsusmed@gmail.com

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daño del endotelio vascular que se produce en la enfermedad hipertensiva del embarazo, con depósito de plaquetas (trombocitopenia) y fibrina local, y el paso de los hematíes por las arteriolas con depósito de fibrina, que deforman y fragmentan los hematíes apareciendo los esquistocitos o células en erizo. La obstrucción del flujo sanguíneo en las sinusoides por los depósitos de fibrina sería la causa de las alteraciones hepáticas, con congestión vascular y aumento de la presión intrahepática, con distensión de la cápsula de Glisson, provocando hematoma subcapsular y ruptura hepática<sup>2</sup>. La hemorragia con ruptura hepática es una rara y letal complicación durante el embarazo; se presenta un caso por cada 45,000 a 260,000 gestaciones. El síndrome HELLP se desarrolla en aproximadamente el 0.1-0.8% de los embarazos y en el 10-20% de las gestantes con preeclampsia grave o eclampsia<sup>3</sup>. Su mortalidad es del 2-3%, y asociado a hematoma subcapsular hepático es del 59-62%<sup>4</sup>. En una larga revisión<sup>2</sup>, la incidencia de hemorragia hepática con ruptura fue de 1 por 45,000 nacidos vivos. Se observó que las pacientes que presentaron hematoma y ruptura hepática eran añosas y multíparas<sup>2</sup>. Indiscutiblemente, es una de las pocas urgencias reales, como cualquier trastorno hemorrágico del organismo, por lo que el diagnóstico debe ser lo más temprano posible y lo más preciso posible para normar la conducta. Clínicamente se manifiesta con dolor abdominal (epigastrio e hipocondrio derecho, en ocasiones irradiado al dorso), náuseas y vómitos, signos de hipoperfusión o anemia aguda (hipotensión, taquicardia, compromiso del estado general, etc.) y sufrimiento fetal agudo<sup>5</sup>. Por lo tanto, es imperante obtener en breve (si se sospechamos en clínica) un estudio de imagen que permita evaluar la anatomía y la estructura hepática, así como el resto de los órganos abdominales (intraperitoneales y extraperitoneales). Esta situación obliga al equipo multidisciplinario a la interrupción inmediata del embarazo, el tratamiento de la ruptura hepática por un cirujano de experiencia y el manejo de la paciente en una unidad de cuidado intensivo (UCI) por el grave compromiso multisistémico<sup>6</sup>.

## Casos clínicos

### Caso 1

Mujer de 27 años, unión libre, secundaria incompleta, dedicada al hogar. Gestas 5, partos 4. Fecha de la última regla: no confiable. Inicia con sangrado

transvaginal escaso, epigastralgia y cefalea, en urgencias de ginecología y obstetricia, con presión arterial 160 / 100 mmHg, frecuencia respiratoria 18 rpm, frecuencia cardíaca 65 lpm, temperatura 36.9 °C, sin datos de abdomen agudo e hiperrefléxica. Se ingresa por embarazo de 35.1 semanas, trabajo de parto en fase dinámica y síndrome HELLP, con hemoglobina 13.1, hematocrito 39.9, leucocitos 8.8, plaquetas 62,000, bilirrubina total 2.2, bilirrubina indirecta 1.8, bilirrubina directa 0.4, aspartato transaminasa 563, alanina aminotransferasa 297, lactato deshidrogenasa 924, fosfatasa alcalina 158, glucosa 96, nitrógeno ureico en sangre 11.37, creatinina 0.66, ácido úrico 24.33. Examen general de orina: proteinuria 300. Se realiza cesárea por bradicardia fetal de 90 lpm y se obtiene un recién nacido con Apgar 6 / 8, que 30 minutos más tarde se ingresa a UCI neonatal por distrés respiratorio. En revisión se observa sangrado de un hematoma subcapsular hepático roto en los segmentos IV, V, VI, VII y VIII, con sangrado activo y hemoperitoneo de 1300 ml. Se inicia transfusión de hemoderivados y se decide realizar empaquetamiento hepático para posterior control de daños, enviándose a UCI intubada. Estudios de control: hemoglobina 5.1, hematocrito 24.8, leucocitos 16.5, plaquetas 120,000 (posterior a transfusión de 10 concentrados plaquetarios), albúmina 2.47, globulina 2.36, bilirrubina total 2.0, bilirrubina indirecta 1.4, bilirrubina directa 0.6, aspartato transaminasa 196, alanina aminotransferasa 138, lactato deshidrogenasa 1426. Examen general de orina: proteinuria 600. A las 4 horas de su ingreso presenta deterioro progresivo y se indica laparotomía exploradora de urgencia. Durante el traslado al quirófano presenta paro cardiorrespiratorio y se realizan maniobras de reanimación avanzada, sin obtención de respuesta. Se declara el fallecimiento por choque hipovolémico, ruptura hepática de hematoma subcapsular y síndrome HELLP.

### Caso 2

Mujer de 28 años. Gestas 5, partos 4. Ingresa con embarazo de 39.2 semanas con preeclampsia con criterios de gravedad. Para mejorar el pronóstico fetal se realiza cesárea, obteniéndose un recién nacido vivo con Apgar 6 / 8, Capurro 40 semanas de gestación y peso 3000 g, que pasa a alojamiento conjunto. En revisión, sangrado de origen hepático por ruptura de hematoma hepático en los segmentos V y VI (y probablemente VII-VIII), por lo que se realizan colecistectomía y ligadura de la arteria hepática derecha

por cirugía general; 2000 ml de hemoperitoneo y 300 ml de cesárea, con transfusión de tres paquetes globulares y dos de plasma fresco congelado. Ingresa a la UCI y se le realiza tomografía computada simple abdominal-pélvica (Figs. 1 a 3), complementándose con ultrasonido abdominal (Figs. 4 y 5). A las 12 horas del evento quirúrgico, la paciente presenta tendencia a la oliguria e hipoglucemia, con aumento de transaminasas y lactato deshidrogenasa, coagulopatía, con datos de falla hepática agua, función renal comprometida (aumento de azoados) e hiperpotasemia, y evolución tórpida. Se inicia hemodiálisis con cuatro sesiones y se recupera la función renal. También mejoran la función hepática y el estado hemodinámico. Se traslada a piso de ginecología para vigilancia, control tomográfico a los 8 días (Fig. 6) y posterior a 5 días se egresa por mejoría.

## Discusión

El síndrome HELLP fue referido por primera vez por Weinstein en 1982 como una forma extremadamente progresiva de gestosis. Además de los síntomas, como proteinuria e hipertensión, el cuadro clínico se caracteriza por hemólisis, microangiopatía, trombocitopenia y, especialmente, deterioro de la función hepática. Dentro de este cuadro clínico pueden ocurrir complicaciones graves, como ataques eclámpicos, disfunción renal, hemorragia intracraneal, hemorragia intrahepática y coagulopatía<sup>7</sup>. Ocurre comúnmente entre las 28 y 36 semanas de gestación, pero también puede ocurrir posparto o incluso durante el trabajo de parto<sup>8</sup>. En los dos casos presentados, la ruptura fue espontánea, sin sintomatología previa. Se asocia con una tasa de mortalidad materna del 3.3%. Sin embargo, cuando hay hematomas hepáticos, o cuando se produce la ruptura hepática, la mortalidad y la morbilidad aumentan significativamente<sup>9</sup>.

Su etiopatogenia aún no ha sido aclarada; se considera la necrosis parenquimatosa periportal y focal secundaria a depósitos hialinos y de fibrina en las sinusoides hepáticas, lo que causa congestión vascular, aumento de la presión intrahepática, dilatación de la cápsula de Glisson y formación del hematoma<sup>10</sup>. Clínicamente se caracteriza por epigastralgia o dolor en barra en el cuadrante superior derecho del abdomen, dolor referido en el hombro derecho, náuseas, vómito, distensión abdominal y choque hipovolémico<sup>10</sup>. En estos casos no se manifestó dolor, sino deterioro del estado hemodinámico y sufrimiento fetal, lo que refleja la heterogeneidad y la variabilidad clínica



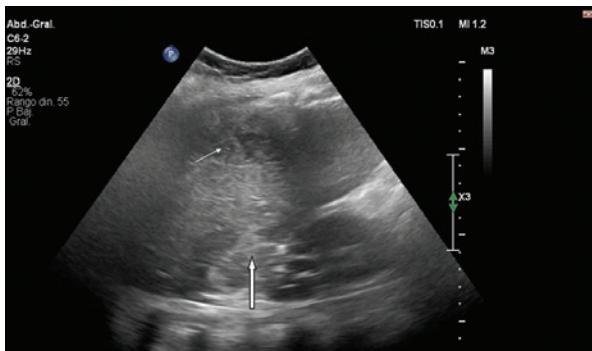
**Figura 1.** Tomografía en reconstrucción coronal, observando en el hígado una imagen tubular a nivel subcapsular hiperdensa, bien definida, con índices de atenuación de 45 UH (densidad sangre), en relación a un hematoma subcapsular.



**Figura 2.** Tomografía en corte axial a nivel de los segmentos VII y VIII hepáticos, identificando en el hígado la misma imagen hiperdensa de la figura 1, subcapsular, conservando el resto del parénquima hepático su densidad normal.



**Figura 3.** En cortes mas inferiores que en la figura 2 se continúa observando la imagen subcapsular en relación a un hematoma activo (por la hiperdensidad), pero bien delimitado.



**Figura 4.** Imagen de ultrasonido obtenida con transductor convexo, en la cual se observa el hígado a nivel del segmento VI (flecha fina), a nivel marginal una imagen hipoeocoica, heterogénea, con áreas de mayor y menor ecogenicidad, y adyacente se observa una zona hiperecogénica difusa, la cual podría corresponder a sangrado activo (flecha gruesa).



**Figura 5.** Imagen de ultrasonido del segmento VI (cruz) en la que se observan los hallazgos antes comentados y puede verse la distribución subcortical del hematoma, con áreas de sangrado activo adyacente (asterisco). El espacio de Morrison (flecha) se observa sin líquido libre ni colecciones, otro dato que descarta líquido libre al momento del ultrasonido.



**Figura 6.** Control tomográfico a los 8 días, con datos de hematoma que no presentó evolución ni progresión (flechas).

de esta patología. El diagnóstico fue intraoperatorio y se realizó durante la cesárea de emergencia indicada por bradicardia fetal, en la cual se observó hemoperitoneo masivo, condicionado por la ruptura de los segmentos IV, V, VI, VII y VIII, lo que a su vez produjo un choque hemorrágico.

De acuerdo con lo mencionado en la literatura, cuando se diagnostica un hematoma subcapsular (que no es el tema) o una ruptura hepática en una paciente obstétrica tenemos la necesidad imperiosa de interrumpir el embarazo (vía abdominal)<sup>11</sup>. Aunque todavía no hay un acuerdo sobre el mejor enfoque para tratar la ruptura hepática, el manejo consiste en una monitorización continua, ya que la paciente presentará inestabilidad hemodinámica (choque, hipotensión, anuria, vasopresores), rotura con hemoperitoneo y pérdida hemática continua. En cualquier caso, cuando se sospecha ruptura hepática, se debe realizar una laparotomía exploradora.

La compresión manual es sin duda uno de los aliados más importantes, con lo cual se permite el control inicial del sangrado con aspiración completa del hemoperitoneo, y estabilizar hemodinámicamente a la paciente, reanimarla y tomar la decisión del paso a seguir; uno de ellos es la maniobra de Pringle<sup>12</sup>, que consiste en la disección del hilio hepático en donde podemos comprimir tanto la vena porta como la arteria hepática para así disminuir el sangrado, y tener mayor oportunidad de controlarlo según su profundidad.

El empaquetamiento hepático<sup>13</sup> consiste en una técnica de control de daños, siendo así el método más utilizado, por ser uno de los más exitosos, incluyendo la pared anterior del tórax, el diafragma y el retroperitoneo. Proporciona hemostasia prácticamente de manera inmediata, obteniendo como respuesta una estabilización hemodinámica en la UCI. Con él se puede lograr un 86% de sobrevida, seccionando los ligamentos falciforme, coronario, triangular derecho y triangular izquierdo (excepto si tienen hematoma entre sus hojas), realizándose en forma temprana durante la laparotomía, teniendo dentro de sus complicaciones un síndrome compartimental abdominal<sup>13</sup>, siendo manejado como abdomen abierto, así como el propio retiro de las compresas, ya que puede iniciar un segundo cuadro hemorrágico, por lo cual es necesario humedecer con solución salina. Tiene la mortalidad más baja (25-30%) y por ello se utiliza como tratamiento quirúrgico de primera opción<sup>14</sup>.

¿Cuándo retirar el empaquetamiento? Existen diferentes opciones (la mayoría de ellas

individualizadas), siendo una de ellas la corrección de la acidosis, la hipotermia y las alteraciones de la coagulación en 24-48 horas<sup>15</sup>. Diferentes autores comentan que existe un 83% de riesgo de sepsis perihepática si es mayor de 3 días y un 27% de riesgo de sepsis abdominal si es menor de 3 días. La recomendación concreta es retirarlo antes de las 72 horas<sup>16</sup>, siendo un retiro efectivo de coágulos y de material desvitalizado. Se puede realizar también un empaquetamiento con el epiplón<sup>17</sup> ocupando el espacio muerto con tejido vivo, ya que favorece la actividad de los macrófagos, obteniendo un 95% de éxito al detener el sangrado, con un 8% de mortalidad, y no es necesario retirarlo. Otras opciones de tratamiento (tras el empaquetamiento), como la lobectomía hepática, la ligadura de la arteria hepática y la embolización hepática, tienen una alta mortalidad, del 75%, el 40% y el 35%, respectivamente; se pueden utilizar si el empaquetamiento no funciona<sup>18</sup>.

Utilizar hemostáticos también es una medida que puede ayudar, como selladores de fibrina<sup>19</sup> para estabilizar el coágulo, que pueden ser de fibrinógeno más fibrina, cloruro de calcio y aprotinina, N-acetil glucosamina acetilada (gasa 4 x 4 cm) y factor VIIa recombinante<sup>20</sup>, que estimula la formación de tapones hemostáticos, existiendo el riesgo de eventos trombóticos, embolia pulmonar y coagulación intravascular diseminada. En casos extremos se puede utilizar la ligadura de la arteria hepática, que puede hacerse de manera quirúrgica o por medio de angiografía, haciendo uso de ella en menos del 1%, debiendo ser durante la laparotomía y posterior a un empaquetamiento fallido, solo en pacientes con disminución del sangrado después de la maniobra de Pringle, teniendo un bajo riesgo de disfunción hepática en pacientes hemodinámicamente estables, riesgo de isquemia, necrosis y sepsis en pacientes en estado de choque, y finalmente puede requerir incluso trasplante hepático<sup>21,22</sup> de urgencia, indicado en pacientes con falla hepática aguda pero sin daño neurológico, hemodinámicamente estables, con corrección de factores de coagulación y que se tenga disponibilidad de donador en menos de 36 horas en fase anhepática<sup>23</sup>.

En lo que respecta a nuestro enfoque quirúrgico, se realizó un empaquetamiento hepático inmediato como primera medida apoyado por el servicio de cirugía general de nuestro hospital; sin embargo, no se pudo contener el sangrado masivo y, condicionado por el estado de coagulopatía de la paciente, no se logró su supervivencia.

La supervivencia y el pronóstico dependen del reconocimiento precoz de los signos y síntomas, así como de la pronta intervención quirúrgica. A pesar del tratamiento quirúrgico oportuno, la mortalidad materna alcanza cifras del 40% y la fetal es aún más elevada. En las pacientes en que desdichadamente no se instala la terapéutica quirúrgica, la mortalidad alcanza cifras del orden del 100%. La hemorragia hepática incontrolable exacerbada a un estado de coagulopatía es la principal causa de la muerte<sup>24</sup>.

Nos es de vital importancia dar a conocer estos casos porque la presentación clínica del hematoma subcapsular roto no fue manifestado por el dolor característico. Esto, aunado a la infrecuencia del cuadro, provoca que muchos casos no sean sospechados, el diagnóstico sea demorado y la terapéutica desconocida, siendo un hallazgo durante la laparotomía, y por lo tanto con un alto índice de mortalidad.

## Conclusiones

Tomando en cuenta la frecuencia de preeclampsia-eclampsia y síndrome HELLP, es importante tener una alta sospecha clínica de esta para establecer el diagnóstico temprano de la ruptura hepática, ya que al ser una complicación poco frecuente asociada al síndrome HELLP representa un cuadro de morbilidad materna extremadamente grave, con una elevada mortalidad. Es indispensable realizar un manejo multidisciplinario oportuno, agresivo en todos los casos y de intervención quirúrgica en quienes desarrollen esta patología, individualizando el manejo, según sea el caso, para mejorar la supervivencia materna.

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## Conflictos de intereses

Los autores declaran no tener ningún conflicto de intereses.

## Responsabilidades éticas

**Protección de personas y animales.** Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

**Confidencialidad de los datos.** Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

**Derecho a la privacidad y consentimiento informado.** Los autores han obtenido el consentimiento informado de los pacientes y/o sujetos referidos en el artículo. Este documento obra en poder del autor de correspondencia.

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# Reporte de caso: hipoglucemia grave como manifestación tardía de síndrome de Sheehan

*Case report: severe hypoglycaemia as a late manifestation of Sheehan's syndrome*

Edgar R. Romero-Vásquez<sup>1\*</sup>, Luis A. Arteaga-Martínez<sup>2</sup>, Germán Lachica-Rodríguez<sup>2</sup> y José Manuel Ornelas-Aguirre<sup>3</sup>

<sup>1</sup>Servicio de Medicina Interna, Unidad Médica de Alta Especialidad, Instituto Mexicano del Seguro Social (IMSS); <sup>2</sup>Servicio de Medicina Interna, Hospital General Regional No. 1, IMSS; <sup>3</sup>Departamento de Ciencias de la Salud, Universidad de Sonora. Ciudad Obregón, Sonora, México

## Resumen

**Antecedentes:** El síndrome de Sheehan es un hipopituitarismo secundario a necrosis de la glándula hipófisis causado por una hemorragia posparto. La presentación frecuentemente es como amenorrea y agalactia; la hipoglucemia como presentación solitaria es infrecuente. **Caso clínico:** Mujer de 68 años con antecedente de hemorragia posparto hace 35 años. Cursó con dos episodios de hipoglucemia. Durante su hospitalización se detecta panhipopituitarismo y se corrobora por resonancia magnética la silla turca vacía. **Conclusiones:** Es recomendable que el personal médico sospeche un síndrome de Sheehan ante cualquier mujer con hipoglucemia inespecífica y sin antecedente de enfermedad crónica degenerativa.

**Palabras clave:** Síndrome de Sheehan. Hipoglucemia. Presentación atípica.

## Abstract

**Background:** Sheehan's syndrome is a hypopituitarism secondary to necrosis of the pituitary gland caused by massive postpartum bleeding. The presentation is frequently amenorrhea and agalactia; hypoglycemia as a solitary presentation is uncommon. **Case report:** 68-year-old female with a history of postpartum hemorrhage 35 years ago. She had two episodes of hypoglycemia. During her hospital stay, panhypopituitarism was detected and the empty sella was confirmed by magnetic resonance imaging. **Conclusions:** It is recommended that medical personnel suspect Sheehan's syndrome in any woman with nonspecific hypoglycemia and no history of chronic degenerative disease.

**Keywords:** Sheehan's syndrome. Hypoglycemia. Atypical presentation.

## Introducción

El síndrome de Sheehan es una complicación de la hemorragia posparto<sup>1</sup>, que fue descrito por primera vez por el patólogo británico H.L. Sheehan en 1937<sup>2</sup>. Se presenta como un hipopituitarismo secundario a

la necrosis de la glándula hipófisis causada por hipotensión arterial sistémica secundaria a sangrado masivo durante el trabajo de parto<sup>3</sup>. Ocurre en el 1-2% de las mujeres<sup>4</sup> y su incidencia en México es de 1/10,000 partos<sup>5</sup>. En Islandia, la prevalencia es de 5 casos por cada 100,000 mujeres<sup>6</sup>.

### Correspondencia:

\*Edgar R. Romero-Vásquez

Prolongación Hidalgo y Huisaguay s/n

Col. Bellavista

C.P. 85130, Ciudad Obregón, Son., México

E-mail: edgar\_romerov22@hotmail.com

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Durante el embarazo se desarrolla una hiperplasia de la glándula hipófisis, sobre todo en la región anterior, con la finalidad de aumentar la producción de prolactina necesaria para la lactancia<sup>6</sup>. La irrigación de la glándula hipófisis predispone a isquemia arterial durante períodos de hipotensión arterial, puesto que la arteria hipofisaria superior penetra en el hipotálamo para formar el sistema portal de capilares, que cursa por el tallo hacia la hipofisis anterior, por lo que es perfundida con presión venosa<sup>6</sup>. La glándula hipófisis está formada por un lóbulo anterior que segregá prolactina, hormona del crecimiento, gonadotropinas, adrenocorticotropina y tirotropina; el lóbulo medio segregá melanotropinas, y en el lóbulo posterior se almacenan la oxitocina y la hormona antidiurética secretadas por el hipotálamo<sup>7</sup>. Durante el parto, la presencia de una hemorragia masiva produce hipotensión arterial, y en consecuencia se pueden generar áreas de necrosis<sup>8</sup>.

Las pacientes suelen presentarse meses o años después del episodio de hemorragia posparto<sup>9</sup>, con un tiempo medio que varía de 2 a 33 años<sup>10</sup>, debido a un daño hipofisario incompleto y una progresión lenta del daño<sup>11</sup>. En las formas tardías, los síntomas son variables dependiendo del déficit hormonal, siendo frecuentes los síntomas inespecíficos en más del 50% de las mujeres<sup>11</sup>, seguidos de amenorrea, esterilidad y disminución del vello por déficit de gonadotropinas, astenia, fatiga, intolerancia al frío y envejecimiento prematuro por déficit de tiroxina y de hormona del crecimiento<sup>4,11</sup>. Las pacientes pueden presentar una crisis suprarrenal por deficiencia de cortisol o coma mixedematoso<sup>11</sup>.

## Caso clínico

Mujer de 68 años con antecedente de hemorragia posparto a los 33 años de edad, sin secuelas clínicas tras dicho evento (agalactia ni amenorrea). Sin antecedentes familiares de insulínoma. Se le diagnosticó trastorno depresivo mayor a los 38 años, en manejo con fluoxetina. En la entrevista negó otras enfermedades crónicas degenerativas. Su padecimiento actual inició el día 12 de abril de 2019, cuando acudió a un hospital privado por presentar astenia, adinamia, diaforesis, debilidad, confusión y somnolencia; el manejo médico inicial incluyó control de deshidratación grave y de hipoglucemia mediante soluciones glucosadas parenterales, siendo egresada al tercer día por aparente mejoría general. Veinticinco días después del inicio de este cuadro presentó de nuevo la misma

**Tabla 1. Estudios de laboratorio al ingreso de la paciente al servicio de urgencias, en los que son evidentes la hipoglucemia grave y la anemia**

Parámetro	Valor	Rango normal
Glucosa	↓ 30 mg/dl	60-100 mg/dl
Nitrógeno ureico en sangre	7 mg/dl	8-20 mg/dl
Urea	15 mg/dl	10-40 mg/dl
Hemoglobina	↓ 9.0 g/dl	14 ± 2 gr/dl
Hematocrito	↓ 24.4 (%)	42 ± 5 (%)
VCM	87 fl	80-97 fl
HCM	31 pg	27-31.2 pg
Leucocitos	↓ 3.9 × 10 <sup>9</sup> /l	4.5-11.5 × 10 <sup>9</sup> /l
Plaquetas	309,000 cel/mm <sup>3</sup>	150,000-450,000 cel/mm <sup>3</sup>

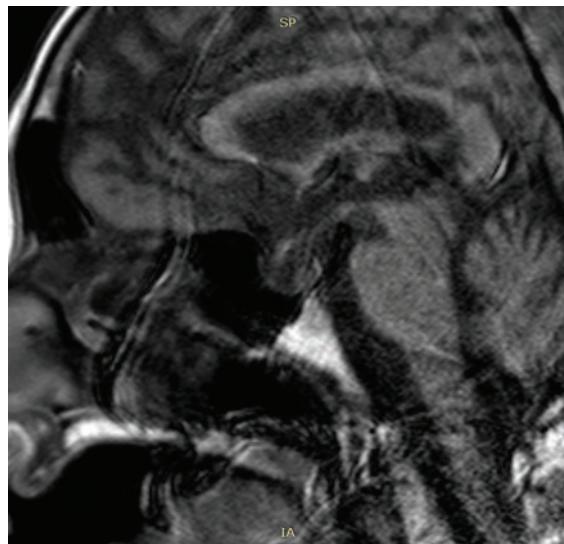
HCM: hemoglobina corpuscular media; VCM: volumen corpuscular medio.

sintomatología, pero en esta ocasión fue llevada al servicio de urgencias de nuestro hospital. A su ingreso, la paciente presentaba un cuadro clínico caracterizado por hipoglucemia grave con debilidad, mareo, confusión y somnolencia. Los exámenes de laboratorio mostraron una concentración de glucosa sérica de 30 mg/dl y una anemia normo-normo (volumen corpuscular medio [VCM] de 87 fl y hemoglobina corpuscular media [HCM] 31 pg) asociada a hemoglobina de 9.0 g/dl, hematocrito del 24.4% y leucocitopenia de 3.9 × 10<sup>9</sup>/l. Se le administró una carga de solución glucosada al 50% por vía parenteral que condicionó un alivio casi inmediato de los síntomas, lo que se conoce como la tríada de Whipple (baja concentración de glucosa en sangre, síntomas de hipoglucemia y mejoría una vez normalizada la glucemia). Fue ingresada al servicio de medicina interna para continuar con el protocolo de estudio de la hipoglucemia. En la tabla 1 se detallan los estudios de laboratorio al ingreso de la paciente en el servicio de urgencias, en los que son evidentes la hipoglucemia grave y la anemia. Tras su ingreso al servicio de medicina interna, la exploración física reveló despigmentación de la piel principalmente de las areolas mamarias, involución mamaria y pérdida del vello axilar y púbico; no se encontraron estígmas de hepatopatía crónica. Los signos vitales eran normales. La presencia de insuficiencia renal, hepatopatía crónica e hipoglucemia secundaria a medicamentos u otras sustancias, tales como insulina, sulfonilureas, glinidas o alcohol, se descartó por la información y los antecedentes obtenidos en la

**Tabla 2. Estudios de laboratorio durante la estancia de la paciente en el servicio de medicina interna, en los que son evidentes el hipopituitarismo y la hipoinsulinemia**

Parámetro	Valor	Rango normal
Hormona del crecimiento	0.07 ng/ml	< 10 ng/ml
Somatomedina	↓ 3 ng/ml	17-241 ng/ml
Hormona estimulante del folículo	↓ 0 mUI/ml	27-133 mUI/ml
Hormona luteinizante	↓ 0.1 mUI/ml	0.9-10.9 mUI/ml
Hormona estimulante de tiroides	↓ 0.27 uU/ml	0.47-5.01 uU/ml
Cortisol sérico matutino	↓ 0.30 µg/dl	6.2-19.4 µg/dl
Tiroxina libre	↓ 0.43 ng/dl	0.70-1.46 ng/dl
Insulina endógena	↓ 1.0 uUI/ml	3.2-16.3 uUI/ml

historia clínica. Se indagó acerca de algún proceso séptico o inanición que explicaran la hipoglucemía, sin éxito. Para la evaluación de hipocortisolismo e hiperinsulinismo como causa de la hipoglucemía se determinaron el cortisol sérico y la insulina endógena; con los resultados obtenidos se pudo determinar la presencia de hipocortisolismo y valores disminuidos de insulina endógena, al contrario de lo que se podría esperar en una hiperinsulinemia. En la tabla 2 se muestran los resultados de los estudios de laboratorio realizados durante la estancia de la paciente en el servicio de medicina interna, en los que son evidentes el hipopituitarismo y el hipotiroidismo. En la tomografía computarizada de abdomen no se evidenciaron masas tumorales en el páncreas ni en la cavidad abdominal, y por lo tanto se descartó la hipótesis de un insulinoma como causante de la hipoglucemía. En virtud de los valores bajos de cortisol sérico se realizó una resonancia magnética de cráneo en busca de alteraciones anatómicas, y el resultado fue la presencia de una silla turca vacía, por lo que con el antecedente de hemorragia posparto, el panhipopituitarismo y el estudio de imagen se consideró que se trataba de un síndrome de Sheehan. En la figura 1 se muestra el resultado de la resonancia magnética de cráneo que mostró la silla turca vacía. Una vez con el diagnóstico, se inició tratamiento con reemplazo hormonal. Se administró prednisona a dosis de 5 mg/24 h por vía oral. Se eligió este fármaco porque es el disponible en nuestra institución. Las guías recomiendan el uso de hidrocortisona por vía oral como primera opción de tratamiento hormonal sustitutivo<sup>12-14</sup>, pero en México no contamos con este preparado. Se administró levotiroxina



**Figura 1.** Resonancia magnética de cráneo en corte sagital en secuencia T1 que muestra la presencia de la silla turca vacía.

ajustada de acuerdo con el peso de la paciente a dosis de 1.6 µg/kg de peso corporal cada 24 horas (dosis final de 100 µg al día) para controlar los síntomas hipotiroideos y prevenir complicaciones como el coma mixedematoso. La mejoraría del cuadro clínico fue evidente a los 14 días de iniciado el tratamiento.

## Discusión

La falla de la glándula pituitaria ocurre bajo varias condiciones: enfermedades hipotalámicas como craneofaringiomas, metastasis de tumores primarios de pulmón o mama, secundaria a radiación del sistema nervioso central, infecciones como meningitis tuberculosa y traumáticas, y enfermedades hipofisiarias como adenomas o quiste de hipófisis, cirugía hipofisiaria, radiación hipofisiaria, hemocromatosis, infección o absceso hipofisario, y causas vasculares como apoplejía y síndrome de Sheehan. El hipopituitarismo relacionado con el síndrome de Sheehan es poco frecuente. El síndrome de Sheehan es más común en los países en vías de desarrollo<sup>15</sup>. Su diagnóstico se fundamenta en el antecedente de hemorragia posparto, falla en la lactancia, deficiencia de hormonas hipofisiarias y presencia de una imagen radiológica de silla turca vacía en un estudio de resonancia magnética de cráneo<sup>16</sup>. Nuestra paciente cumplía todos los criterios, pero su presentación atípica ocurrió 35 años después del evento de hemorragia posparto y sin falla en la lactancia ni amenorrea. En los últimos años se

han publicado varias series de casos sobre la presentación clínica tardía del síndrome de Sheehan<sup>17-22</sup>.

En un estudio realizado en la India en 2016<sup>18</sup> se reportó la pérdida hormonal en un grupo de 21 mujeres con diagnóstico de síndrome de Sheehan, y se encontró que la pérdida más frecuente fue para prolactina, gonadotropinas y hormona del crecimiento<sup>16-19,22-24</sup>, con manifestación clínica de insuficiencia para la lactancia y amenorrea. Es común encontrar que la caída en las cifras de cortisol se presente en un 50% de los casos. Otro estudio publicado en Xinjiang, China, en 2015, con 97 mujeres con síndrome de Sheehan, obtuvo resultados similares: la presentación clínica más frecuente fue la pérdida del vello axilar o púbico en el 85.6% de los casos estudiados, amenorrea en el 82.5% y agalactia en el 74.2%<sup>24</sup>.

Otros estudios han sugerido que la presentación aguda más común se asocia a crisis suprarrenal con colapso cardiovascular, hipoglucemias, hiponatremia y choque<sup>15,17</sup>. La presentación crónica más frecuente es con amenorrea por déficit de gonadotropinas, agalactia e involución mamaria, pudiendo iniciarse incluso después de varios años del evento hemorrágico posparto con crisis suprarrenal o hipotiroidismo, como sucedió en este caso<sup>7,15,22,23-27</sup>.

El principal diagnóstico diferencial es la hipofisitis linfocítica, la cual puede presentarse en niños y adultos de ambos sexos, comúnmente asociada a otras enfermedades autoinmunitarias, ocurre sin el antecedente de hemorragia posparto, las hormonas más habitualmente afectadas son el eje corticoides y tiroideo, se asocia a hiperprolactinemia y diabetes insípida, y en la resonancia magnética se observa como masa hipofisaria<sup>11,27</sup>, por lo que, por las características, el cuadro clínico y los resultados de laboratorio y de imagen de la paciente, es improbable este diagnóstico.

La presentación clínica de nuestra paciente consistió en dos episodios de hipoglucemias con un mes de diferencia, lo cual es una presentación atípica no reportada en otros estudios. La hipoglucemias como parte de una crisis suprarrenal aguda es un evento clínico relativamente frecuente, pero en este caso la paciente no cursó con crisis suprarrenal, sino solo con hipoglucemias aisladas. En una serie de casos publicado por Ozkan y Colak<sup>28</sup> en 2005 se encontró la presencia de hipoglucemias e hipotiroidismo en el 15% de las pacientes, lo cual confirma la baja prevalencia de esta presentación clínica. Kumar, et al.<sup>29</sup> reportaron el caso de una hipoglucemias recurrente comopresentación tardía del síndrome de Sheehan.

Otra forma de presentación reportada es con episodios de hipoglucemias e hiponatremia<sup>30</sup>.

En este caso, una vez que se realizó el diagnóstico de síndrome de Sheehan se inició su tratamiento hormonal sustitutivo que produjo mejoría clínica y alta del hospital en poco tiempo. Es necesario que el personal médico tenga conocimiento de este hecho, dado que un diagnóstico y un tratamiento de reemplazo oportuno tienen un gran impacto en la morbilidad y la mortalidad de las pacientes.

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## Conflicto de intereses

Los autores declaran no tener conflicto de intereses. Se obtuvo el consentimiento por parte de la paciente.

## Responsabilidades éticas

**Protección de personas y animales.** Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

**Confidencialidad de los datos.** Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

**Derecho a la privacidad y consentimiento informado.** Los autores han obtenido el consentimiento informado de los pacientes y/o sujetos referidos en el artículo. Este documento obra en poder del autor de correspondencia.

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# Avances en tumores del estroma gastrointestinal: ¿hacia dónde vamos?

*Recent advances in gastrointestinal stromal tumors: Where are we going?*

Juan A. Fernández-Hernández<sup>1</sup>, Sonia Cantín-Blázquez<sup>1</sup>, Elena García-Somacarrera<sup>1</sup>, Evaristo Varo-Pérez<sup>1</sup>, José A. González-López<sup>1</sup>, José M. Asencio-Pascual<sup>1</sup>, Marta Mendiola<sup>2,3,4</sup>, César Serrano<sup>5,6</sup>, Eduardo García-Granero<sup>1</sup> y Vicente Artigas-Raventós<sup>1\*</sup>

<sup>1</sup>Sección de Tumores Mesenquimales y Sarcomas, Asociación Española de Cirujanos, Madrid; <sup>2</sup>Sección de Patología Molecular, Instituto de Genética Médica y Molecular (INGEMM), Madrid; <sup>3</sup>Laboratorio de Patología Molecular y Dianas Terapéuticas, Instituto de Investigación Hospital Universitario La Paz (IdIPAZ), Madrid; <sup>4</sup>Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Hospital Universitario La Paz, Madrid;

<sup>5</sup>Laboratorio de Investigación Traslacional en Sarcomas, Vall d'Hebron Instituto de Oncología, Barcelona; <sup>6</sup>Departamento de Oncología Médica, Hospital Universitario Vall d'Hebron, Barcelona. España

## Resumen

Los tumores del estroma gastrointestinal (GIST) suponen el 1-2% de los tumores digestivos, siendo su localización más frecuente el estómago (55-60%) y el intestino delgado (30%). Los avances más importantes sucedidos en los últimos años se centran en cuatro áreas: biología molecular, abordaje quirúrgico laparoscópico, manejo técnico del GIST en localizaciones inusuales y tratamiento e integración de la cirugía en el manejo del GIST avanzado. Los avances en el conocimiento de la biología molecular del GIST han dado lugar a la progresiva identificación de nuevas mutaciones oncogénicas que hacen del concepto wild type obsoleto. Estos avances han permitido el desarrollo de dos nuevos fármacos, avapritinib y ripretinib, lo que permite el tratamiento de pacientes con mutaciones resistentes a las tres líneas terapéuticas clásicas. El tratamiento quirúrgico del GIST se rige por unos principios técnicos bien establecidos que el abordaje laparoscópico debe cumplir, abordaje que queda limitado por dos factores clave: localización y tamaño. El GIST de localización infrecuente (esófago, duodeno o recto, o extradigestivo) supone un reto terapéutico. Estos pacientes deben ser manejados en un contexto multidisciplinario. La cirugía queda integrada en el manejo del GIST avanzado, considerándose como adyuvante a los inhibidores de la tirosina cinasa.

**Palabras clave:** Tumor del estroma gastrointestinal (GIST). Inhibidores de la tirosina cinasa (ITQ). Imatinib. Laparoscopia. Equipo multidisciplinario.

## Abstract

Gastrointestinal Stromal Sarcomas (GIST) are mesenchymal neoplasms whose incidence accounts for 1-2% of digestive tumors, being located in the stomach (55-60%) and small intestine (30%). The advances in its knowledge and management succeeded in the last years have been spectacular. This review aims to summarize the most important of them for surgeons. We identified four areas of interest: molecular oncology, laparoscopic approach, management of GIST located at unusual locations, and management of advanced GIST. Advances in the field of molecular oncology lead to the discovery of new oncogenic mutations making the term Wil Type GIST obsolete. Moreover, these advances allow for the development of 2 new drugs: Avapritinib and Ripretinib, that added to the previous 3 commercially available drugs (imatinib, sunitinib and regorafenib)

### Correspondencia:

\*Vicente Artigas-Raventós

E-mail: vartigas@santpau.cat

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make possible the management of GIST with resistant mutations. The principles of the surgical management of primary GIST are well established which laparoscopic approach must accomplish. This approach is limited by 2 main factors: location and size. The diagnosis of GIST in unusual locations as esophagus, duodenum, rectum or out of the gastrointestinal tract (EGIST), implies an extraordinary therapeutic challenge, being imperative to manage them by surgeons and oncologist among others in the setting of a multidisciplinary team. The management of advanced/metastatic GIST has changed in a revolutionary fashion because surgery is now part of its treatment as adjuvant to tyrosine kinase inhibitors.

**Keywords:** Gastrointestinal stromal tumors (GIST). Tyrosine kinase inhibitors (TKI). Imatinib. Laparoscopy. Multidisciplinary teams.

## Introducción

La presente revisión trata de resumir los avances sucedidos en el campo de los tumores del estroma gastrointestinal (GIST) en los últimos años. Este texto está dirigido a cirujanos generales con interés en esta patología.

Los principales avances quedan circunscritos a cuatro áreas bien definidas: biología molecular tumoral y desarrollo de nuevos fármacos; consolidación de los principios técnicos de la cirugía del GIST y el papel de la laparoscopia; y manejo del GIST en localizaciones infrecuentes y del GIST avanzado.

### Avances en la biología molecular y farmacología del tumor del estroma gastrointestinal

#### Biología molecular del tumor del estroma gastrointestinal

La identificación de la mutación oncocénica en GIST es básica, tanto desde un punto de vista pronóstico como terapéutico. La mayoría de los GIST presentan alteraciones en la secuencia de c-KIT que en la mayoría de los casos afectan al exón 11, seguido de alteraciones en el exón 9, siendo menos frecuentes las mutaciones en los exones 13 y 17, que se asocian a fenómenos de resistencia<sup>1</sup>. En 2003 se identificaron alteraciones en PDGFRA, que son excluyentes respecto de las de c-KIT, y que se localizan en los exones 12, 14 y 18, con mayor presencia de la mutación de resistencia primaria, D842V, localizada en el exón 18<sup>2</sup>. Aquellos casos en los que no se identifican alteraciones en estos genes se conocen como *wild type* (15%). Las alteraciones a lo largo de la secuencia de estos dos receptores influyen en el diagnóstico, pronóstico y predicción de respuesta al tratamiento, por lo que su determinación inicial se considera como imprescindible para el manejo de estos pacientes<sup>3</sup>.

El 15% de casos sin alteraciones en c-KIT o PDGFRA incluyen muy diversas alteraciones moleculares (Tabla 1). Las dos más frecuentes son las de la vía BRAF y del complejo SDH<sup>4</sup>. Los tumores sin alteraciones en KIT, PDGFRA, BRAF o SDH se denominan cuádruple *wild type*. En este grupo se incluyen alteraciones como la presencia de fusiones que afectan al receptor neurotrófico de tipo 3 (NRTK3) y al factor de crecimiento de fibroblastos (FGFR1), o el factor de transcripción ETV<sup>5</sup>. Así pues, el término de GIST *wild type* ha ido evolucionando y fraccionándose con el tiempo, englobando en primer lugar aquellos tumores sin alteraciones en c-KIT, e incluyendo posteriormente a tumores sin alteraciones en PDGFRA, BRAF y SDH. Por ello parece más adecuado abandonar la terminología GIST *wild type* y sustituirla por la de «tumores sin mutaciones identificadas» (GIST NOS)<sup>6</sup>.

#### Nuevos fármacos y estrategias de combinación

La activación oncocénica de los receptores tirosina cinasa KIT o PDGFRA constituye el evento central que rige el curso evolutivo de los GIST. La función de KIT o PDGFRA continúa siendo esencial en el mantenimiento del fenotipo tumoral<sup>1</sup>, hasta el punto de que las estrategias farmacológicas aprobadas a día de hoy, y también las que se encuentran en investigación, están centradas en su inhibición.

La mutación oncocénica en c-KIT o PDGFRA es el evento fundamental de la biología del GIST. Su bloqueo con imatinib ha mostrado un gran beneficio clínico comunicándose tasas de respuesta (TR) del 51% con un 90% de beneficio clínico y una supervivencia libre de progresión (SLP) cercana a los dos años<sup>7</sup>. Este fármaco también ha sido aprobado para su uso de forma adyuvante tras resección quirúrgica<sup>8</sup>.

La mayor parte de los pacientes con GIST avanzado o metastásico desarrollan a la larga una resistencia al tratamiento con imatinib, normalmente a los dos

**Tabla 1. Fragmentación y subdivisión del tumor del estroma gastrointestinal (GIST) *wild type***

<b>GIST wild type (KIT/PDGFRa)</b>				
SDH Deficientes				
BRAF				
NF-1				
Cuádruple WT	Mutaciones Somáticas	CBL APC CTDNN2 TP53 ARID1A	MAX MEN-1 BCOR CHD4	
Fusión de genes		FGFR1 p.N546K FGFR1-KOOK3 FGFR1-TACC1 ETV6-NTRK3	KIT-PDGFRa MARK2-PPFIA-1 SPRED2-NELFCd	

Adaptada de Liegl et al<sup>9</sup>

años de su inicio, aunque hasta un 33% de pacientes tienen la enfermedad controlada durante cinco años o más, y hasta un 6-9% durante 10 años o más<sup>7</sup>. El principal mecanismo de resistencia (90% de los casos) consiste en el crecimiento de subpoblaciones celulares o clones con mutaciones secundarias que confieren resistencia al fármaco<sup>9</sup>. Durante los últimos 15 años se han desarrollado inhibidores de la tirosina cinasa (ITQ) con un espectro de actividad más amplio frente a diversas mutaciones secundarias en KIT. Así, en 2006 se aprobó el sunitinib<sup>10</sup> y en 2012 el regorafenib<sup>11</sup>, ambos con un amplio espectro de inhibición. Tras progresión a imatinib, la TR es pobre (<10%), con un intervalo libre de progresión de 4-6 meses independientemente de la línea de tratamiento empleada (Tabla 2)<sup>10,11</sup>.

En 2020 asistimos al desarrollo de múltiples ITQ (Tabla 3) y la aprobación por parte de la FDA (*Food and Drug Administration*) de dos nuevos y revolucionarios ITQ: avapritinib y ripretinib.

El avapritinib (BLU-285) se une de forma específica, y con gran potencia de inhibición, a la forma activa de KIT y PDGFRA, siendo altamente específico frente a mutaciones en el dominio de activación, lo que es muy relevante en GIST con la mutación D842V en el exón 18 de PDGFRA. Esta mutación es intrínsecamente resistente a cualquier ITQ aprobado hasta la fecha. Así, se observa que hasta el 95% de los pacientes con esta mutación tratados con avapritinib obtuvieron una disminución del tamaño tumoral, exhibiendo TR del 86%, la mayoría durante >12 meses. El avapritinib es eficaz en pacientes con mutaciones

**Tabla 2. Inhibidores de la tirosina cinasa (ITQ) aprobados o investigados tras progresión a imatinib**

ITQ	Línea terapéutica	Tasas de respuesta (%)	SLP (meses)	Estado (fase)
Sunitinib	2. <sup>a</sup>	7	6.1	Aprobado
Regorafenib	3. <sup>a</sup>	4.5	4.8	Aprobado
Dasatinib	2. <sup>a</sup>	ND	2.0	II
Dovitinib	≥ 2. <sup>a</sup>	5	4.6	II
Masitinib	2. <sup>a</sup>	ND	3.7	II
Nilotinib	3. <sup>a</sup>	0	6.0	II
	3. <sup>a</sup>	3	3.7	II
	3. <sup>a</sup>	< 1	3.6	III
Pazopanib	≥ 2. <sup>a</sup>	0	1.9	II
	≥ 2. <sup>a</sup>	0	3.4	II
Ponatinib	≥ 2. <sup>a</sup>	8	4.3	II
Sorafenib	≥ 2. <sup>a</sup>	13	4.9	II
	≥ 3. <sup>a</sup>	13	5.2	II

SLP: supervivencia libre de progresión; ND: no definido.

**Tabla 3. Estrategias terapéuticas en desarrollo en tumor del estroma gastrointestinal (GIST)**

Estrategia	Ejemplo (s)
Inhibidores pan-KIT	Ripretinib (DCC-2618)
Inhibidores selectivos de mutaciones	Avapritinib (BLU-285)
Estabilidad proteica de KIT	Inhibidores de HSP90 o de HDAC
Vías de señalización de KIT	Inhibidores de PI3K o de MEK
Adaptación a la inhibición de KIT	Inhibidores de MET o de FGFR
Heterogeneidad de KIT	Rotación rápida de ITQ

ITQ: inhibidores de la tirosina cinasa.

primarias en progresión a todas las líneas de tratamiento estándar, con TR del 22% con una duración media de 10 meses<sup>12</sup>.

El ripretinib (DCC-2618) es un inhibidor pan-KIT que interfiere en la activación de la cinasa independientemente del tipo de mutación secundaria existente. Su uso en pacientes refractarios a todo tipo de tratamientos para enfermedad metastásica ha demostrado lograr tasas de SLP de 6.3 meses con TR cercanas al 10%<sup>13</sup>.

**Tabla 4. Mutaciones y sensibilidad al tratamiento del tumor del estroma gastrointestinal (GIST) según tipo de mutación**

Mutación	Tratamiento (sensibilidad)
KIT exón 11	Imatinib, regorafenib
KIT exón 9	Imatinib (800 mg/día). Sunitinib
KIT exón 13	Sunitinib, ripretinib
KIT exón 14	Sunitinib, regorafenib, ripretinib
KIT exón 17	Regorafenib, ripretinib
KIT exón 18	Dasatinib, ripretinib
PDGFRA D842V	Avapritinib, crenolanib
exón 18	Resistencia al imatinib.
No mutación KIT/	Regorafenib (si SHD deficiencia).
PDGFRA WT	Dasatinib

La posibilidad de tratar a estos pacientes con cinco líneas de tratamiento (Tabla 4) supondrá un aumento de la supervivencia global de estos pacientes, lo que hará plantearnos su manejo a lo largo del tiempo, el orden en el empleo de estos fármacos y la posibilidad de tomar decisiones quirúrgicas a lo largo de la evolución de la enfermedad.

## Avances en la cirugía del tumor del estroma gastrointestinal

### Principios de la cirugía del tumor del estroma gastrointestinal y su manejo laparoscópico

La cirugía del GIST primario localizado consiste en la extirpación de la lesión con márgenes quirúrgicos libres (R0) sin linfadenectomía<sup>14</sup>. En este contexto, el abordaje laparoscópico del GIST se ha visto muy favorecido, pues tanto las características de estos tumores como los principios que rigen su cirugía (Tabla 5) son fácilmente aplicables<sup>14,15</sup>. A estos principios<sup>14</sup>, que son los mismos que en cirugía abierta, habría que añadir una serie de consideraciones (Tabla 6)<sup>14</sup>:

- Se debe evitar su uso si no fuera posible obtener una resección R0.
- No debe emplearse en tumores >10 cm debido al alto riesgo de rotura tumoral. Su uso debe restringirse a GIST <5 cm en localizaciones anatómicas favorables<sup>16</sup>.
- Debe limitarse a tumores localizados en la curvatura mayor, *fundus* y cara anterior gástrica. Localizaciones con la unión gastroesofágica, cardias, curvatura menor, cara posterior o antro/píloro plantean problemas técnicos que favorecen el empleo del abordaje abierto.

**Tabla 5. Consideraciones técnicas en la cirugía del tumor del estroma gastrointestinal (GIST) primario localizado**

Objetivos y principios técnicos generales de la cirugía del GIST
Exploración abdominal completa
Resección macroscópicamente completa con márgenes negativos (R0)
Márgenes amplios innecesarios (1 cm)
Pseudocápsula intacta sin rotura tumoral
La linfadenectomía no está indicada
Si márgenes microscópicos afectos (R1) considerar la re-resección caso a caso

**Tabla 6. Consideraciones técnicas en la cirugía laparoscópica del tumor del estroma gastrointestinal (GIST) primario localizado**

Objetivos y principios técnicos generales de la cirugía laparoscópica del GIST
Mismos principios técnicos que en cirugía abierta
Solo por grupos con experiencia
Extracción de la pieza en bolsa protectora
Aceptable si permite resección R0
Límite de su aplicación marcado por el tamaño tumoral (>5 cm?)

- La extracción de la pieza quirúrgica siempre debe efectuarse en bolsa a fin de evitar implantes en la pared abdominal a nivel del orificio de extracción.
- La experiencia del equipo quirúrgico es clave. No solo cuenta la experiencia en cirugía laparoscópica, sino también en estos tumores en particular.

El empleo de este abordaje proporciona una serie de ventajas propias a todo abordaje laparoscópico: utilización de incisiones más pequeñas, menor manipulación intestinal, reducción del dolor postoperatorio, más rápida recuperación de la funcionalidad digestiva y una disminución de la estancia hospitalaria<sup>14-17</sup>.

En la actualidad no existen estudios prospectivos aleatorizados que comparan el abordaje abierto frente al laparoscópico. Sin embargo, sí que se dispone de diversos metaanálisis<sup>17,18</sup> que evidencian, en primer lugar, la existencia de un fuerte sesgo de selección a favor del grupo laparoscópico: estos pacientes poseen un menor tamaño tumoral; y además, la localización de los tumores suele ser más favorable al situarse con

más frecuencia en la curvatura mayor. Por el contrario, en el grupo abierto existe una tendencia a GIST localizados en posiciones poco favorables, lo que junto a su mayor tamaño obliga con mayor frecuencia a resecciones gástricas mayores. En segundo lugar, se advierte un menor tiempo operatorio en el abordaje laparoscópico, lo que se explica porque la resección «en cuña» es técnicamente más sencilla, con menores tasa de complicaciones postoperatorias y bajas tasas de conversión a cirugía abierta (4.7-5.2%), lo que enfatiza la reproducibilidad y seguridad del procedimiento laparoscópico. Además, este abordaje se asocia a una reducción en la estancia hospitalaria, con un menor dolor postoperatorio y una rápida reincorporación socio-laboral. Finalmente, cuando se efectúa un análisis de los resultados oncológicos por grupos en igualdad de técnica quirúrgica, tamaño o localización, no se aprecian diferencias en el intervalo libre de enfermedad o en la supervivencia global<sup>17,18</sup>.

Las evidencias disponibles en GIST yeyuno-ileal son mucho menores<sup>19</sup>. En esta situación se recomienda una cirugía precoz, a fin de evitar una obstrucción intestinal o hemorragia grave. La cirugía «en cuña» solo es factible en lesiones <1 cm, indicándose en el resto la resección segmentaria. Los principales factores que desaconsejan el abordaje laparoscópico en esta localización son la presencia de adherencias, la perforación tumoral, la proximidad al duodeno, la presencia de enfermedad avanzada y la necesidad de resecciones concomitantes<sup>19</sup>.

Finalmente, comentar el auge experimentado en los últimos años de la cirugía laparoscópica ayudada por la endoscopia intraoperatoria<sup>20</sup>. Su uso facilita la localización de GIST intragástricos, no objetivables en la superficie gástrica; permite asegurar una resección oncológica con márgenes óptimos; permite el chequeo de la sutura mecánica y permite, finalmente, comprobar la ausencia de estenosis postoperatorias. Otros abordajes de alta complejidad descritos recientemente incluyen la cirugía intragástrica o intraluminal<sup>21</sup>, efectuada a través de una gastrotomía en la cara anterior, que permite el manejo de tumores de la pared posterior y el *fundus*, técnica que puede efectuarse asistida con la mano o combinada con endoscopia, y la cirugía robótica<sup>22</sup>.

### **Manejo del tumor del estroma gastrointestinal en localizaciones infrecuentes**

Los GIST se suelen localizar en el estómago (55-60%) e intestino delgado (30%). Otras localizaciones muy

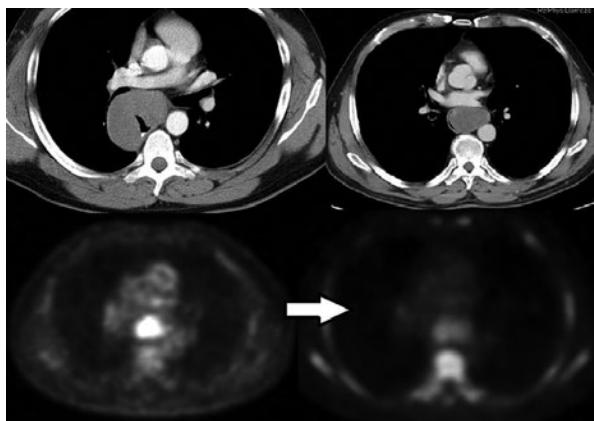


**Figura 1.** Tránsito esófago-gástrico donde se evidencia defecto de repleción en 1/3 medio esofágico de gran tamaño que corresponde a tumor del estroma gastrointestinal esofágico.

infrecuentes son el esófago, el duodeno o el recto y localizaciones extradigestivas como el omento, el mesenterio, la pelvis o el retroperitoneo. En estos casos no se dispone de recomendaciones claras respecto de su diagnóstico y tratamiento, por lo que su manejo supone un reto extraordinario.

En una reciente revisión, el GIST esofágico suponía el 23% de los tumores en esta localización, habiéndose descrito en los últimos 15 años alrededor de 150 casos en todo el mundo<sup>23</sup>. Afecta predominantemente a varones con una edad media de 60 años. La mayoría de los pacientes manifiestan disfagia (36-51%) y pérdida de peso (20%), siendo el 30% de ellos asintomáticos<sup>23</sup>.

El diagnóstico diferencial<sup>41</sup> se plantea con diversos tumores, aunque el más importante es con el leiomioma<sup>24</sup>. El tránsito esófago-gástrico (Fig. 1) y la ecoendoscopia (EE) ayudan a diferenciar entre lesiones submucosas y mucosas<sup>24</sup>, advirtiéndose que la ulceración mucosa es característica del GIST. La EE permite valorar tamaño, forma, aspecto intratumoral y relación con las capas musculares del esófago. La tomografía computarizada (TC) y la resonancia magnética (RM) describen los GIST, a diferencia de los



**Figura 2.** Imágenes de tomografía computarizada donde se aprecian masas ocupantes de espacio a nivel esofágico discretamente homogéneas.



**Figura 3.** Imagen de tomografía computarizada en donde se evidencia tumor del estroma gastrointestinal duodenal en 2.<sup>a</sup> porción.

leiomiomas, como tumores grandes, distales e hipervascularizados y de aspecto heterogéneo (Fig. 2). En la tomografía por emisión de positrones, el GIST posee una captación intensa y homogénea que casi nunca poseen los leiomiomas<sup>25</sup>. La biopsia, mediante punción aspirativa con aguja fina (PAAF/PAB) guiada por EE permite el estudio histológico e inmunohistoquímico del tumor<sup>42</sup>. El 80% de estos tumores se localizan en el tercio distal esofágico, suelen ser >5 cm y con >5 mitosis/50 CGA, por lo que deben ser considerados como tumores con alto riesgo de recidiva<sup>22,25</sup>.

La principal controversia terapéutica consiste en saber si es la enucleación o la esofagectomía la técnica quirúrgica de elección. Así, la enucleación ofrece una mayor seguridad técnica, aunque puede favorecer resecciones incompletas<sup>26</sup>; mientras que la esofagectomía ofrece una mayor seguridad oncológica a expensas de una mayor morbilidad. En las series publicadas, la enucleación posee mejores resultados a largo plazo que la esofagectomía, pues trata tumores de menor tamaño y por ello se asocian a un menor riesgo de recidiva. Es decir, que el factor pronóstico clave en el GIST esofágico es el tamaño tumoral y el número de mitosis<sup>26</sup>. En caso de rotura tumoral o resección R1, independientemente de la técnica quirúrgica empleada, la tasa de recurrencias alcanza el 35-50%, mientras que es del 0% en caso de ausencia de estos factores. La elección de una u otra técnica dependerá, pues y sobre todo, del tamaño tumoral y la experiencia del grupo quirúrgico. En general, se recomienda la enucleación en pacientes asintomáticos con tumores <2 cm<sup>27</sup>. En grupos

experimentados incluso es posible la enucleación vía toracoscópica en tumores de hasta 5 cm. Cuando el GIST esofágico es >10 cm se recomienda la esofagectomía. El manejo en casos con tamaño intermedio, entre 2 y 10 cm, es mucho más controvertido y dependerá de la presencia de ulceración mucosa, del índice mitótico y de su proximidad a la unión esófago-gástrica. Por tanto, los factores determinantes para la selección de la técnica son el tamaño, localización, presencia o no de ulceración mucosa, riesgo operatorio y experiencia del equipo quirúrgico.

En GIST cercanos a la unión gastro-esofágica existe una clara controversia entre los defensores de la enucleación, que se apoyan en la eficacia de los ITQ preoperatorios; y los que defienden la esofagogastrectomía<sup>23-27</sup>. El uso neoadyuvante de ITQ puede mejorar la situación local del tumor y favorecer una resección más conservadora. Los pacientes con importantes factores individuales de alto riesgo pueden beneficiarse de un tratamiento exclusivo y de por vida con ITQ<sup>23-27</sup>.

Globalmente, la supervivencia observada es del 45-85% a los cinco años, con una tasa de recurrencia del 22-39%, identificándose como principales factores de riesgo el tamaño tumoral (>5 cm) y el índice mitótico (>5 / 5 mm<sup>2</sup>)<sup>26</sup>.

Los GIST duodenales, normalmente localizados en la 2.<sup>a</sup> porción (Fig. 3), suponen el 30% de todos los tumores duodenales y solo el 2-3% de todos los GIST<sup>28</sup>. En caso de enfermedad localizada o localmente avanzada, se recomienda el tratamiento con ITQ neoadyuvante con el fin de reducir el tamaño tumoral<sup>29</sup>. Serán candidatos ideales aquellos

pacientes en los que la cirugía que efectuar de entrada sea una duodeno-pancreatectomía cefálica; y aquellos con tumores en los que una reducción de volumen tumoral favorezca una resección con márgenes negativos e incluso la posibilidad de realizar resecciones limitadas<sup>29</sup>.

Las técnicas quirúrgicas que emplear dependen del tamaño tumoral, de la relación con la cabeza del páncreas, ampolla de Vater y coléodo terminal, y de su situación mesentérica o antimesentérica. Las diferentes opciones quirúrgicas incluyen:

- Resección limitada en cuña de la pared o *wedge resection*. Aplicable en tumores pequeños (<3-4 cm), localizados a una distancia >2 cm de la papila y que asientan en el borde antimesentérico<sup>30</sup>.
- Resección segmentaria duodenal. Empleada en tumores ubicados en la tercera o cuarta porción duodenal, su reconstrucción pasa por el empleo de un asa en Y de Roux anastomosada a la 2.<sup>a</sup> porción duodenal. Es un procedimiento potencialmente ejecutable vía laparoscópica<sup>30,31</sup>.
- Duodenectomía con preservación pancreática. Consiste en la resección de todo el duodeno y la posterior colocación de un asa de yeyuno a la que se anastomosa el duodeno yuxtapilírico, la vía biliar y el conducto pancreático<sup>32</sup>.
- Duodenopancreatectomía cefálica. Indicada en GIST >5 cm localizados en la 2.<sup>a</sup> porción duodenal con invasión de la papila de Vater o páncreas. Suelen ser tumores de alto índice mitótico y comportamiento más agresivo, lo que explica su peor pronóstico, no relacionado con la cirugía *per se*<sup>29,33</sup>.

El abordaje laparoscópico en los GIST duodenales es posible, especialmente en tumores <5 cm en localizaciones anatómicas favorables (1.<sup>a</sup> y 3.<sup>a</sup>/4.<sup>a</sup> porción duodenal), aunque solo debería emplearse por grupos de alta experiencia. Los GIST de gran tamaño (>5-7 cm) tienen un mayor riesgo de ruptura, por lo que en estos casos es más recomendable la cirugía abierta<sup>31</sup>.

Se considera que los GIST duodenales tienen un comportamiento menos agresivo que los GIST ubicados en otras localizaciones, con una tasa de supervivencia a cinco años del 94.9%. A pesar de ello, presentan una tasa de recidiva del 10-20%, incluso tras cirugía R0. La tasa libre de enfermedad a uno y tres años después de una resección completa varía del 86 al 100%<sup>33</sup>.

Los GIST rectales representan la tercera localización más frecuente, aunque solo suponen el 1.6-5%

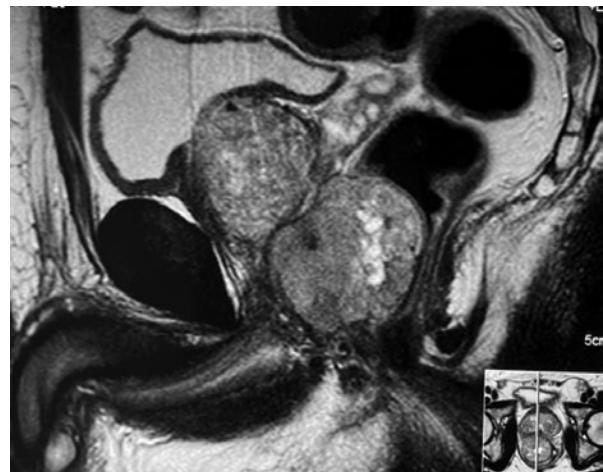


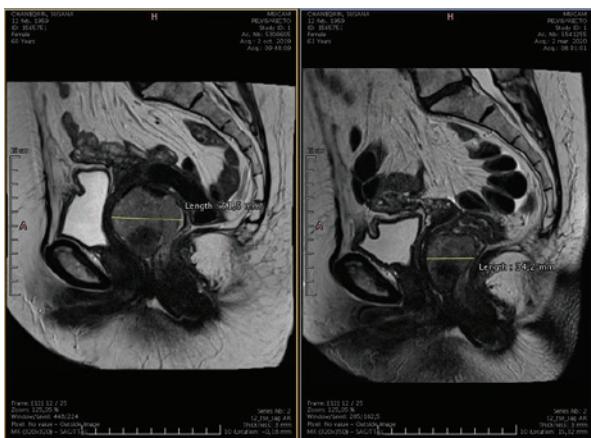
Figura 4. Resonancia magnética de tumor del estroma gastrointestinal rectal que permite apreciar sus relaciones anatómicas en pelvis.

de todos los GIST<sup>34</sup>. No tienen síntomas específicos, por lo que frecuentemente se confunden con otras patologías anorrectales. Los síntomas más frecuentes son el sangrado (28.9%) y el dolor anal (17.8%). En ocasiones son hallazgos incidentales. La TC y la RM (Fig. 4) son muy útiles para su diagnóstico y estadificación, además de permitir determinar una posible afectación de órganos pélvicos. La ecografía endorrectal localiza el tumor y determina el tamaño y su relación con los esfínteres<sup>35,36</sup>.

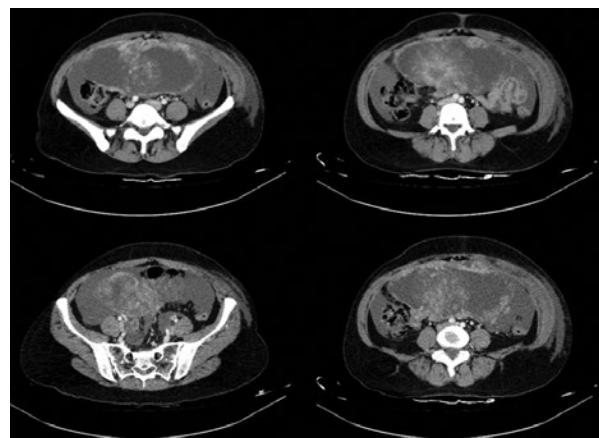
La elección del tipo de cirugía debe individualizarse según el estado del paciente, la localización y tamaño del tumor, el grado de la extensión e invasión local y la experiencia del equipo quirúrgico<sup>35,36</sup>. La resección quirúrgica puede ser muy difícil en situaciones de pelvis profunda y estrecha, tal y como ocurre en varones; o en caso de tumores muy próximos a esfínteres anales u otros órganos vecinos. En estas condiciones, la resección R0 solo se llega a conseguir en un 40-60% de los pacientes.

Las opciones técnicas son:

- Escisión local. Indicada en GIST pequeños (<2 cm) localizados en recto distal con posibilidad de márgenes >1 cm sin afectación del esfínter anal. En tumores de situación anterior existe el riesgo de fístula recto-vaginal en mujeres, o de lesión uretral en hombres<sup>37</sup>.
- Resección local bajo visión directa. Indicada en tumores muy próximos al margen anal. Técnicas como la TAMIS (cirugía transanal a través de puerto único), la TEM (microcirugía transanal) e incluso la TAMIS robótica<sup>37,38</sup> mejoran la visión,



**Figura 5.** Efectos del tratamiento neoadyuvante en tumor del estroma gastrointestinal rectal, antes (izquierda) y después (derecha) del tratamiento con imatinib, apreciándose una importante disminución del tamaño tumoral.



**Figura 6.**Imagen de resonancia magnética de tumor del estroma gastrointestinal mesentérico.

facilitándose la resección. Otras vías de resección local incluyen la vía transesfinteriana, la transvaginal o la trans-sacra de Kraske<sup>38,39</sup>.

- Resecciones amplias de recto. Indicadas en lesiones de mayor tamaño ( $\geq 2$  cm) con invasión profunda y afectación esfinteriana. En estos casos se debe de tener en cuenta las comorbilidades del paciente, el tamaño y localización del tumor, y las posibilidades de preservación esfinteriana<sup>36</sup>. Se puede optar entre una cirugía radical sin escisión del mesorrecto como la resección anterior baja, la amputación abdomino-perineal (de elección en tumores de recto distal con imposibilidad de preservación esfinteriana) y la exanteración pélvica, indicada en tumores los localmente avanzados<sup>36</sup>.

Los GIST rectales localmente avanzados, no candidatos a una cirugía de resección «de entrada», deben someterse a tratamiento neoadyuvante (Fig. 5) para reducir su tamaño y facilitar la preservación esfinteriana<sup>40,41</sup>. La combinación de neoadyuvancia y cirugía es factible en más de la mitad de los casos<sup>40,41</sup>.

La presencia de células intersticiales de Cajal (CIC) en varios órganos o tejidos conectivos del organismo puede explicar la aparición de GIST en localizaciones extragastrointestinales (EGIST)<sup>42-44</sup>. El GIST mesentérico posee una incidencia muy baja (5-12%), suele ser solitario y afecta más a mujeres entre los 60 y 65 años, con un tamaño medio de 12 cm<sup>42-44</sup>. Los síntomas más frecuentes son el dolor y/o la presencia de una masa abdominal de crecimiento lento e indolente,

lo que facilita grandes tumores (Fig. 6). El tratamiento de elección del EGIST localizado es la cirugía exérética «en bloque». En caso de enfermedad avanzada deben ser tratados de inicio con ITQ, y solo en caso de obtener una buena respuesta podría plantearse una cirugía de rescate. Los principales factores de mal pronóstico son el tamaño, la presencia de necrosis, un elevado índice de mitosis por campo y un ki-67 elevado<sup>42-44</sup>.

### **Tumor del estroma gastrointestinal diseminado y/o metastásico**

El principal avance en el manejo del GIST avanzado ha sido la incorporación de la cirugía como adyuvante al tratamiento médico. Este tratamiento médico está basado en el uso continuado de ITQ, el cual posee algunas peculiaridades<sup>45,46</sup>:

- El imatinib es el fármaco de elección, dada la más frecuente mutación c-KIT en el exón 11. En caso de mutaciones en PDGFRA (exón 18) o sin mutación KIT/PDGFRA (*wild type*), se deben emplear otros ITQ (Tabla 4). Así, en caso de mutaciones PDGFRA D842V deberían emplearse fármacos como el avapritinib o el crenolanib; mientras que el subgrupo WT SDH deficiente puede ser candidato a tratamiento con sunitinib, pero con TR bajas.
- El tratamiento debe durar un mínimo de 6-9 meses previamente a una resección, debido a que la exposición mantenida al fármaco favorece el

- desarrollo de resistencias antes de los dos años en hasta el 50% de los pacientes.
- Los ITQ deben emplearse también de forma adyuvante incluso en aquellos pacientes en los que se han podido resecar todas las lesiones metastásicas, y además, de forma indefinida hasta la aparición de resistencias, pues su suspensión se asocia a una rápida progresión de la enfermedad.
  - Tratamientos como la ablación o la radioterapia paliativa también pueden ser de utilidad en casos bien seleccionados con progresión locorregional no subsidiaria de resección quirúrgica.

Los GIST que desarrollan sarcomatosis peritoneal o GISTosis<sup>47,48</sup>, de forma espontánea o secundaria a una ruptura del tumor durante la cirugía, tienen un mal pronóstico. En esta situación, la cirugía de citorreducción de inicio no supone ningún beneficio, siendo la administración de ITQ el tratamiento de elección. La cirugía citorreductora estaría indicada cuando puede conseguirse una resección completa en pacientes con una buena respuesta al imatinib. En caso de resistencia al imatinib, la cirugía de citorreducción estaría tan solo indicada en aquellos pacientes con progresión limitada en los que pueda conseguirse una resección completa.

Cerca del 20% de los GIST presentan, en el momento del diagnóstico o bien en el curso evolutivo de la enfermedad, metástasis hepáticas. Se calcula que la cirugía del GIST metastásico puede realizarse únicamente en el 30% de los casos, con una supervivencia media de 19 meses. En este contexto, la cirugía adyuvante puede prolongar la supervivencia en pacientes seleccionados con respuesta a ITQ, siendo ineficaz en caso de progresión tras la administración de ITQ<sup>49,50</sup>. Un estudio de la European Organisation for Research and Treatment of Cancer (EORTC)<sup>51</sup> evidencia la posibilidad de conseguir elevadas tasas de resecciones R0 y de una mayor supervivencia, especialmente si la cirugía es completa (R0) y si es seguida de un tratamiento continuado con ITQ. Esta estrategia es claramente aceptada cuando las metástasis hepáticas son técnicamente resecables<sup>49-51</sup>. En 2015, el Grupo Español para Investigaciones en Sarcomas (GEIS) publicó<sup>52</sup> un análisis sobre 171 pacientes con GIST metastásico no resecable y no refractario al tratamiento con imatinib, concluyéndose que con base en la superior supervivencia obtenida en los pacientes incluidos en el grupo con cirugía de rescate, esta estrategia debe ser valorada en todos los pacientes con GIST metastásico hepático siempre que muestren una buena respuesta

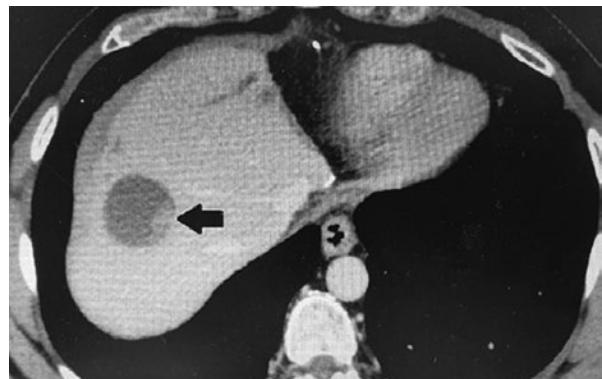


Figura 7. Imagen radiológica (tomografía computarizada) en donde se aprecia una recurrencia dentro de un nódulo («nódulo dentro de nódulo»).

a ITQ preoperatorio. La indicación de la cirugía de rescate debe hacerse a partir de los seis meses de iniciar el tratamiento con imatinib, ya que es en este momento cuando aparece la máxima respuesta tumoral. Esta cirugía debe efectuarse dejando el menor intervalo posible preoperatorio y postoperatorio sin tratamiento con imatinib<sup>46</sup>. En pacientes sin estabilización de las lesiones metastásicas, la exéresis de toda la masa tumoral posible (*debulking*), asociada o no a otras terapias de destrucción tisular como la radiofrecuencia<sup>53</sup>, puede conseguir ocasionalmente una mejor supervivencia, pero en ningún caso superior a la de los pacientes con una buena respuesta a imatinib. Es por ello que esta indicación quirúrgica debe ser restringida y valorada en casos excepcionales en un contexto multidisciplinario<sup>54</sup>.

Los pacientes sometidos a una exéresis de metástasis hepáticas de GIST, tras una buena respuesta a imatinib, pueden crear resistencias y desarrollar de nuevo una progresión hepática en forma de «nódulo dentro de nódulo hialinizado» (Fig. 7). En esta situación, la re-resección de estas metástasis ofrece una mejor supervivencia que si fueran tratados solo con imatinib<sup>54</sup>.

La cirugía adyuvante al tratamiento con ITQ en GIST metastásico hepático es una estrategia terapéutica de gran valor en enfermos seleccionados. Otras opciones como la radiofrecuencia<sup>53</sup> o la embolización arterial<sup>55</sup> también deben ser consideradas caso a caso. La posibilidad del trasplante en hepático en GIST metastásico irresecable es una opción recientemente explorada<sup>56</sup>.

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## Conflicto de intereses

No existe ningún conflicto de intereses por parte de los autores.

## Responsabilidades éticas

**Protección de personas y animales.** Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

**Confidencialidad de los datos.** Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

**Derecho a la privacidad y consentimiento informado.** Los autores declaran que en este artículo no aparecen datos de pacientes.

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# Alta frecuencia del alelo ancestral del polimorfismo SNV rs11212617 del gen ATM en población mestiza mexicana del Noroccidente

*High frequency of the ancestral allele from SNV rs11212617 polymorphism of the ATM gene in a Mexican Norwest population*

Claudia B. Montaño-Montejano<sup>1</sup>, Diana García-Cruz<sup>1,2</sup>, José Sánchez-Corona<sup>3</sup>, Héctor V. Ortega<sup>4</sup> y Sergio A. Ramírez-García<sup>5\*</sup>

<sup>1</sup>Departamento de Biología Molecular y Genómica, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jalisco, México; <sup>2</sup>Departamento de Biología Molecular y Genómica, Instituto de Genética Humana Dr. Enrique Corona Rivera, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jalisco, México; <sup>3</sup>División de Medicina Molecular, Centro de Investigación Biomédica de Occidente, Centro Médico Nacional de Occidente, Instituto Mexicano del Seguro Social, Guadalajara, Jalisco, México; <sup>4</sup>Departamento o Servicio, Thomas Jefferson University, Filadelfia, Pensilvania, Estados Unidos; <sup>5</sup>Instituto de Nutrición de la Universidad de la Sierra Sur, Miahuatlán de Porfirio Díaz, Oaxaca, México

Sr. Editor:

El gen *ATM* con locus en 11q22.3 codifica para la proteína cinasa nuclear de la ataxia telangiectasia (*ATM*), que regula el ciclo celular a través de las proteínas P53, BCRA1y RB<sup>1</sup>. Lo conforman 66 exones y 65 intrones (Fig. 1A)<sup>1</sup>. Algunas de sus variantes genéticas se relacionan con enfermedades como la ataxia telangiectasia y otras patologías inmunometabólicas (Fig. 1)<sup>1,2</sup>. En población mexicana solo se han reportado variantes de este gen en el cáncer de mama<sup>3</sup>. El SNV rs11212617, el cual consiste en una transversión A>C en un marco de lectura abierto (C11orf65), ha sido asociado también con diabetes y patologías cardiovasculares<sup>4</sup>, mas no se ha estudiado en México. Con estas consideraciones se analizó el SNV rs11212617 en mexicanos mestizos de acuerdo con los criterios de selección de Chakraborty para la proporción del alelo menor del SNV, por lo cual se incluyeron 269 muestras de DNA de individuos sanos<sup>4</sup>. La detección del SNV se realizó mediante PCR-RFLP (*Polymerase Chain*

*Reaction-Restriction Fragment Length Polymorphism*) y electroforesis por isoelectroenfoque por SSCP (*Single-Strand Chain Polymorphism*), como se reportó previamente (Fig. 1B)<sup>5</sup>, y fue corroborado por secuenciación automatizada. Así, la distribución de alelos en la población analizada muestra las siguientes frecuencias relativas: alelo ancestral A 0.7918 (n = 426) y 0.2081 (n = 112) para el alelo C. Genotipos: homocigotos A 0.639 (n = 172), heterocigotos 0.304 (n = 82) y homocigotos C 0.055 (n = 15). La distribución no presenta diferencias significativas con las frecuencias esperadas ( $\chi^2 = 1.528$ ; p = 0.216), por lo que la variante está en equilibrio Hardy Weinberg (Tabla 1). La heterocigosidad observada fue de 0.82, la esperada de 0.88 y la máxima de 0.5 (p = 0.71).

En conclusión el presente reporte es el primer estudio regional y nacional del SNV rs11212617 del gen *ATM* en mexicanos mestizos, y crea un referente para la realización de futuros estudios de asociación en enfermedades metabólicas, vasculares, oncológicas e infecciosas en población mexicana.

## Correspondencia:

\*Sergio A. Ramírez-García

Calle Guillermo Rojas Mijangos S/N.

Colonia Ciudad Universitaria,

C.P. 70800, Miahuatlán de Porfirio Díaz, Oax., México

E-mail: sergioNABMSP@gmail.com

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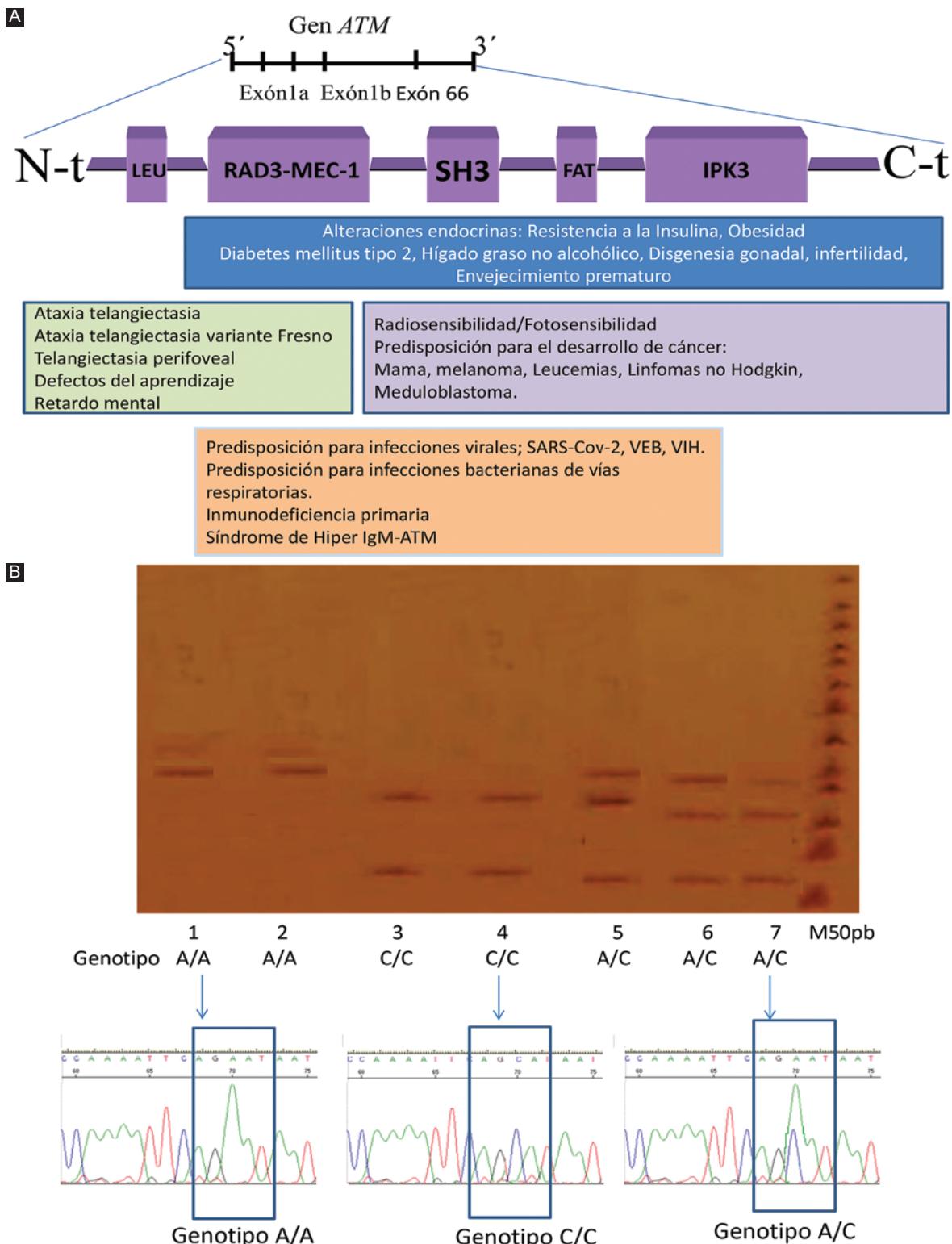
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**Figura 1.** A: espectro clínico del varioma y proteoma del gen de la ataxia telangiectasia (ATM). B: electroforesis PAGE20% homogénea y electroferograma de la secuenciación por Sanger de los productos de PCR-FRLP del SNV rs11212617. Las condiciones de amplificación de la PCR y digestión enzimática con HpyCH4III fueron las descritas previamente<sup>5</sup>. La electroforesis de los productos de digestión de PCR se corrieron mediante el equipo PhastSystem™ (Amersham Biosciences) por 1.5 horas. Fase 1.1 10 Vh, 10 mA, 2.0 W, 5 °C, 55 Vh. Fase 1.2 150 V, 1 mA, 2.5 W, 5 °C, 10 Vh, y se diferenciaron por los tamaños y cortes. El fragmento de 209 pb genera dos productos, uno de 153 pb y otro de 56 pb. La banda de 209 pb corresponde al genotipo homocigoto (A/A) (carriles 1 y 2 del gel). Cuando están presentes tres bandas, 209, 153 y 56 pb, respectivamente, corresponde al genotipo heterocigoto (A/C) (carriles 5, 6 y 7 del gel). Finalmente, si hay dos bandas, 153 y 56 pb, corresponde al genotipo homocigoto (C/C) (carriles 3 y 4 del gel), lo cual se corrobora por la secuenciación por Sanger.

**Tabla 1. Frecuencias globales alélicas y genotípicas del SNV rs11212617 del gen ATM**

Población	Frecuencia alélica			Frecuencia genotípica				
	N.º sujetos	A	C	AA	AC	CC	$\chi^2$	p
Presente estudio	269	<b>0.7918</b>	0.2081	0.639	0.304	0.055	1.5280	0.2164
Sur de India*	112	0.65	0.35	0.39	0.52	0.09	2.2219	0.1361
Caucásicos*	113	0.54	0.47	0.27	0.54	0.19	0.8784	0.3486
China*	43	0.31	0.69	0.09	0.44	0.47	0.0284	0.8662
Japón*	86	0.38	0.67	0.19	0.39	0.42	2.3156	0.1281
África*	113	0.19	0.81	0.02	0.34	0.65	1.3993	2.2368
África GnomAD	8682	0.2752	0.7248	NR	NR	NR	NR	NR
Asia								
1000 genomas/Sur de Asia	978	0.627	0.373	NR	NR	NR	NR	NR
gnomAD/Este de Asia	1552	0.3595	0.6405	NR	NR	NR	NR	NR
Europa								
ALFA	82410	0.5793	0.4206	NR	NR	NR	NR	NR
gnomAD	18866	0.5760	0.4239	NR	NR	NR	NR	NR
América								
PAGE/Nativos americanos	1260	0.523	0.477	NR	NR	NR	NR	NR
PAGE/Nativos de Hawái	4534	0.400	0.599	NR	NR	NR	NR	NR
PAGE/África-americanos	32516	0.277	0.722	NR	NR	NR	NR	NR
PAGE/Ancestría mexicana	10808	<b>0.621</b>	0.378	NR	NR	NR	NR	NR
PAGE/Puerto Rico	7918	0.520	0.479	NR	NR	NR	NR	NR
PAGE/Cuba	4230	0.557	0.442	NR	NR	NR	NR	NR
PAGE/República Dominicana	3828	0.448	0.551	NR	NR	NR	NR	NR

Nota: dbSNP 2021.

ALFA: frecuencias agregadas de alelos y genotipos; gnomAD: base de datos de agregación del genoma;

NR: datos no reportados; PAGE: Estudio de Arquitectura de la Población usando Genómica y Epidemiología; SGDP\_PRJ: Proyecto de diversidad del genoma Simons.

\*Datos tomados de Vilvanathan S et al.<sup>6</sup>

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## Conflictos de intereses

No existe conflicto de intereses por parte de los autores.

## Responsabilidades éticas

**Protección de personas y animales.** Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

**Confidencialidad de los datos.** Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

**Derecho a la privacidad y consentimiento informado.** Los autores han obtenido el consentimiento informado de los pacientes y/o sujetos referidos en el artículo. Este documento obra en poder del autor de correspondencia.

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# Emergencia por COVID-19 en la Sierra Sur de Oaxaca y la agenda 2030 del desarrollo sostenible

*Emergency due to COVID-19 in the Southern Sierra of Oaxaca and the agenda 2030 for sustainable development*

María E. Aguilar-Aldrete<sup>1</sup>, Sergio A. Ramírez-García<sup>2</sup>, José Domínguez-Rodas<sup>3</sup>,

Manuel G. Chávez-Ángeles<sup>1</sup>, Hady Keita<sup>4</sup>, Melecio H. Juárez-Pérez<sup>2</sup>, M. Alejandra Sánchez-Bandala<sup>3</sup>,

Nicole M. Stark-Carrillo<sup>5</sup> y Carlos E. Cabrera-Pivaral<sup>1\*</sup>

<sup>1</sup>Departamento de Salud Pública, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jalisco; <sup>2</sup>Instituto de Nutrición, Universidad de la Sierra Sur, Sistema de Universidades Estatales de Oaxaca (SUNEO), Miahuatlán de Porfirio Díaz, Oaxaca; <sup>3</sup>Servicios Médicos Profesionales, Particulares, A.C., Miahuatlán de Porfirio Díaz, Oaxaca; <sup>4</sup>División de Estudios de Posgrado, Universidad de la Sierra Sur, SUNEO, Miahuatlán de Porfirio Díaz, Oaxaca; <sup>5</sup>Escuela de Medicina, Universidad de Guadalajara Lamar, Guadalajara, Jalisco. México

Sr. Editor:

Retomamos con gran interés el artículo de Cervantes et al.<sup>1</sup>, y en este sentido Oaxaca está muy alejado de la *Agenda 2030 para el Desarrollo Sostenible* asociado a la pandemia de COVID-19. En los municipios con el sistema de «Partidos Políticos»<sup>2</sup>, como es el caso de Miahuatlán de Porfirio Díaz, Oaxaca, está agravada la crisis sanitaria por la falta de capacidades del municipio en el control sanitario, asociado a factores epidemiológicos como la negación de la enfermedad o la participación en tertulias religiosas (Tabla 1). A nivel económico, el municipio es una población comerciante y ganadera, y en este sentido no existe un adecuado manejo sanitario de comercios, mercado y puestos ambulantes relacionados con esta actividad. Demográficamente, persiste el incremento de migrantes extranjeros, mexicanos y universitarios, lo cual implica la

movilización de diferentes variantes genéticas de interés (VOI), siendo las más frecuentes la clase alfa y beta en adultos, y preocupantes (VOC) como la delta en jóvenes<sup>3</sup>. En la práctica médica privada son limitados los médicos certificados para el manejo de la COVID-19, y se realizan prácticas de diagnóstico viral inadecuadas, como el test de antígeno rápido, que se traducen en un incremento de presintomáticos. Ha faltado la vigilancia genómica mediante técnicas de secuenciación masiva para el monitoreo de las VOI y las VOC en los usuarios de los servicios de Salud, IMSS, ISSSTE, DIF, hospitales y clínicas particulares para iniciar un tratamiento temprano<sup>3,4</sup>. También hay falta de subsidio de medicamentos emergentes. Por otra parte, no se realiza el *Pooled Testing qRT-PCR* en los servicios públicos, comercios, centros de trabajo ni escuelas, lo cual ha reducido la detección de portadores asintomáticos<sup>5</sup>. Existe un desacoplamiento entre el

## Correspondencia:

\*Carlos E. Cabrera-Pivaral

Sierra Mojada, 950

Col. Independencia

C.P. 44340, Guadalajara, Jal., México

E-mail: cabrera\_pivaral@prodigy.net.mx;

sergioNABMSP@gmail.com

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**Tabla 1. Factores epidemiológicos de la crisis sanitaria por COVID-19 en Miahuatlán de Porfirio Díaz, Oaxaca, México**

Factores socioculturales y religiosos	Factores sanitarios	Factores demográficos	Factores de la práctica médica	Políticas públicas
Negación de la existencia de la enfermedad	Renuncia a la vacunación	Migrantes extranjeros (turismo)	Falta de médicos certificados para la atención de COVID-19	Falta de campañas de detección de portadores asintomáticos y presintomáticos por <i>Pooled Testing RT-PCR</i> , así como por secuenciación genómica
Procesiones de culto religioso y misas (católicos)	Falta del uso de cubrebocas	Migrantes paisanos que radican fuera de México	Uso de tratamientos no adecuados por las instituciones oficiales de salud	No se han comprado medicamentos emergentes con actividad antiviral
Reuniones y asambleas religiosas o de sectas (no católicos)	No se conserva la cultura de la sana distancia	Migrantes universitarios del Estado de Oaxaca (alumnos)	Tratamientos exagerados en el ámbito privado, se aplican más de 20 medicamentos simultáneamente	No se subsidia a la población la compra de medicamentos de sostén y de tanques con oxígeno
Tertulias religiosas, bautizos, bodas, comuniones, confirmaciones	Falta de la cultura de la sanitización y lavado de manos	Migrantes universitarios de fuera de Oaxaca (alumnos)	No hay detección subclínica por falta de pericia	No se subsidian estudios de secuenciación genómica para identificar variantes genéticas de interés y preocupantes de SARS-CoV-2
Realización de cabos funerarios; semanal, mensuales, anuales	No control sanitario del mercado municipal	Migrantes universitarios del Estado de Oaxaca (docente)	Falta pericia para la detección de la coinfección con neumonías bacterianas, neumonía de la comunidad y neumonía por influenza	No se subsidian los estudios de carga viral y actividad patogénica a los pacientes infectados
Festejos familiares abiertos a público	No control sanitario de los comercios ambulantes y estables	Migrantes universitarios de fuera de Oaxaca (docente)	Diagnóstico mediante prueba rápida de antígeno	Desacoplamiento entre la práctica médica institucional y privada
Cabalgatas, así como jaripeos públicos y privados	Falta control sanitario del tianguis para la venta de ganado	Falta de confinamiento entre las personas de las colonias y barrios	No hay médicos certificados en rehabilitación pulmonar y oxigenoterapia	No hay una liberación de vacunas para la venta al público

gobierno municipal y el sector de salud institucional y privado, y no se ha generado un manual policéntrico con las pautas para el manejo local, lo cual explica la existencia de más casos de los que reportan las instituciones oficiales que atienden COVID-19, cuyo control escapa a las funciones orgánicas de la regiduría de salud local (Fig. 1).

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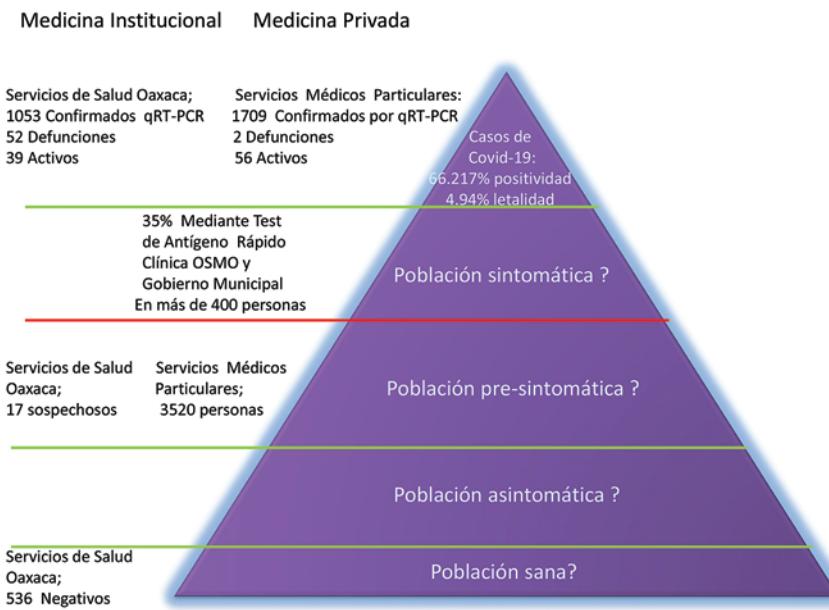
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## Conflictos de intereses

No existe conflicto de intereses por parte de ninguno de los autores.



**Figura 1.** Crisis sanitaria por COVID-19 en Miahuatlán de Porfirio Díaz, Oaxaca, México. Los pacientes que se detectan en la práctica privada superan los casos confirmados por las instrucciones oficiales del semáforo epidemiológico en el municipio. Los casos activos solo representan la punta del iceberg, pero en realidad la cantidad de personas contagiadas es mayor.

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# El tratamiento multidisciplinario del cáncer de laringe

*Multidisciplinary treatment of laryngeal cancer*

José F. Gallegos-Hernández\*

Departamento de Tumores de Cabeza y Cuello, Hospital de Oncología, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Ciudad de México, México

Sr. Editor:

Existen puntos de controversia en el tratamiento del cáncer de laringe, lo cual es evidente en el interesante artículo de Gurrola et al.<sup>1</sup> recientemente publicado. Lo más importante es obtener los estándares de control local y supervivencia con base en la evidencia existente de las diversas asociaciones terapéuticas. Por ello llama la atención que solo el 65% de los pacientes con etapas III-IVA fueran considerados operables, cuando se agrupan en ellas desde T1,N1 hasta T4A,N2, que son por definición operables y muchos de ellos no candidatos a preservación de órgano. Los autores reportan que la asociación de cetuximab y radioterapia, que no es el tratamiento estándar<sup>2</sup>, ofrece la mejor supervivencia; sin embargo, casi un tercio (27%) de los pacientes recurren y solo el 9% pueden ser rescatados, lo cual implica mal control si, por ejemplo, de pacientes T3,N0 se trataba. En esta serie, los que reciben inducción con quimioterapia tienen mejor supervivencia, pero el papel de esta es identificar pacientes candidatos a conservación no quirúrgica y no tiene impacto alguno en la supervivencia<sup>3</sup>. En etapa IVA (T1,N2 a T4A,N2, cuyo tratamiento estándar es la cirugía) se reporta algo similar; aunque no se desglosan los tratamientos, la supervivencia es mejor con quimioterapia de inducción seguida de bio-radioterapia, pero solo controla al 56% y hay recurrencia en

casi la mitad (41%), y solo el 8% pueden ser rescatados. La inadecuada selección del tratamiento inicial con intento conservador no quirúrgico ha traído como consecuencia un incremento en la mortalidad por cáncer laringeo, y esto parece reflejarse en la presente serie, en la cual la supervivencia a 5 años en etapa III es del 46.5% y en etapa IV es del 28.3%, cuando los estándares son el 80% y el 70%, respectivamente. El tratamiento estándar con intento conservador no quirúrgico es la asociación de quimio-radioterapia<sup>3</sup>. La quimioterapia de inducción selecciona pacientes a esta terapéutica. Los pacientes que no tienen función laríngea adecuada, independientemente de la etapa, deben ser sometidos a laringectomía, la cual ofrece el mejor control y la mayor supervivencia.

## Financiamiento

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El autor declara no tener conflictos de intereses.

## Responsabilidades éticas

**Protección de personas y animales.** Los autores declaran que para esta investigación no se han

### Correspondencia:

\*José F. Gallegos-Hernández

Avda. Cuauhtémoc 330

Col. Doctores

C.P. 06725, Ciudad de México, México

E-mail: gal61@prodigy.net.mx

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realizado experimentos en seres humanos ni en animales.

**Confidencialidad de los datos.** Los autores declaran que en este artículo no aparecen datos de pacientes.

**Derecho a la privacidad y consentimiento informado.** Los autores declaran que en este artículo no aparecen datos de pacientes.

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