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# Volumetric computed tomography Hounsfield unit analysis: a superior method for opportunistic osteoporosis screening and assessment

*Análisis volumétrico de unidades Hounsfield en tomografía computarizada: un método superior para la detección oportunistica y la evaluación de la osteoporosis*

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## Abstract

**Objectives:** This study investigated the correlation between two-dimensional and volumetric Hounsfield unit (HU) measurements from computed tomography (CT) and T-scores from dual-energy X-ray absorptiometry (DXA), assessing their interchangeability for opportunistic osteoporosis (OP) screening. **Methods:** A retrospective analysis included 97 patients (15 males, 82 females; mean age  $66.48 \pm 9.97$  years) who underwent lumbar CT and DXA within 7 months. Two-dimensional HU values were measured from axial images (L1-L4), whereas volumetric HU values were obtained using 3D segmentation. Correlations with DXA T-scores were analyzed, and agreement between methods was assessed using Bland-Altman analysis and intraclass correlation coefficients (ICC). **Results:** Both HU methods significantly correlated with DXA T-scores ( $p < 0.001$ ), with volumetric HU showing stronger correlations ( $r = 0.572$  vs.  $r = 0.532$ ). Osteoporotic patients had lower HU values, with volumetric HU offering better differentiation. Bland-Altman analysis revealed a systematic bias, with two-dimensional HU underestimating values. ICC showed excellent agreement, with volumetric HU achieving higher reliability (ICC = 0.963 vs. ICC = 0.918). **Conclusions:** Volumetric HU measurements provide a more reliable and sensitive assessment of trabecular bone density, making them a superior method for opportunistic OP screening and treatment monitoring.

**Keywords:** Osteoporosis screening. Hounsfield units. Dual-energy X-ray absorptiometry. Volumetric density. Trabecular bone.

## Resumen

**Objetivo:** Evaluar la correlación de las mediciones de unidades Hounsfield (HU) en la tomografía computarizada (bidimensional y volumétrica) y los T-scores de absorciometría de rayos X de energía dual (DXA), analizando su intercambiabilidad para la detección oportunistica de osteoporosis (OP). **Métodos:** Se incluyeron 97 pacientes (15 hombres y 82 mujeres, edad media  $66.48 \pm 9.97$  años) con TC lumbar y DXA en un intervalo de 7 meses. Se midieron los valores HU bidimensionales en imágenes axiales (L1-L4) y los valores volumétricos mediante segmentación 3D. Se analizaron las correlaciones con DXA y la concordancia entre métodos mediante Bland-Altman y coeficiente de correlación intraclass (CCI). **Resultados:** Ambas mediciones se correlacionaron significativamente con los T-scores de DXA ( $p < 0.001$ ), con una correlación más fuerte en HU volumétrico ( $r = 0.572$  vs.  $r = 0.532$ ). Los pacientes con osteoporosis mostraron valores HU más bajos, con mejor diferenciación en HU volumétrico. Bland-Altman indicó un sesgo sistemático con subestimación en HU bidimensional.

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*El CCI mostró alta concordancia, con mejor fiabilidad en HU volumétrico (CCI = 0.963 vs. CCI = 0.918). Conclusiones: Las mediciones volumétricas de HU ofrecen una evaluación más fiable y sensible de la densidad ósea trabecular, siendo un método superior para la detección de osteoporosis y el seguimiento de su tratamiento.*

**Palabras clave:** Detección de osteoporosis. Unidades Hounsfield. Absorciometría de rayos X de energía dual. Densidad volumétrica. Hueso trabecular.

## Introduction

Osteoporosis (OP) is becoming a more and more important public health problem as it causes significant morbidity and mortality, especially in postmenopausal women. OP causes a decrease in bone strength with the loss of bone mass and leads to an increased tendency to fragility fractures.<sup>1-3</sup> Therefore, early and accurate diagnosis is essential to prevent its progression and increase life quality. Dual-energy X-ray absorptiometry (DXA), the current gold standard of bone mineral density (BMD) evaluation, is based on a person's BMD T-score at the hip and lumbar spine. T-scores are derived as the difference between the individual's BMD and a reference population mean, divided by the reference population standard deviation. The World Health Organization defines OP as a BMD 2.5 standard deviations (SD) or less below the reference population mean, i.e., a T-score of  $-2.5$ , whereas osteopenia is a condition of low bone mass characterized by a BMD T-score between  $-1$  and  $-2.5$ .<sup>1,4</sup>

Every year, an increasing number of diagnostic multidetector computed tomography (CT) examinations are performed worldwide to image different anatomical regions, including vertebrae. In the literature, some studies report that there is a significant correlation between bone Hounsfield Unit (HU) obtained from lumbar CT examinations performed for diagnostic purposes other than OP and BMD measurements obtained from DXA.<sup>5-7</sup> There are studies where a large data pool is obtained from these diagnostic CT examinations performed with "opportunistic OP screening." It was stated that L1 trabecular attenuation has normative values, and these values can be a quick reference in OP screening at risk.<sup>8</sup> In most of these studies, trabecular component HU measurement was performed using the two-dimensional axial image of the vertebra. In regions such as the vertebra and proximal femur, trabecular bone density and microstructure may not be uniform.<sup>9</sup> It is reported that there is a decrease in thickness and number of horizontal and vertical trabeculae in OP.<sup>9,10</sup> Therefore, it might be

thought that HU measurements obtained from two-dimensional axial CT images may not provide sufficient information about the whole vertebra due to the heterogeneity of trabecular bone. To our knowledge, there is no study comparing volumetric HU values and HU values obtained from two-dimensional axial images.

In this study, we aimed to reveal whether there is a correlation between two-dimensional and volumetric HU value measurements obtained from CT examination and T scores obtained from DXA. In addition, we aimed to find out whether these two HU measurement methods can be used interchangeably.

## Methods

### Patient selection

We retrospectively reviewed the patients who had undergone either an abdominal or lumbar spinal CT scan, as well as a lumbar spine DXA scan, between January 2017 and December 2020. The time interval between CT and DXA scans required for inclusion was a maximum of 7 months. Patients with lumbar spine surgery or who were below 50 years of age were excluded from the study. Out of 1200 patients initially reviewed, 97 patients (15 males and 82 females) were ultimately included in the study (Fig. 1). The median time between CT and DXA scans for the included cohort was 4.5 months.

Balikesir University Clinical Research Ethics Committee approved this study with the decision number of 2021/219 in 2021.

The requirement for informed consent was waived due to the retrospective design of the study, which involved the analysis of pre-existing data.

### Imaging technique and analysis

DXA scans were performed using a GE Lunar machine (Lunar Prodigy model 8743; GE Lunar, Madison, WI, USA). The T-score and (BMD,  $\text{g}/\text{cm}^2$ ) of the L1 to L4 vertebrae were obtained from posteroanterior DXA scans.

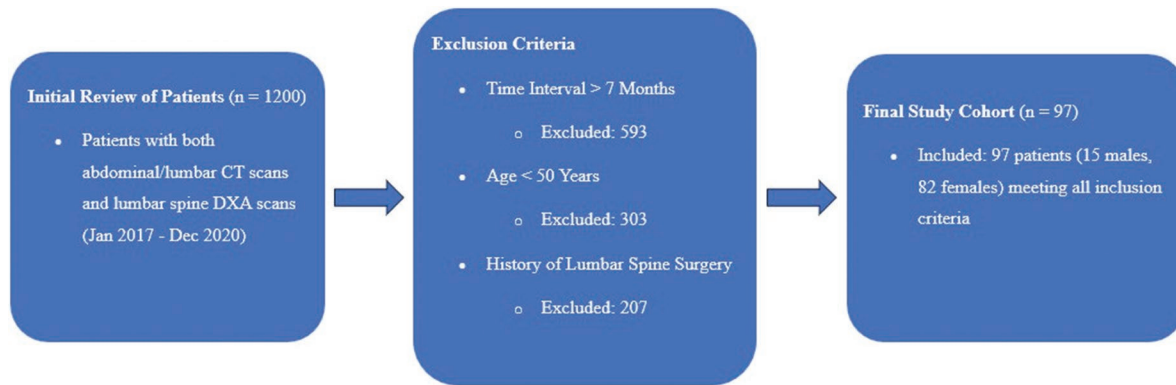


Figure 1. Flowchart of the patient selection.

CT scans were performed with a helical 64-channel multidetector CT scanner (Toshiba Aquillion 64, Tokyo, Japan). The CT imaging parameters for all patients were a slice thickness of 0.625 mm, tube voltage of 120 kVp, and tube current of 300 mA (with AEC Sure Exposure). Bone reconstruction settings were used (window width/window level –3000/300), and multiplanar reformatted images were acquired for analysis.

HU values were measured on the three axial images (immediately inferior to the superior end plate, mid-body of vertebra, and superior to the inferior end plate) of CT scans from each of the L1-4 vertebrae. Mean HU values were calculated for the regions of interest using the Extreme Picture Archiving and Communication System (Extreme PACS, Ankara, Türkiye) (Fig. 2). Volumetric HU values were calculated using 3D Slicer software version 5.0.3 ([www.slicer.org](http://www.slicer.org)). The segmentation process involved drawing a spherical volume of interest from the superior to the inferior end plate of the vertebra, excluding the basivertebral venous plexus. Mean HU values for each individual vertebra, overall L1-4, and overall L2-4 were obtained from these segmentations via 3D Slicer (Fig. 3).

The HU measurements were performed by two experienced radiologists who were blinded to the T scores of DEXA scans and the mean values of the other patients.

Interobserver reliability was assessed using a subset of 30 randomly selected cases, with measurements performed independently by two radiologists to ensure unbiased results.

### Statistical analysis

All the statistical analyses were conducted using the Statistical Package for the Social Sciences version 22

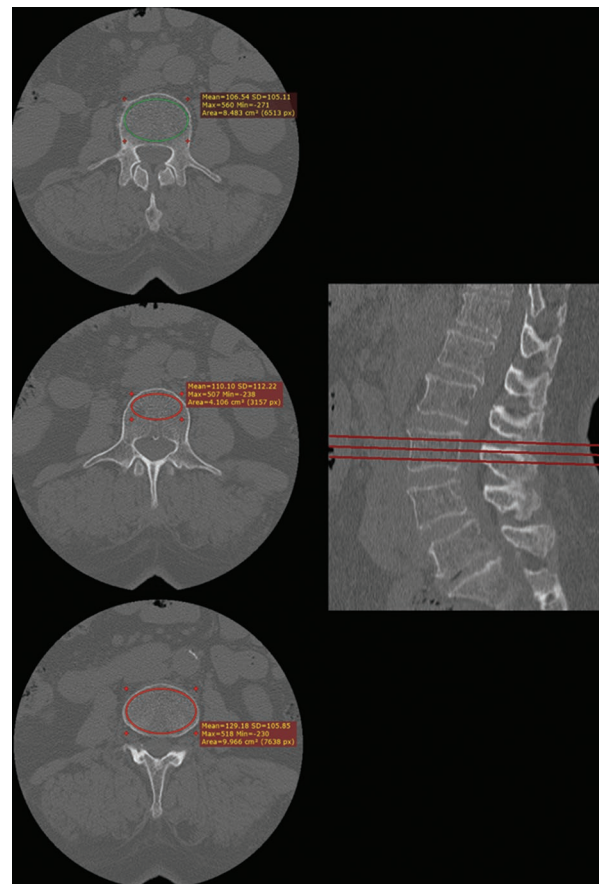


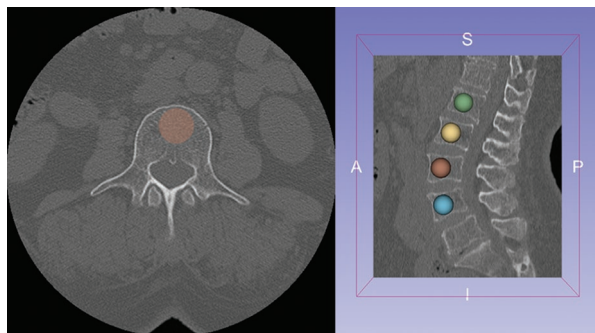
Figure 2. Demonstration of the two-dimensional Hounsfield unit measurement.

and Number Cruncher Statistical System version 11 software for Windows. The normality of the variables was assessed using both visual methods (histogram and probability plots) and the Shapiro-Wilk test. Variables showing normal distribution in groups were analyzed using the Pearson test, whereas variables showing non-normal distribution were analyzed with the Spearman test. Descriptive analyses were given

**Table 1. Summary of demographic data and bone mineral density status for the study cohort, including gender distribution, age, BMI, and DXA T-scores across L1-L4 vertebrae**

| Characteristic           | Total (n = 97) | Osteoporotic (n = 30) | Osteopenic (n = 42) | Normal (n = 25) |
|--------------------------|----------------|-----------------------|---------------------|-----------------|
| Age (years)              | 66.48 ± 9.97   | 70.1 ± 8.3            | 65.5 ± 9.2          | 63.2 ± 10.4     |
| BMI (kg/m <sup>2</sup> ) | 29.61 ± 5.94   | 30.2 ± 6.1            | 28.8 ± 5.7          | 29.1 ± 5.9      |
| Mean T-score (L1-L4)     | -1.00 ± 1.60   | -2.8 ± 0.6            | -1.6 ± 0.4          | -0.3 ± 0.5      |
| Gender distribution      |                |                       |                     |                 |
| Male, n (%)              | 15 (15.5)      | 5 (16.7)              | 7 (16.7)            | 3 (12.0)        |
| Female, n (%)            | 82 (84.5)      | 25 (83.3)             | 35 (83.3)           | 22 (88.0)       |

CT: computed tomography; HU: Hounsfield unit; DXA: dual-energy X-ray absorptiometry; BMD: bone mineral density; BMI: body mass index.



**Figure 3.** Demonstration of the volumetric Hounsfield unit measurement.

by means and SD after checking normal distribution. Bland-Altman analysis was performed to evaluate agreement between two-dimensional and volumetric HU measurements, and intraclass correlation coefficients (ICC) were calculated to assess interobserver reliability. The interobserver reliability was assessed by calculating the two-way mixed effect model of ICC with absolute agreement.  $p < 0.05$  was considered statistically significant.

## Results

### Patient demographics and clinical characteristics

A total of 97 patients were included in this study, consisting of 15 males (15.5%) and 82 females (84.5%), with a mean age of  $66.48 \pm 9.97$  years (range: 50-90 years). The body mass index (BMI) of the participants ranged from 18.73 to 42.75 kg/m<sup>2</sup>, with a mean of  $29.61 \pm 5.94$  kg/m<sup>2</sup> (Table 1). All patients had both abdominal and lumbar CT and lumbar DXA scans available, with a maximum interval of 7 months between the two imaging methods.

### DXA T-scores and BMD

The mean T-score for the L1-4 vertebrae was  $-1.00 \pm 1.60$ , with scores ranging from  $-4.90$  to  $3.90$ . Of the 97 patients, 30 (30.9%) were classified as osteoporotic (T-score  $\leq -2.5$ ), 42 (43.3%) as osteopenic (T-score between  $-1$  and  $-2.5$ ), and 25 (25.8%) as normal (T-score  $> -1$ ) (Table 1). The mean Z-score for the L1-4 vertebrae was  $-1.30 \pm 1.67$ , with values ranging from  $-5.50$  to  $3.14$ .

### Correlation between CT HU values and DXA T-scores

Pearson correlation analysis demonstrated statistically significant positive correlations between CT-derived HU values and DXA T-scores across all vertebral levels ( $p < 0.001$  for each correlation). The mean two-dimensional HU value for the L1-4 vertebrae correlated with the mean T-score at  $r = 0.532$ , whereas the mean volumetric HU value for L1-4 vertebrae exhibited a slightly stronger correlation with the mean T-score at  $r = 0.572$ . Similarly, the mean volumetric HU value for L2-4 showed a robust correlation with the mean T-score at  $r = 0.570$ . Individual correlations for both two-dimensional and volumetric HU measurements by vertebral level are presented in table 2, where volumetric HU correlations consistently demonstrated higher values than two-dimensional HU measurements.

### Subgroup analysis by OP status

When stratified by osteoporosis status (osteoporotic vs. non-osteoporotic), significant differences were found in both two-dimensional and volumetric HU values across all vertebral levels ( $p < 0.001$  for all

**Table 2. Pearson correlation coefficients showing the relationship between CT-derived HU values (both two-dimensional and volumetric) and DXA T-scores across individual vertebral levels (L1-L4) and averaged segments (L1-L4 and L2-L4)**

| Vertebral level | Two-dimensional HU correlation (r) | Volumetric HU correlation (r) |
|-----------------|------------------------------------|-------------------------------|
| L1              | 0.528                              | 0.579                         |
| L2              | 0.540                              | 0.591                         |
| L3              | 0.493                              | 0.524                         |
| L4              | 0.552                              | 0.593                         |
| L1-L4 (mean)    | 0.532                              | 0.572                         |
| L2-L4 (mean)    | 0.510                              | 0.570                         |

CT: computed tomography; HU: Hounsfield unit; DXA: dual-energy X-ray absorptiometry.

comparisons). Among osteoporotic patients, the mean two-dimensional HU value for L1-4 was  $90.30 \pm 35.67$ , whereas it was  $112.45 \pm 39.82$  for non-osteoporotic patients. In volumetric measurements, the difference was more pronounced, with osteoporotic patients showing a mean L1-4 HU value of  $85.62 \pm 32.91$  compared to  $115.73 \pm 37.90$  for non-osteoporotic patients (Table 3).

### **Bland-Altman analysis**

Bland-Altman analysis was conducted to assess agreement between two-dimensional and volumetric HU measurements at each vertebral level. The mean bias for all vertebral levels is shown in table 4, with their 95% limits of agreement.

### **ICC**

The ICC analysis demonstrated excellent agreement between two-dimensional and volumetric HU measurement methods. The ICC for volumetric HU measurements was 0.951 (95% confidence interval [CI]: 0.927-0.963), whereas the ICC for two-dimensional HU measurements was slightly lower at 0.908 (95% CI: 0.838-0.924).

### **Interobserver reliability**

Interobserver reliability was high for both measurement methods. The ICC for volumetric HU measurements was 0.963 (95% CI: 0.934-0.974), whereas the

ICC for two-dimensional HU measurements was 0.918 (95% CI: 0.874-0.972).

### **Statistical significance and distribution of data**

The normality of the HU data was assessed using the Shapiro-Wilk test. For two-dimensional HU measurements, L1, L2, L3, L4, L1-4, and L2-4 demonstrated normal distribution ( $p > 0.05$ ). In the volumetric HU measurements, L1, L2, L4, L1-4, and L2-4 followed a normal distribution ( $p > 0.05$ ), whereas L3 did not, with a Shapiro-Wilk  $p = 0.023$ .

### **Discussion**

This study reveals significant correlations between CT-derived HU values and DXA T-scores, with volumetric HU measurements consistently exhibiting stronger correlations across all vertebral levels. The observed differences in correlation strength between two-dimensional and volumetric measurements may indicate that volumetric assessments capture bone density more comprehensively, particularly in the trabecular structure, where osteoporosis is most impactful. The Shapiro-Wilk normality test further validates these measurements for parametric analysis, with most levels demonstrating a normal distribution, except for L3 volumetric values. This deviation may reflect specific structural variability in the L3 vertebra, which could influence the consistency of HU values at this level.

Bland-Altman analysis indicated a systematic bias between two-dimensional and volumetric measurements, with two-dimensional HU values tending to underestimate compared to volumetric values. Despite this bias, the 95% limits of agreement across all vertebral levels were within clinically acceptable ranges, supporting the potential interchangeability of these methods. However, volumetric HU measurements may offer higher sensitivity, particularly for research purposes and in populations with heterogeneous bone density distributions, as evidenced by the slightly higher ICCs for volumetric measurements.

The subgroup analysis showed significantly lower HU values for both two-dimensional and volumetric methods in osteoporotic patients, reinforcing the relevance of HU measurements as potential diagnostic tools for opportunistic osteoporosis screening. The

**Table 3. Mean HU values (both two-dimensional and volumetric) across vertebral levels (L1-L4) for osteoporotic and non-osteoporotic groups, highlighting HU differences associated with osteoporosis**

| Vertebral level | Osteoporotic<br>(two-dimensional HU) | Non-osteoporotic<br>(two-dimensional HU) | Osteoporotic<br>(volumetric HU) | Non-osteoporotic<br>(volumetric HU) |
|-----------------|--------------------------------------|------------------------------------------|---------------------------------|-------------------------------------|
| L1              | 85.62                                | 115.73                                   | 90.30                           | 112.45                              |
| L2              | 84.20                                | 116.25                                   | 91.80                           | 114.10                              |
| L3              | 82.30                                | 110.50                                   | 88.10                           | 109.90                              |
| L4              | 83.40                                | 108.80                                   | 89.60                           | 107.90                              |
| L1-L4 (mean)    | 85.60                                | 112.25                                   | 90.95                           | 111.10                              |
| L2-L4 (mean)    | 83.30                                | 111.00                                   | 89.10                           | 110.20                              |

HU: Hounsfield unit.

**Table 4. Bland-Altman analysis of two-dimensional and volumetric HU measurements across L1-L4 vertebral levels, including mean HU values, bias, limits of agreement, and correlation coefficients for each vertebral level and averaged segments**

| Vertebral level | Mean HU<br>(two-dimensional) | Mean HU<br>(volumetric) | Mean bias<br>(two-dimensional-volumetric) | 95% Limits of<br>agreement (HU, HU) | Correlation<br>coefficient |
|-----------------|------------------------------|-------------------------|-------------------------------------------|-------------------------------------|----------------------------|
| L1              | 107.30                       | 118.26                  | -10.96                                    | (-35.86, 13.93)                     | 0.95                       |
| L2              | 104.80                       | 115.25                  | -10.44                                    | (-45.28, 24.40)                     | 0.91                       |
| L3              | 99.22                        | 108.62                  | -9.40                                     | (-57.83, 39.03)                     | 0.84                       |
| L4              | 100.39                       | 108.18                  | -7.79                                     | (-39.57, 24.00)                     | 0.92                       |
| L1-L4           | 102.40                       | 113.25                  | -10.85                                    | (-36.45, 14.75)                     | 0.94                       |
| L2-L4           | 101.22                       | 112.47                  | -9.70                                     | (-41.02, 21.62)                     | 0.90                       |

HU: Hounsfield unit.

high interobserver reliability observed for both methods underscores the clinical applicability and reproducibility of HU measurements, though the enhanced reliability in volumetric measurements makes them particularly suitable for longitudinal studies where precise assessment of trabecular integrity is essential.

These results contribute to the literature by emphasizing the utility of CT-derived HU measurements, especially volumetric methods, as a complement to DXA in osteoporosis assessment. The distinct patterns in L3 volumetric measurements also suggest that vertebral level-specific characteristics could be further explored to improve the accuracy of CT-based bone health evaluations. Future studies may benefit from refining HU thresholds for clinical use, especially in opportunistic screening, and from investigating vertebra-specific variability, such as that observed at L3, to enhance the precision of osteoporosis diagnosis and risk stratification.

Our findings align with several previous studies that reported significant correlations between CT-derived HU values and DXA T-scores.<sup>11-31</sup> The literature has consistently demonstrated that HU values obtained from diagnostic CT scans can serve as a proxy for BMD, particularly in opportunistic screening contexts. Notably, studies by Lee et al. and Schreiber et al. have established the value of L1 vertebral attenuation in predicting BMD and identifying patients at risk for OP. However, these studies primarily utilized two-dimensional HU measurements.<sup>12,13</sup>

By introducing and evaluating volumetric HU measurements, our study expands upon this body of work. Volumetric assessments provide a 3D representation of trabecular bone, which has been shown to have non-uniform density and microstructure, particularly in osteoporotic bones. The findings suggest that volumetric HU measurements offer a more accurate representation of overall bone health, particularly in

patients with advanced OP, where trabecular thinning and heterogeneity are more pronounced. One of the key implications of our study is the potential for volumetric HU measurements to enhance the accuracy of opportunistic OP screening during routine diagnostic CT scans. Given the strong correlation between volumetric HU values and T-scores, this method could be integrated into clinical workflows to identify at-risk patients without requiring additional imaging or radiation exposure. Furthermore, the ability to assess bone quality volumetrically could have implications not only for screening but also for monitoring OP treatment. Volumetric measurements may allow for more precise tracking of changes in trabecular structure over time, providing clinicians with valuable insights into treatment efficacy. To our knowledge, this is the first study to compare the correlation between two-dimensional and volumetric HU values with DXA T-scores. Our findings highlight the potential of volumetric HU measurements as a novel and promising method for opportunistic OP screening, demonstrating a stronger correlation with DXA T-scores compared to two-dimensional HU values. This is also the second study to evaluate bone health in the lumbar spine using volumetric HU measurements. In their study, Fujimoto et al. compared two-dimensional and volumetric HU values with DXA-derived BMD and demonstrated that volumetric HU values exhibited a stronger correlation with BMD. This finding further supports the growing evidence that volumetric assessments may provide a more comprehensive and accurate representation of trabecular bone density.<sup>32</sup>

Another significant clinical implication of this study is the potential for using CT HU measurements in therapeutic decision-making. As demonstrated, volumetric HU assessments reflect bone density more comprehensively than two-dimensional methods. Future research could explore the role of these measurements in adjusting treatment protocols, particularly for patients who show varying responses to OP therapy.

Our study also highlights the importance of understanding the trabecular architecture in OP diagnosis. Trabecular bone is composed of horizontal and vertical trabeculae, and its microstructure is often compromised in osteoporotic patients.<sup>33</sup> Volumetric methods, by capturing a 3D image of the entire vertebral body, offer a more nuanced understanding of trabecular deterioration, including vertical trabecular thinning, which is particularly critical in predicting fracture risk.

This is the superiority of volumetric measurements over two-dimensional slices, which may only capture a limited view of trabecular bone architecture.

While our study suggests that CT-derived HU values are promising for opportunistic screening, it is important to consider the associated radiation dose. Diagnostic CT scans expose patients to significantly higher levels of radiation compared to DXA, which remains the gold standard for OP diagnosis.<sup>1,2,34</sup> However, technological advances in CT imaging, including dose reduction techniques, may mitigate these concerns, making CT-based screening more feasible in the future. Studies focused on reducing radiation exposure without sacrificing image quality could further support the integration of CT HU measurements into routine clinical practice.

Beyond the technical and diagnostic advantages, opportunistic screening using CT scans could have a positive impact on healthcare costs. Early identification of OP through routine CT scans could prevent fractures and reduce the long-term costs associated with treating osteoporotic fractures. Implementation of HU measurements as part of routine diagnostics may prove to be a cost-effective strategy, particularly in healthcare systems where high-risk populations undergo frequent CT imaging for other reasons without additional radiation exposure.<sup>8,35-38</sup>

A major strength of this study is the innovative use of 3D segmentation software for volumetric HU measurements. While almost all the previous studies have primarily focused on two-dimensional measurements, our study demonstrates that volumetric assessments provide a more comprehensive evaluation of trabecular bone density. The high (ICC > 0.9) between observers further confirms the reliability of these measurements, suggesting that they can be consistently applied in both clinical and research settings.

Despite its strengths, this study has several limitations that warrant attention. First, the sample size of 97 patients is relatively small, limiting the ability to establish clinical thresholds for HU values. Larger studies are needed to define reliable cutoff values. In addition, the study population, restricted to individuals aged 50 and older, limits the generalizability of findings to younger populations. The 7-month interval between CT and DXA scans introduces potential variability, particularly in older adults. Furthermore, this study focused solely on trabecular bone, without considering cortical bone, which also contributes to overall bone strength.

## Conclusions

This study demonstrates that both two-dimensional and volumetric CT HU measurements are strongly correlated with DXA T-scores, with volumetric measurements offering a more comprehensive assessment of trabecular bone density. These findings support the potential for volumetric HU measurements to be integrated into clinical practice for opportunistic OP screening, as well as for monitoring treatment efficacy. Further research is needed to establish standardized HU thresholds for clinical use, particularly in larger and more diverse populations. In addition, future studies should explore the incorporation of cortical bone assessments and investigate strategies to minimize radiation exposure.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

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

**Confidentiality, informed consent, and ethical approval.** The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

**Declaration on the use of artificial intelligence.** The authors declare that an artificial intelligence tool was used to support the preparation of the manuscript.

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# Traumatic intracranial pseudoaneurysm treated with flow diverters: Case report and meta-analysis

## *Pseudoaneurisma intracraneal traumático tratado con desviadores de flujo: caso clínico y metaanálisis*

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### Abstract

**Introduction:** It is controversial to treat traumatic intracranial pseudoaneurysms (TIPAs) with flow diverters (FDs). We present an 18-year-old girl who underwent a transcranial carotid-cavernous fistula of ruptured TIPA treated with FDs, and then report the results of the largest meta-analysis aimed to evaluate the safety and effectiveness of flow diversions in this situation. **Methods:** A systematic search of Web of Science databases, Embase, and PubMed was performed for articles published between 2010 and September 2022. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, studies reporting FD for TIPA with  $\geq 3$  patients were included. We assessed the complete occlusion rate, complications related to the operation, and clinical outcome. A meta-analysis based on heterogeneity was carried out using random or common effects models. **Results:** We included 7 non-comparative studies with a total of 58 target TIPAs. 17 aneurysms were explicitly described as being ruptured. All FDs were successfully released. Overall, 5 (8.6%) aneurysms were treated with overlapped diverters. During a mean angiographic follow-up of 17.3 months, the complete occlusion rate was 86.0% (46/56; 95% confidence interval [CI], 74-95%;  $I^2 = 7\%$ ;  $p = 0.37$ ). The operation-related complications rate was 9% (95% CI = 1-23%;  $I^2 = 0.00\%$ ;  $p = 0.52$ ). Two patients died of javascript: void(0); non-aneurysmal hemorrhage. The percentage of good clinical outcomes was 85.7% (95% CI = 78-98%;  $I^2 = 23.7\%$ ;  $p = 0.25$ ) at the last follow-up. **Conclusions:** FD provides significant advantages in the treatment of TIPA. Nevertheless, operation-related complications are not negligible. Additional prospective and randomized investigations are needed to determine the long-term effects of FD on TIPA.

**Keywords:** Traumatic intracranial pseudoaneurysm. Endovascular procedures. Flow diverter. Complication. Outcome. Meta-Analysis.

### Resumen

**Introducción:** El tratamiento de los pseudoaneurismas intracraneales traumáticos (TIPAs) con desviadores de flujo (FDs) es un tema controvertido. Presentamos el caso de una joven de 18 años que se sometió a un tratamiento con desviadores de flujo (FD) para una fístula carótido-cavernosa transcraneal derivada de una TIPA rota, y a continuación presentamos los resultados del metaanálisis más amplio realizado para evaluar la seguridad y la eficacia de los desviadores de flujo en esta situación. **Métodos:** Se realizó una búsqueda sistemática en las bases de datos Web of Science, Embase y PubMed de artículos publicados entre 2010 y septiembre de 2022. De acuerdo con las directrices PRISMA, se incluyeron los estudios que informaban sobre DF para PAIT con  $\geq 3$  pacientes. Se evaluaron la tasa de oclusión completa, las complicaciones relacionadas con la

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operación y el resultado clínico. Se realizó un metaanálisis basado en la heterogeneidad utilizando modelos de efectos aleatorios o comunes. **Resultados:** Se incluyeron siete estudios no comparativos con un total de 58 PAIT diana. Se describió explícitamente la rotura de 17 aneurismas. Todos los DF se liberaron con éxito. En total, 5 (8.6%) aneurismas se trataron con desviadores solapados. Durante un seguimiento angiográfico medio de 17.3 meses, la tasa de oclusión completa fue del 86.0% (46/56; IC 95%: 74-95; I<sup>2</sup> = 7%;  $p = 0.37$ ). La tasa de complicaciones relacionadas con la operación fue del 9% (IC 95%: 1-23; I<sup>2</sup> = 0.00%;  $p = 0.52$ ). Dos pacientes fallecieron por hemorragia no aneurismática. El porcentaje de buenos resultados clínicos fue del 85.7% (IC 95%: 78-98; I<sup>2</sup> = 23.7%;  $p = 0.25$ ) en el último seguimiento. **Conclusiones:** Los DF proporcionan ventajas significativas en el tratamiento del PAIT. No obstante, las complicaciones relacionadas con la operación no son desdeñables. Son necesarias investigaciones prospectivas y aleatorizadas adicionales para determinar los efectos a largo plazo de los DF en los PAIT.

**Palabras clave:** Pseudoaneurisma intracraneal traumático. Procedimientos endovasculares. Desviador de flujo. Complicación. Resultados. Metaanálisis.

## Introduction

Traumatic intracranial aneurysm (TIPA) is a rare high-risk subtype of cerebral aneurysm secondary to head trauma or surgery with open craniotomy.<sup>1,2</sup> Although the incidence is low, representing only 0.15-0.40% of all intracranial aneurysms,<sup>3</sup> it is a difficult clinical problem with high morbidity and mortality.<sup>4,5</sup> Because of their weak walls, these lesions have a very high incidence of early rebleeding and postoperative recurrence histologically.<sup>6</sup> Both surgical and endovascular treatments (EVTs) are challenging as these lesions involve defective vessel walls.<sup>7</sup> Traditional therapy, including parent artery occlusion, coil embolization, and covered stent<sup>8</sup> implantation seemed to show high rates of complications and recurrence.<sup>3</sup>

More recently, Flow-Diverter Stents have been introduced as an alternative technique for complex aneurysms, and they have shown incredible results in facilitating endovascular remodeling.<sup>9,10</sup> However, treating percutaneous transhepatic intrahepatic portosystemic shunts (PTIPs) with flow diverters (FDs) is controversial due to the unique challenges these aneurysms present. PTIPs have fragile, thin walls lacking normal vascular layers, which increases the risk of rupture. While FDs redirect blood flow to induce thrombosis, in PTIPs, this can put additional pressure on the already fragile aneurysm, potentially causing rupture. Furthermore, the efficacy of FDs in PTIPs is not well-supported by clinical evidence, and their use requires dual antiplatelet therapy, which can increase the risk of bleeding or complicate the management of these fragile aneurysms. Other treatment options, such as surgical trapping or coiling, may be considered due to these concerns. So far, there have been only a few retrospective case series and case reports. Therefore, we conducted a meta-analysis

exploring FD's angiographic and clinical outcomes for TIPA.

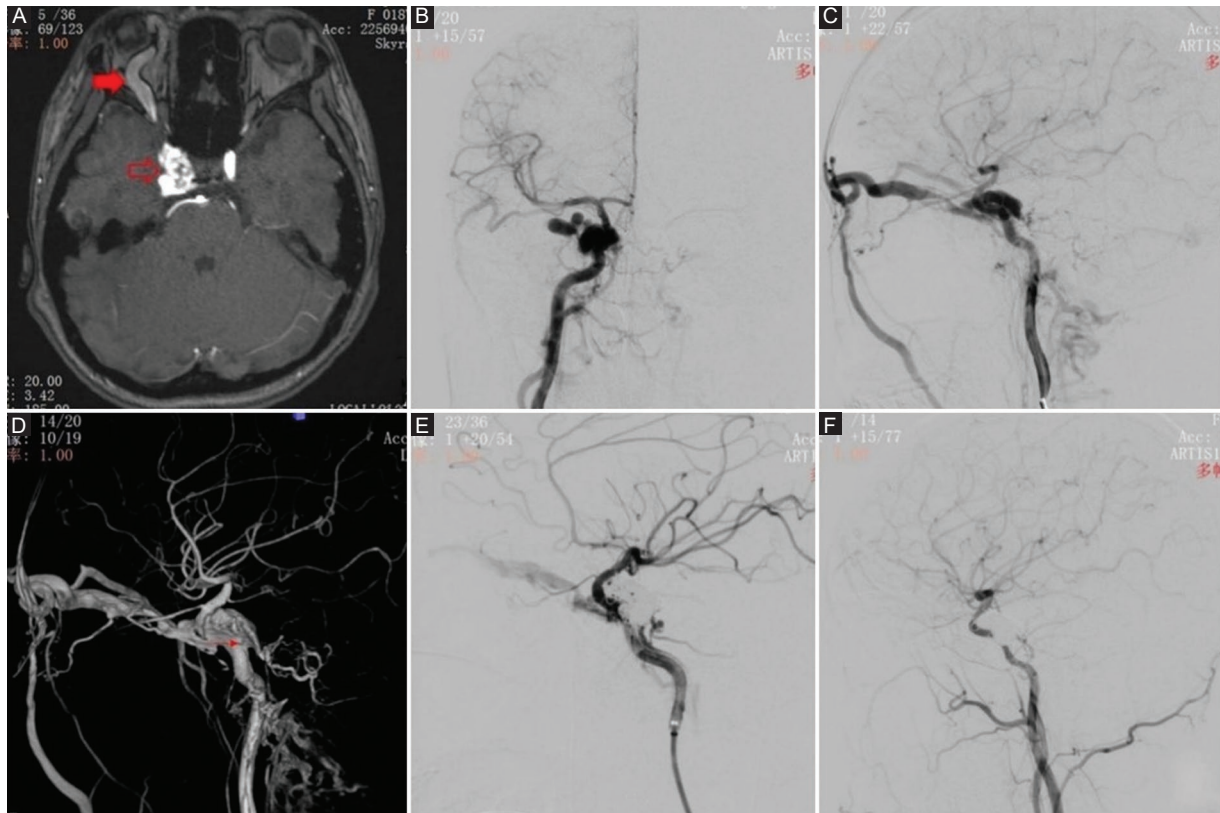
## Methods

### Case report

An 18-year-old girl suffered head trauma 1 month ago when she fell from a bicycle. Head computed tomography (CT) showed intracranial hemorrhage with skull base fracture. However, nearly 3 days ago, swelling of the right eye, blurred vision, and pulsatile murmur developed, and he came to our hospital. Magnetic resonance imaging and digital subtraction angiography (DSA) were performed, and the diagnosis was confirmed as transcranial carotid-cavernous fistula, which drained into the superior ophthalmic vein through the cavernous sinus. The cause was considered to be the rupture of a TIPA in the cavernous segment of the internal carotid artery. Then, the FD implantation combined with coil embolization was performed under general anesthesia. Although there was still a small amount of residue on angiography immediately after the operation, the patient's murmur disappeared. Three months after the operation, the fistula disappeared, the cavernous segment of the internal carotid artery was completely repaired, the eye symptoms disappeared, and there was no neurological dysfunction. The images were shown in figure 1.

### Literature search strategy

A comprehensive literature search of Web of Science databases, PubMed, and Embase was conducted for studies published between 2010 and September 2022. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. The keywords "aneurysm," "intracranial



**Figure 1.** Case images. An 18-year-old girl with transcranial carotid-cavernous fistula (TCCF) was treated with flow diverter. **A:** the magnetic resonance imaging suggested a TCCF on the right side (The hollow red arrow shows the enhanced cavernous sinus, and the solid red arrow indicates the thickened ophthalmic vein). **B:** anteroposterior angiography of the right internal carotid artery. **C:** lateral angiography of the right internal carotid artery. **D:** 3D reconstruction image (A single arrow shows a pseudoaneurysm in the cavernous segment). **E:** immediate angiography after operation. **F:** angiography after 3 months.

aneurysm,” “pseudoaneurysm,” “PSA,” “trauma,” “traumatic,” “injury,” “flow diverter,” “flow diversion,” and “pipeline” were used in both “AND” and “OR” combinations.

### Selection criteria

The systematic review used the following inclusion criteria: (1) diagnosed TIPA treated with FDs, (2)  $\geq 3$  patients undergoing FD implantation for TIPA, (3) clinical or angiographic outcomes were reported. Exclusion criteria were as follows: (1) Extracranial aneurysm, (2) *in vitro* studies and animal studies, (3) technical notes, guidelines, and review articles.

### Data extraction and critical appraisal

For each study, the patient demographic data and endovascular strategies were extracted. We looked at total occlusion, procedure-related complications, progress, death, and overall satisfactory result.

Data were retrieved from the paper text, tables, and figures, and each article was examined independently by two investigators. A senior investigator reviewed the final results. Because all of the analyses were based on previously published studies, there was no need for ethical approval or patient permission.

### Statistical analysis

The Newcastle–Ottawa Scale was used to assess the quality of included studies. Quality assessment was performed by two authors independently, and a third author solved potential discrepancies.

Meta-analysis was performed using the Meta package of the R software program (version 4.2.2). There are mean values for continuous variables and odds ratios and 95% confidence intervals (CIs) for dichotomous variables. Statistical heterogeneity was assessed using  $I^2$ . We used a common effects model

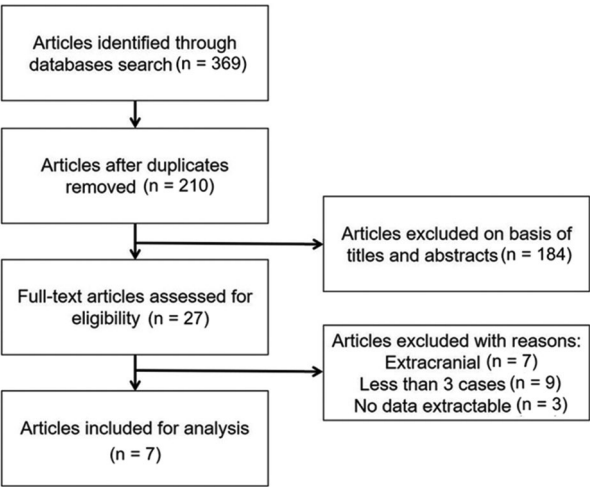


Figure 2. Flowchart of the study selection.

if  $I^2 < 50\%$ , but a random effects model if  $I^2 > 50\%$ , and a sensitivity analysis was conducted. It was determined that  $p < 0.05$  was statistically significant.

Outcome measures

The term “aneurysm occlusion” was defined as complete occlusion as determined by imaging examinations (magnetic resonance angiography, CT angiography, and DSA) after the procedure. Complications were defined as any surgical treatment-related complications, including repeat bleeding, late hemorrhage, artery dissection, vessel occlusion, and brain infarction. Recurrent is defined as aneurysm enlargement or redevelopment. A good outcome was defined as 0-2 on the modified Rankin Scale or 4-5 on the Glasgow Outcome Scale.

Results

Through searches of 3 electronic databases, 369 articles were identified. After carefully examining the title or abstract, screening, and exclusion of duplicate or irrelevant articles, 7 studies with 57 patients were included. The literature search process is shown in figure 2. All studies were single-arm retrospective cohorts and had good quality. Their characteristics are summarized in table 1.

The mean age was 34.8 years, and 68.4% were male. There were 58 TIPAs in 57 patients. 17 TIPAs were explicitly described as being ruptured. Among the 58 TIPAs, 46 (79.3%) were treated with a pipeline embolization device (PED) (Medtronic Neurovascular,

Table 1. Evaluation of the included studies using the modified Newcastle–Ottawa scale

| Study                            | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts based on the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | total |
|----------------------------------|------------------------------------------|-------------------------------------|---------------------------|--------------------------------------------------------------------------|----------------------------------------------------------|-----------------------|-------------------------------------------------|----------------------------------|-------|
| Barburoglua et al. <sup>32</sup> | 1                                        | 0                                   | 1                         | 1                                                                        | 0                                                        | 1                     | 1                                               | 1                                | 6     |
| Sami et al. <sup>30</sup>        | 1                                        | 0                                   | 1                         | 1                                                                        | 0                                                        | 1                     | 1                                               | 1                                | 6     |
| Chen et al. <sup>29</sup>        | 1                                        | 0                                   | 1                         | 1                                                                        | 0                                                        | 1                     | 1                                               | 1                                | 6     |
| Deng et al. <sup>17</sup>        | 1                                        | 0                                   | 1                         | 1                                                                        | 0                                                        | 1                     | 1                                               | 1                                | 6     |
| Zhao et al. <sup>18</sup>        | 1                                        | 0                                   | 1                         | 1                                                                        | 0                                                        | 1                     | 1                                               | 1                                | 6     |
| Budohoski et al. <sup>10</sup>   | 1                                        | 0                                   | 1                         | 1                                                                        | 0                                                        | 1                     | 1                                               | 1                                | 6     |
| Dogan et al. <sup>31</sup>       | 1                                        | 0                                   | 1                         | 1                                                                        | 0                                                        | 1                     | 1                                               | 1                                | 6     |

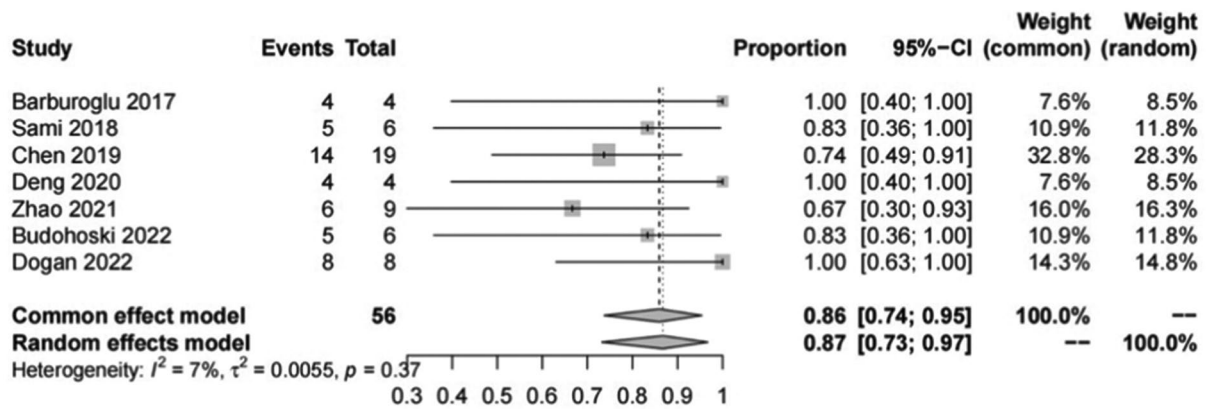


Figure 3. Plot showing the occlusion rate of 56 flow diverter-treated traumatic intracranial pseudoaneurysms reported by 7 studies.

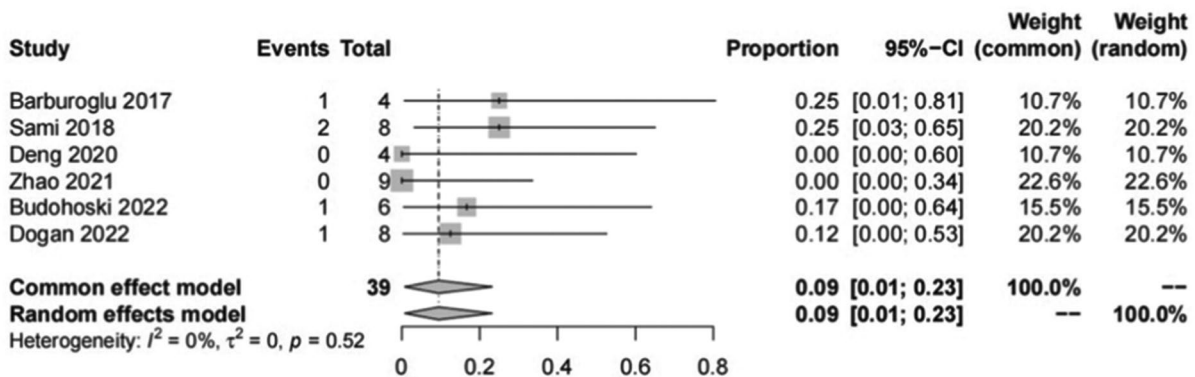


Figure 4. Plot showing the complications of 39 flow diverter-treated TICAs reported by 6 studies.

Irvine, CA, USA). Other FDs include Surpass (Stryker Neurovascular, Fremont, California.), Silk (Balt Extrusion, Montmorency, France.), and Tubridge (Weichuang, Shanghai, China), which were used in 2 (3.5%), 2 (3.5%), and 8 (13.8%) TIPAs, respectively. Overall, 5 (8.6%) aneurysms were treated with overlapped FDs. During a mean angiographic follow-up of 17.3 months, the overall rate of complete occlusion was 86.0% (46/56; 95% CI = 74-95%;  $I^2 = 7\%$ ;  $p = 0.37$ ); (Fig. 3). Six studies reported complications in 5 aneurysms. The complication rate was 9% (5/39; 95% CI = 1-23%;  $I^2 = 0.00\%$ ;  $p = 0.52$ ; Fig. 4). One perioperative complication of distal middle cerebral artery rupture had a significant impact on life at follow-up, which led the patient to die. The remaining one mortality died from a traumatic SDH and brainstem hemorrhage unrelated to Pipeline placement. The rate of good clinical outcome was 85.7% (95% CI = 78-98%;  $I^2 = 23.7\%$ ;  $p = 0.25$ ). Data are shown in table 2.

## Discussion

Our meta-analysis has demonstrated that flow-diverter stents are technically feasible with a high rate of complete aneurysm occlusion and technical success for the treatment of TIPAs. The procedure has a generally favorable clinical outcome. In spite of this, the complications associated with these aneurysms were not insignificant.

TIPA is a serious type of traumatic vascular injury.<sup>11</sup> Although the incidence is not high, its natural course prognosis is poor. The mortality rate in ruptured TICA is 30-50%.<sup>3,12</sup> Unruptured TIPAs are more likely to rupture than non-TIPAs.<sup>13,14</sup> Thus, definitive and immediate treatments are particularly important for the prognosis of TIPAs patients.

TPIA is fusiform and fragile, without a true neck, and is most commonly linked with dissection.<sup>12</sup> Historically, neurosurgical treatment was mostly restricted to the

Table 2. TIPAs treated with flow diverters

| Study                           | Mean age (years) | Males/female | Aneurysms (n) | Rupture (n) | Devices used          | Complications (n)                          | follow-up (months) | Aneurysm occlusion (n) | mRS (0-2)/(3-6) |
|---------------------------------|------------------|--------------|---------------|-------------|-----------------------|--------------------------------------------|--------------------|------------------------|-----------------|
| Barburoglu et al. <sup>32</sup> | 14               | 3/1          | 4             | 2           | Surpass (2), Silk (2) | parent artery occluded (1)                 | 42.5               | 4                      | 4/0             |
| Sami et al. <sup>30</sup>       | 37               | 6/1          | 8             | -           | PED (12)              | Distal MCA rupture (1), ICA dissection (1) | 15.2               | 5                      | 5/2             |
| Chen et al. <sup>29</sup>       | 50               | 11/8         | 19            | 7           | PED (26)              | -                                          | 7                  | 14                     | 10/1            |
| Deng et al. <sup>17</sup>       | 25.8             | 3/1          | 4             | 0           | PED (4)               | 0                                          | 12                 | 4                      | 4/0             |
| Zhao et al. <sup>18</sup>       | 41.4             | 5/4          | 9             | -           | PED (1), Tubridge (8) | 0                                          | 18                 | 6                      | 8/1             |
| Budohoski et al. <sup>10</sup>  | 11.3             | 5/1          | 6             | 3           | PED (7)               | vessel occlusion (1)                       | 5.2                | 5                      | 3/3             |
| Dogan et al. <sup>31</sup>      | 34.4             | 6/2          | 8             | 5           | PED (8)               | ICH (1)                                    | 17.9               | 8                      | 8/0             |

TIPAs: traumatic intracranial pseudoaneurysms; PED: pipeline embolization device; MCA: middle cerebral artery; ICA: internal carotid artery.

sacrifice of the parent artery or bypass,<sup>15</sup> which was heavily reliant on the existence of sufficient collateral circulation. Due to the great trauma and poor effect of open surgery, endovascular therapy has been relatively a more common treatment in recent years.<sup>3</sup> Detachable balloons, Coil, Onyx, Stent, etc., are used in the embolization of TIPAs.<sup>11,16</sup> These methods did not reverse the pathological process of vascular injury, and a few pseudoaneurysms recurred during the follow-up. Following, covered stents are used for EVT of TIPAs.<sup>11,17</sup> The therapeutic strategy was also gradually changed from the initial sacrificial parent artery to the parent artery reconstruction. However, the rigid design of these systems leads to poor vascular compliance. It is often difficult to achieve full adherence to intracranial vessels, and it is relatively difficult to deliver in more tortuous vessels. In addition, its completely covered surface has the risk of blocking the perforator artery. All of these limit its application to a small number of special cases.<sup>8,18,19</sup>

FDs were introduced recently in the treatment of giant or large wide-necked aneurysms along the petrous to a superior hypophyseal segment of the internal carotid artery.<sup>20</sup> Moreover, due to its effect on endoluminal parent vessel reconstruction, the use of FD for intracranial aneurysms has increased in popularity with new indications continuing to be reported.<sup>9,21,22</sup> FDs have already been successfully used in a few TIPAs.<sup>23-28</sup> Giorgianni et al.<sup>27</sup> reported a 20-year-old man with two traumatic ACA pseudoaneurysms treated

with PED that resolved after 6 months on angiography in 2015, which is perhaps one of the earliest reported in the literature. An analysis of the angiographic and clinical outcomes of TIPAs treated with FDs was conducted to determine whether FDs are feasible compared to traditional EVT. In our meta-analysis of 46 FD-treated TIPAs, the complete occlusion rate was 86.0%. Stephanie et observed one case of progression of the pseudoaneurysm in short-term follow-up, which was suggested to be associated with nonapposition of the PED on the cavernous carotid wall. Zhao<sup>11</sup> et al. report 9 TIPAs treated with FD. They discovered 3 failures of complete occlusion at the 6-month follow-up because of no use of coils. Although coiling is a useful technique, it is risky in the setting of a recent hemorrhage and unstable TIPA capsule. All of them were completely occluded at the second follow-up, indicating that the treatment of pseudoaneurysm with FD required a longer repair time.

Although the flow-directed device has changed the local hemodynamics of the aneurysm, it does not completely isolate the aneurysmal sac and remains at risk of recurrence and rebleeding.<sup>29</sup> Meanwhile, greater attention must be paid to operation-related complications. We assessed the complication rate as 9%. Sami<sup>30</sup> et al., and Dogan<sup>31</sup> et al., reported iatrogenic rupture of the distal arterioles due to a microwire during the procedure. Barburoglu and Arat<sup>32</sup> demonstrated an individual who had an asymptomatic occlusion of the parent artery that was discovered by chance during

a 7-month follow-up angiography. This patient acknowledged stopping clopidogrel for many weeks between 3- and 7-month follow-up examinations.

The present meta-analysis presents several limitations. The main limitation is the minimal number of articles analyzed due to the scarcity of literature on this subject. All of the included studies were non-comparative, single-center, retrospective case series. In addition, the baseline characteristics varied across the included studies. The lack of stratification prevented us from analyzing the effect of age, gender, FDs brand, and aneurysm location.

## Conclusions

FDs are feasible and provide significant advantages in the treatment of TIPA. Nevertheless, operation-related complications are not negligible. We emphasize the therapeutic potential of FDs in TIPAs and argue that further well-designed prospective and randomized trials are needed.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

**Protection of humans and animals.** The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki.

**Confidentiality, informed consent, and ethical approval.** The authors have followed their institution's confidentiality protocols, obtained informed consent from patients.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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# Conocimiento de los cirujanos mexicanos sobre quirófano sostenible y prácticas *net zero*: resultados de una encuesta

## *Knowledge of Mexican surgeons about sustainable operating rooms and net zero practices: a survey*

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### Abstract

**Objective:** To make an initial assessment of the attitudes and knowledge of Mexican general surgeons regarding sustainable operating rooms and net zero policies. Operating rooms are the primary producers of greenhouse gas emissions in the healthcare system. The implementation of measures to achieve sustainable operating rooms must be preceded by an understanding of current practices, the surgical staff's interest in the topic, and potential areas of opportunity. **Methods:** Observational, prospective, cross-sectional study based on an anonymous virtual survey distributed by email to all members of the Mexican Association of General Surgery between October 2023 and March 2024. The questions focused on five topics: general data, use of textiles, anesthesia techniques, waste generation and use of disposable materials and consumption of water and energy. **Results:** A total of 726 responses were obtained. 12% were familiar with the term net zero and incorporated related measures into their daily practice. 8.4% reported that their hospital has an action plan in this regard. **Conclusions:** The survey reveals a low level of knowledge about sustainable operating rooms and net-zero practices among the surveyed surgeons, as well as a scarcity of action plans to achieve green operating rooms in Mexico; however, it highlights the respondents' interest in learning more about the topic.

**Keywords:** Sustainable surgery. Carbon footprint. Operating room. Greenhouse gas. Environmental impact.

### Resumen

**Objetivo:** Realizar una aproximación inicial a las actitudes y el conocimiento de los cirujanos generales mexicanos sobre los quirófanos sostenibles y las políticas net zero. Los quirófanos son los principales productores de emisiones de gases con efecto invernadero del sistema de salud. La implementación de medidas para lograr quirófanos sustentables debe ir precedida del conocimiento de las prácticas actuales, del interés del personal quirúrgico sobre el tema y de las posibles áreas de oportunidad. **Métodos:** Estudio observacional, prospectivo, de corte transversal, basado en una encuesta anónima y virtual distribuida por correo electrónico a todos los socios de la Asociación Mexicana de Cirugía General entre octubre de 2023 y marzo de 2024. Las preguntas se enfocaron en cinco temas: datos generales, uso de textiles, técnicas de anestesia, generación de desechos y uso de materiales desechables, y consumo de agua y energía. **Resultados:** Se obtuvieron 726 respuestas.

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El 12% conocían el término *net zero* e incorporaban medidas relacionadas en su práctica diaria. El 8.4% refirieron que en su hospital existe un plan de acción al respecto. **Conclusiones:** La encuesta revela un bajo nivel de conocimiento sobre el quirófano sostenible y las prácticas *net zero* entre los cirujanos encuestados, así como la escasez de planes de acción para alcanzar quirófanos «verdes» en México; sin embargo, destaca el interés de los encuestados en aprender sobre el tema.

**Palabras clave:** Cirugía sostenible. Huella de carbono. Quirófano. Gases con efecto invernadero. Impacto ambiental.

## Introducción

El cambio climático es una urgencia mundial. El aumento de la temperatura global en 1.5 °C (en comparación con la era preindustrial) tendrá como consecuencia la destrucción de ecosistemas y la extinción de especies que condicionarán la persistencia del ser humano. El deshielo secundario al calentamiento del planeta y el aumento del nivel del mar, tan solo 10 mm, ha generado un impacto ambiental sin precedentes<sup>1</sup>.

Sequías, inundaciones, incendios, aumento en las enfermedades transmitidas por vectores, epidemias, entre otras, generan una presión de adaptación en los sistemas de salud del mundo, los cuales intentan desarrollar estrategias para responder a estas situaciones, a la vez que generan una huella de carbono y emisiones de gases invernadero del casi el 5% de las emisiones globales totales<sup>2</sup>.

Se estima que los quirófanos producen del 50% al 70% de la basura generada en un hospital. El impacto ambiental que generan es tres a seis veces mayor que el del resto del hospital, secundario al consumo intensivo de energía, entre otras causas<sup>3</sup>.

Desde el acuerdo de París (1996)<sup>4</sup> y recientemente en las reuniones anuales de la Conferencia de las Naciones Unidas sobre el Cambio Climático, los gobiernos del mundo se han comprometido a disminuir al 50% las emisiones de carbono para el año 2030 y lograr en 2050 un sistema de emisiones netas cero<sup>5</sup>.

México ocupa el lugar 16 de 266 países como productor de emisiones de carbono, y nuestro sistema de salud se encuentra en el lugar 11 de la lista de los más contaminantes del mundo<sup>6</sup>.

Asumir nuestra responsabilidad como líderes y como parte responsable de la generación de emisiones de carbono en el quirófano debe de ser un imperativo moral en nuestro actuar personal y profesional inmediato.

El objetivo de este trabajo fue conocer, a través de una encuesta, cuánto saben los socios de la Asociación Mexicana de Cirugía General (AMCG) sobre la contaminación que generan los quirófanos y sus

causas, e identificar las características generales en cuanto a emisión de equivalentes de carbono en los quirófanos de distintas regiones del país, para en el futuro cercano diseñar estrategias ecológicas acordes a la realidad mexicana.

## Métodos

El presente fue un estudio observacional, prospectivo, de corte transversal, basado en una encuesta anónima y virtual llevada a cabo entre octubre de 2023 y marzo de 2024. La encuesta se diseñó internamente entre los autores, tomando como referencia encuestas previas publicadas en relación con el medio ambiente y sistemas de salud<sup>7,8</sup>. Se incluyeron 20 preguntas de opción múltiple para obtener información sobre cinco dominios: datos generales (edad, localización geográfica, sistema de salud, nivel de atención), uso de textiles (uniformes y campos quirúrgicos), anestesia (técnica, gases anestésicos, disposición de medicamentos), generación de desechos y consumibles de un solo uso, y consumo de agua y energía.

Previo a su distribución, la encuesta fue probada con cuatro cirujanos y modificada con su retroalimentación. La versión final fue diseñada en la plataforma Google Forms® para su contestación en línea. La invitación a participar se realizó a través de un correo electrónico distribuido por la AMCG a todos sus asociados (3804). Ningún participante recibió incentivo material o económico. La encuesta se aplicó entre noviembre de 2023 y marzo de 2024; se enviaron tres correos en distintas fechas con la invitación a participar. El cuestionario se contestó en línea a través de la plataforma Google Forms®. Se incluyeron tanto residentes como cirujanos generales o subespecialistas, y se excluyeron aquellos que no trabajaban en la República Mexicana o que no contaban con actividad quirúrgica activa (por ejemplo, retirados).

El análisis estadístico de los datos se llevó a cabo con el programa estadístico STATA (Version 14, StataCorp, College Station, Texas, USA). Las respuestas de cada pregunta se calcularon con distribución de frecuencias y se muestran en porcentajes.

## Resultados

### Datos generales

Se remitió la encuesta a 3804 miembros de la AMCG, de los cuales 726 la contestaron (tasa de respuesta del 19%). La mayoría de quienes participaron fueron cirujanos entre los 46 y 60 años (264; 36.4%), seguidos por los de 30 a 45 años (230; 31%), los mayores de 60 años (188; 25.9%) y los menores de 30 años (44; 6.1%).

Participaron asociados de las 32 entidades federativas. Las más representativas fueron Ciudad de México (201; 27.7%), Estado de México (81; 11.2%), Jalisco (41; 5.6%), Nuevo León (35; 4.8%), Guanajuato (30; 4.1%) y Veracruz (29; 4%). Los Estados de donde menos respuestas se obtuvieron fueron Baja California Sur (3; 0.4%), Campeche (3; 0.4%), Colima (5; 0.7%), Durango (5; 0.7%) y Yucatán (6; 0.8%).

Respecto a si los cirujanos encuestados laboran en el sector público o privado, aproximadamente una tercera parte trabajan únicamente en el medio privado (262; 36.1%) y el resto tiene práctica al menos en una institución gubernamental (464; 63.9%). Más de la mitad de los encuestados refirieron trabajar en un hospital de segundo nivel (444; 61%) y el resto en hospitales de tercer nivel (277; 38%); cinco respuestas no se contestaron de manera correcta.

Entre los cirujanos trabajadores en hospitales públicos, la mayoría de las respuestas se obtuvieron de personal de la Secretaría de Salud (SS) (175; 37.5%) y del Instituto Mexicano del Seguro Social (IMSS) (168; 36%). Otras instituciones públicas fueron el Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE) (55; 11.8%), el IMSS - Bienestar (32; 6.8%) y la Secretaría de la Defensa Nacional (SEDENA) (10; 2.1%). Los Hospitales del Gobierno de la Ciudad de México, el Instituto de Seguridad Social del Estado de México y Municipios (ISSEMYM), los Hospitales de Petróleos Mexicanos (PEMEX) y otros hospitales fueron el 5.4% de la muestra (Tabla 1).

### Textiles

Los cirujanos encuestados confirmaron que los textiles reutilizables en la mayoría de los hospitales son los uniformes quirúrgicos (520; 71.6%), los campos y las batas quirúrgicas (452; 62.2%). Los gorros quirúrgicos (89; 12.2%) y los cubrezapatos (52; 7%) son reutilizables en menor proporción.

**Tabla 1. Datos generales de la población estudiada**

| Variable             | n   | %    |
|----------------------|-----|------|
| Rango de edad (años) |     |      |
| < 30                 | 44  | 6.1  |
| 30 a 45              | 230 | 31   |
| 46 a 60              | 264 | 36.4 |
| > 60                 | 188 | 25.9 |
| Sistema hospitalario |     |      |
| Privado              | 262 | 36.1 |
| Público              | 464 | 63.9 |
| SS                   | 175 | 37.5 |
| IMSS                 | 168 | 36   |
| ISSSTE               | 55  | 11.8 |
| IMSS-Bienestar       | 32  | 6.8  |
| SEDENA               | 10  | 2.1  |
| Otros*               | 10  | 2.1  |
| GCDMX                | 7   | 1.5  |
| ISSEMYM              | 5   | 1.0  |
| PEMEX                | 4   | 0.8  |
| Nivel de atención    |     |      |
| Segundo nivel        | 447 | 61   |
| Tercer nivel         | 274 | 37   |
| Respuestas anuladas  | 5   | 2    |

GCDMX: Hospitales del Gobierno de la Ciudad de México; IMSS: Instituto Mexicano del Seguro Social; IMSS-Bienestar: Instituto Mexicano del Seguro Social-Bienestar; ISSEMYM: Instituto de Seguridad Social del Estado de México y Municipios; ISSSTE: Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado; PEMEX: Hospitales de Petróleos Mexicanos; SEDENA: Secretaría de la Defensa Nacional; SS: Secretaría de Salud.

\*Otros: SEMAR: Secretaría de Marina; OPD: organismo público descentralizado Hospital Civil de Guadalajara, OPD Hospital Civil Fray Antonio Alcalde, Magisterio, Ichisal, Hospital Civil de Culiacán, Hospital de Maestros del Sindicato Nacional de Trabajadores de la Educación (SNTE) Secc. 50.

El 17.6% (128) de los cirujanos respondieron que ningún textil quirúrgico es reutilizable en su hospital. De ellos, la mayoría (53; 41.4%) refieren trabajar en la Ciudad de México y en el Estado de México (25; 19.5%). Otros Estados en los que en algunos hospitales ningún textil se reutiliza son Jalisco (10; 7.8%), Nuevo León (5; 3.9%), Veracruz (5; 3.9%), Hidalgo (4; 3.1%), Chihuahua (4; 3.1%), Sinaloa (3; 2.3%), Coahuila (2; 1.5%), Querétaro (2; 1.5%), Quintana Roo (2; 1.5%), Tabasco (2; 1.5%), Baja California Norte (1; 0.7%), Chiapas (1; 0.7%), Colima (1; 0.7%), Guanajuato (1; 0.7%), Morelos (1; 0.7%), Oaxaca (1; 0.7%), San Luis Potosí (1; 0.7%), Tamaulipas (1; 0.7%) y Yucatán (1; 0.7%).

Más de la mitad de los hospitales en los que no se reutilizan textiles pertenecen al tercer nivel de atención (78; 60.9%) y son privados (68; 53.9%). Los hospitales públicos en los que ningún textil es reutilizable (60; 46%) pertenecen principalmente a la SS (22; 36.6%), al ISSSTE (17; 28.3%) y al IMSS (13; 21.6%).

### Anestesia

En relación con la solicitud de estudios preoperatorios en pacientes de bajo riesgo, la mayor parte

de los encuestados (332; 45.7%) refieren hacerlo de acuerdo con las guías de su institución, en concordancia con lineamientos internacionales. Otras respuestas fueron que solicitan únicamente los laboratorios que consideran indispensables (232; 31.8%), que los indican por rutina establecida por costumbre para todos los pacientes (115; 15.8%) y que solicitan lo que el anestesiólogo requiera para no cancelar la cirugía (48; 6.6%). La mayoría de los encuestados que escogieron alguna de las dos últimas respuestas se encuentran en el rango de edad entre 31 (85; 52%) y 45 años (59; 36.5%). Casi todos los asociados que contestaron que solicitan los estudios que su anestesiólogo necesite para no cancelar el procedimiento laboran en un hospital público (45; 93.7%).

En la mitad (370; 50.9%) de los procedimientos que realizan los cirujanos de la AMCG se utiliza anestesia general y en casi la otra mitad (334; 46%) se utiliza anestesia regional. La mayoría de los procedimientos con anestesia regional corresponden a hospitales públicos (258; 77.2%).

De acuerdo con los resultados de la encuesta, la anestesia total intravenosa se utiliza en muy pocos procedimientos (15; 2%). Una tercera parte de los encuestados (205; 28.2%) desconoce cuál es el gas anestésico que se utiliza en sus cirugías con anestesia general; entre los que lo saben, el gas más usado es el sevoflurano (455; 62.6%) y en muy baja proporción se utilizan el desflurano (32; 4.4%) y el isoflurano (30; 4.1%). La mayoría de los cirujanos que utilizan desflurano en sus procedimientos trabajan en la Ciudad de México y en el Estado de México (14; 43.7%). No se encontró diferencia en su uso entre hospitales privados (16; 50%) y públicos (16; 50%).

La disposición final que se da a los fármacos sobrantes al término de la cirugía es desconocida por el 38.7% (281) de los encuestados. Una tercera parte (235; 32.3%) realiza una adecuada disposición en contenedores especiales destinados para ese fin. En más de una cuarta parte de los casos (210; 28.9%) se desechan de manera no óptima: en bolsas para residuos con potencial biológicamente infeccioso (RPBI) (118; 16.2%), en bolsas de basura municipal (78; 10.7%) o en el lavabo (14; 1.9%).

## ***Desechos***

El 44% (318) de los cirujanos respondieron que la mayoría de la basura que se genera en sus quirófanos se trata de basura municipal que se desecha en bolsa

negra, una tercera parte que se trata de basura hospitalaria no infectocontagiosa que se desecha en bolsa amarilla (232; 32%), el 16.8% (122) refirieron que la mayoría de la basura que generan durante sus cirugías es altamente infecciosa y la desechan en bolsa roja, y el 7.4% (54) dijeron no conocer o no haber puesto atención al tipo de desechos generados en sus quirófanos.

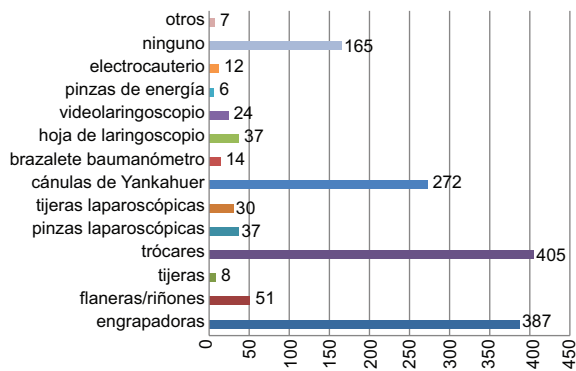
Respecto a la disposición de los RPBI generados en el quirófano, más de tres cuartas partes de los cirujanos (571; 78.6%) respondieron que son recolectados por un servicio externo al hospital, y una proporción pequeña mencionó que se incineran (22; 3%) o que se depositan en vertederos (5; 0.6%). El 17.6% (128) desconocen el paradero final de los RPBI de su hospital.

Se proporcionó a los encuestados una lista de ítems para que indicaran cuáles desechaban cotidianamente en la bolsa roja de RPBI: toallas desechables, tubos de intubación orotraqueal, tubos o cánulas de aspiración, soluciones intravenosas, sondas urinarias, bolsas de recolección de orina, cubrebocas, gorros quirúrgicos, campos quirúrgicos, yesos y vendas, envolturas o empaques, gasas con alcohol, pañales usados, flaneras desechables y guantes. La última opción de respuesta correspondía a «ninguno» y fue elegida en el 31.7% (227) de los casos. De todos los objetos enlistados, las vendas y yesos fueron seleccionados al menos por 21 participantes (2.9%) y las sondas urinarias por 334 (46%) (Fig. 1).

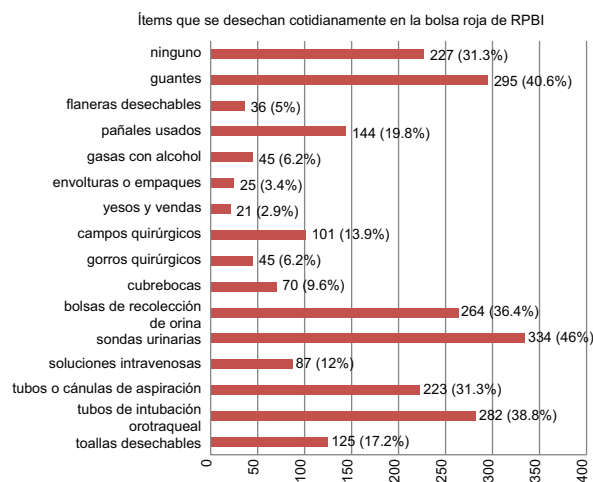
## ***Desechables y cadena de abasto***

Se proporcionó una lista de consumibles para que los encuestados identificaran cuáles eran desechables en sus quirófanos. De los consumibles enlistados, los trócares laparoscópicos (405; 55.7%) y las engrapadoras quirúrgicas (387; 53.3%) fueron los insumos desechables más seleccionados. Las cánulas de Yankauer se identificaron como desechables en el 37.4% (272) de los casos. El 22.7% (165) de los encuestados refirieron que, en su hospital, ninguno de los consumibles de la lista era desechable (Fig. 2).

En la opción abierta para enumerar otros consumibles desechables que se utilizaban en sus hospitales, los cirujanos (7; 1%) mencionaron cánulas de Guedel, compresas de secado, sistemas colectores de aspiración y drenaje, bolsas extractoras de piezas, electrodos, grapas, bolsas para equipo laparoscópico, asas, catéteres centrales, sondas urinarias y sondas de descompresión tipo Nelaton.



**Figura 1.** Consumibles desechables identificados por los encuestados en sus quirófanos.



**Figura 2.** Materiales y consumibles que se desechan cotidianamente en la bolsa roja de residuos con potencial biológicamente infeccioso (RPBI), de acuerdo con los encuestados.

## Sistema de ventilación e iluminación

Una cuarta parte de los encuestados (181; 24.9%) desconocen cómo funcionan en su quirófano los sistemas de recambio de aire, temperatura e iluminación. Otra parte similar (179; 24.6%) refieren que estos sistemas en sus quirófanos se mantienen activos las 24 horas del día, es decir, que las luces permanecen encendidas incluso si no hay nadie en la sala, y el número de recambios de aire no disminuye.

Solo el 34.8% (253) de las personas encuestadas contestaron que los sistemas de ventilación, temperatura e iluminación de los quirófanos en los que trabajan se activan únicamente cuando es necesario, y el 15.5% (113) manifestaron que en sus unidades no hay sistemas de ventilación.

## Lavado quirúrgico y agua

Un alto porcentaje de los encuestados (516; 71%) cuentan con lavabos quirúrgicos con sensor, lo cual contribuye al ahorro de agua durante el lavado quirúrgico.

Casi la mitad (342; 47.1%) utilizan agua y cepillo desechable precargado para realizar el lavado quirúrgico antes de un procedimiento; sin embargo, un tercio (218; 30%) del personal quirúrgico encuestado refiere utilizar cepillos reusables y solo el 7.8% (57) utiliza soluciones antisépticas que no requieren enjuague. El 14.9% (108) restante refieren que realizan el lavado con agua y clorhexidina.

## Conocimiento

El 46.2% (336) de los encuestados no conocen el término *net zero* y no saben a qué se refiere; el 41.4% (301) lo habían escuchado alguna vez, pero no tienen claro su significado. Solo el 12% (89) lo conocen e incorporan medidas para alcanzarlo en su práctica diaria. Este 12% predomina de manera importante en la Ciudad de México (32; 35.9%). Otros Estados en los que se menciona realizar alguna medida *net zero* en sus quirófanos son el Estado de México (8; 8.9%), Puebla (7; 7.8%), Morelos (5; 5.6%), Nuevo León (5; 5.6%), Guanajuato (4; 4.4%) y Veracruz (4; 4.4%). La mayoría de los cirujanos que refieren utilizar medidas *net zero* en su práctica diaria son mayores de 46 años (76; 85.3%), y en mayor proporción se encuentran entre los 46 y 60 años.

El 91.5% (n = 659) de los participantes refirieron que en sus hospitales no existe un plan de acción establecido para alcanzar quirófanos «verdes». Los encuestados que contestaron que sí hay en sus hospitales un plan de acción (61; 8.4%) se distribuyen por el Estado de la República Mexicana, como se muestra en la figura 3. La mayoría de los hospitales con un plan de acción son hospitales privados (42; 68.8%); los 19 hospitales públicos de todo el país con planes de eco-cirugía pertenecen al IMSS, la SS, el ISSSTE, el IMSS-Bienestar y PEMEX.

Positivamente, casi todos (704; 97%) los participantes contestaron que sí les interesa saber qué hacer para disminuir las emisiones de carbono que se generan durante una cirugía.

## Discusión

Cada vez más países se suman al esfuerzo mundial para lograr un sistema de salud neutro en cuanto a



**Figura 3.** Estados de la República en los que, de acuerdo con los encuestados, existen hospitales con planes de acción para alcanzar quirófanos «verdes». El primer número corresponde al total de hospitales en ese estado con un plan de acción, el segundo número corresponde a los hospitales privados, y las siglas siguientes corresponden a los hospitales públicos que tienen un plan de acción en ese estado.

la generación de gases con efecto invernadero. México es el país de América Latina que más emisiones de dióxido de carbono genera, y el segundo con el sistema de salud más contaminante, solo por detrás de Brasil<sup>6</sup>. Los quirófanos contribuyen de manera considerable, por lo que son un sitio importante para generar un cambio a favor del medio ambiente.

Modificar las conductas establecidas que se realizan de manera cotidiana en cualquier actividad humana, por ejemplo durante el proceso quirúrgico en los hospitales de nuestro país, es un reto. Para intentarlo es indispensable conocerlas antes de suponer cambiarlas. Como punto de partida, esta encuesta se diseñó para explorar el conocimiento y la actitud del personal quirúrgico mexicano respecto a la contaminación que causa el uso de los quirófanos.

El término *net zero carbon emission* se traduce del inglés como «cero emisiones netas de carbono» y hace referencia a alcanzar un balance neutro entre la cantidad de gases con efecto invernadero que se produce y la cantidad de estos que se logra eliminar de la atmósfera<sup>5</sup>. Coincidente con otros estudios<sup>7-9</sup>, casi todos los encuestados tienen interés en saber cómo disminuir las emisiones de carbono que se generan durante una cirugía, pero solo una pequeña proporción conoce el término *net zero* y realiza medidas para alcanzarlo en su práctica diaria (12%), y un porcentaje aún menor (7.5%)

reconoce que en su hospital exista un plan de acción para implementar quirófanos «verdes».

La falta de información es la primera barrera a vencer para poder disminuir la huella de carbono que se genera en un quirófano<sup>10</sup>. En una encuesta a más de 3000 profesionales de 117 países del mundo, al preguntar sobre las dificultades para lograr un quirófano «verde» los participantes contestaron en su mayoría la baja tasa de planes sostenibles, la falta de información sobre iniciativas «verdes» y la falta de líderes en el área<sup>10</sup>.

En octubre de 2023 se instauró en la AMCG el comité de eco-cirugía; en nuestro conocimiento, es la primera vez que una asociación médico-quirúrgica mexicana conforma un grupo de trabajo de profesionales afines al tema. El primer objetivo a corto plazo (1 año) fue visibilizar el problema, realizar difusión del conocimiento y concientizar al personal involucrado. Difundir y enseñar a las nuevas generaciones también es prioritario, por lo que incluir el tema de sostenibilidad y economía circular en los programas de pregrado y posgrado de las diferentes universidades sería importante. En una encuesta aplicada a otorrinolaringólogos canadienses<sup>8</sup>, el 38.8% dedicaron cero horas al estudio climático y su impacto en la salud durante la residencia, y el 7.5% entre 1 y 5 horas. La mayoría coincidieron en que los médicos en entrenamiento deberían recibir educación formal en sostenibilidad ambiental.

Los resultados de la presente encuesta evidencian que el bajo conocimiento no se limita al concepto de *net zero*, sino que se extiende a otras áreas del quehacer quirúrgico cotidiano que de manera indirecta impactan en la generación de emisiones de carbono. Por ejemplo, la indicación incorrecta de estudios preoperatorios en pacientes de bajo riesgo, el desecho inadecuado de medicamentos sobrantes, la separación deficiente de desechos municipales y RPBI, el desconocimiento sobre los gases anestésicos que se utilizan en sus cirugías y el funcionamiento de los sistemas de recambio de aire, temperatura e iluminación en cada quirófano, entre otros.

De acuerdo con nuestros resultados, el uso de gas desflurano en México es limitado, probablemente por su alto costo en comparación con otros gases anestésicos, que son más económicos y además contaminan menos, como el sevoflurano<sup>11</sup>; el uso de técnicas anestésicas alternativas, como la sedación total intravenosa, es bastante limitado. Educar, difundir y concientizar a cirujanos y anestesiólogos sobre el impacto ambiental de los gases y las alternativas más verdes, como el uso de medicamentos intravenosos o el bloqueo regional, es un área de oportunidad.

Se espera que la mayor proporción de basura generada en un hospital y en el quirófano sea basura municipal y se deseche en bolsas negras. De acuerdo con la Organización Mundial de la Salud<sup>12</sup>, de todos los residuos generados por las actividades de atención sanitaria aproximadamente el 85% son desechos comunes y el 15% restante se considera material peligroso, que puede ser infeccioso, tóxico o radiactivo. La cantidad de desechos RPBI que genera un hospital se calcula según el número de camas que tiene. «Los países de ingresos elevados generan en promedio hasta 0.5 kg de desechos peligrosos por cama hospitalaria y día, mientras que en los de ingresos bajos ese promedio ronda los 0,2 kg. Sin embargo, en estos últimos países los desechos sanitarios peligrosos a menudo no se separan del resto de residuos, de modo que en la práctica su cantidad es mucho mayor»<sup>12</sup>. En un estudio mexicano realizado en el Instituto Nacional de Psiquiatría, en 2003 el promedio diario de RPBI generados ascendía a 1400 g/día por cama, mientras que en el primer semestre de 2007 el promedio había disminuido más de un 90% para alcanzar un equilibrio de solo 180 g/día por cama. Este resultado se logró con la capacitación continua del personal involucrado y fue un factor determinante en el momento de clasificar y separar los residuos, y de mejorar las prácticas de manejo de los RPBI<sup>13</sup>.

Las experiencias publicadas<sup>13,14</sup> sobre la difusión y el acercamiento al conocimiento dirigido a los especialistas han demostrado ser efectivas y útiles, por ejemplo, en la disminución de la producción de gases con efecto invernadero en el quirófano y en la adecuada separación de desechos.

De acuerdo con García-Morales et al.<sup>15</sup>, en el caso de residuos de fármacos, su persistencia y entrada continua a los mantos acuíferos originan efectos negativos sobre la vida y el ambiente acuático, debido a que no se eliminan totalmente en los procesos de tratamiento de aguas residuales a causa de su estabilidad química. El desecho adecuado de fármacos reduce la contaminación del subsuelo y de los mantos freáticos. El uso de contenedores con sustancias que inactivan los compuestos químicos de los fármacos sobrantes debería implementarse en todas las salas quirúrgicas de nuestro país.

En cuanto al uso de textiles desechables, un área de oportunidad será desarrollar estrategias y alternativas seguras para disminuir el uso de gorros desechables y cubrezapatos, los cuales son reusables en un porcentaje muy pequeño en nuestro país. Utilizar batas y uniformes reusables ha demostrado que produce menos gases con efecto invernadero que los desechables, incluyendo distintos factores del ciclo de vida de cada uno hasta en 1000 usos<sup>16</sup>.

Este trabajo se trata de una encuesta transversal, por lo que la información refleja la situación en un momento específico. También existe un posible sesgo de selección en los resultados, dado que la encuesta pudiera haber sido respondida únicamente por asociados de la AMCG interesados en el tema. Esto podría hacer que los hallazgos sean aún más preocupantes, ya que, a pesar del interés de los participantes en las políticas de eco-cirugía, su nivel de conocimiento sobre el tema es considerablemente bajo.

## Conclusiones

La presente encuesta revela un bajo nivel de conocimiento sobre el quirófano sostenible y las prácticas *net zero* entre los cirujanos asociados a la AMCG, así como la escasez de planes de acción para alcanzar quirófanos «verdes» en México. Sin embargo, destaca el interés de los encuestados en aprender sobre el tema y en conocer medidas que contribuyan a reducir la producción de gases de efecto invernadero en el entorno quirúrgico.

Esta investigación ha mostrado un panorama nacional que era desconocido, sobre un tema actual y urgente, en el que es necesario educar y contribuir en

la disminución de barreras. Será prioridad entre las acciones inmediatas del comité de eco-cirugía de la AMCG la generación de guías y lineamientos específicos que permitan implementar medidas factibles amigables con el ambiente en los quirófanos de México.

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## Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

## Consideraciones 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, consentimiento informado y aprobación ética.** El estudio no involucra datos personales de pacientes. Se han seguido las recomendaciones de las guías SAGER, según la naturaleza del estudio.

**Declaración sobre el uso de inteligencia artificial.** Los autores declaran que no utilizaron ningún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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# Surgical resection of the primary tumor improves survival in patients with pancreatic neuroendocrine tumors associated with liver metastases: a meta-analysis

*La resección quirúrgica del tumor primario mejora la supervivencia en pacientes con tumores neuroendocrinos pancreáticos asociados a metástasis hepáticas: un metaanálisis*

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## Abstract

**Objective:** The role of palliative pancreatic neuroendocrine tumor resection (pPanNEN-R) is controversial. The aim of this study was to conduct a meta-analysis of relevant studies to compare pPanNEN-R and non-surgical management (PanNEN-nR). **Methods:** All studies published until May 31, 2024, comparing pPanNEN-R and PanNEN-nR were reviewed. The primary outcome was overall survival (OS). Meta-analysis was performed after the data extraction process. **Results:** A total of 10 studies and 1152 patients were included, of whom 373 (32.38%) received pPanNEN-R, and 779 (67.62%) received PanNEN-nR. The overall quality of the included studies was fair. Patients receiving pPanNEN-R had a significantly lower risk of death compared with those receiving PanNEN-nR (odds ratio = 0.32, 95% confidence interval [0.24-0.43],  $p < 0.00001$ ). **Conclusions:** The use of pPanNEN-R in patients with unresectable liver metastases seems to be associated with a better OS compared to non-surgical treatments, but due to the limitations of the included studies, no firm conclusions can be drawn.

**Keywords:** Primary tumor resection. Pancreatic neuroendocrine tumor. Liver metastases. Overall survival. Meta-analysis.

## Resumen

**Objetivo:** El papel de la resección paliativa de tumores neuroendocrinos pancreáticos (pPanNEN-R) es controvertido. El objetivo de este estudio fue realizar un metaanálisis de los estudios pertinentes para comparar la resección neuroendocrina pancreática paliativa y el tratamiento no quirúrgico (resección neuroendocrina pancreática no paliativa [PanNEN-nR]). **Métodos:** Se revisaron todos los estudios publicados hasta el 31 de mayo de 2024 que comparaban pPanNEN-R y PanNEN-nR. El resultado primario fue la supervivencia global. Se realizó un metaanálisis tras el proceso de extracción de datos. **Resultados:** Se incluyeron 10 estudios con 1152 pacientes, de los cuales 373 (32.38%) recibieron pPanNEN-R y 779 (67.62%) recibieron PanNEN-nR. La calidad general de los estudios incluidos fue regular. Los pacientes con pPanNEN-R tuvieron un riesgo significativamente menor de muerte en comparación con los tratados con PanNEN-nR (odds ratio: 0.32; intervalo de confianza del 95%: 0.24-0.43;  $p < 0.00001$ ). **Conclusiones:** El uso de pPanNEN-R en pacientes con metástasis hepáticas irresecables parece asociarse a una mejor supervivencia global en comparación con el tratamiento no quirúrgico, pero debido a las limitaciones de los estudios incluidos no se pueden extraer conclusiones firmes.

**Palabras clave:** Resección del tumor primario. Tumor neuroendocrino pancreático. Metástasis hepáticas. Supervivencia global. Metaanálisis.

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## Introduction

Pancreatic neuroendocrine tumors (PNETs) are rare, with tumors accounting for only about 1% of all pancreatic tumors by incidence, although their prevalence is very close to 10%.<sup>1,2</sup> The incidence of liver metastases exceeds 50% of patients affected by PNETs (80% of bilobar cases).<sup>3</sup> In some cases, these malignancies are not amenable to resection extending to both liver lobes due to local vascular infiltration or hepatic metastases or due to extrahepatic metastases. Surgery is considered the only feasible approach to the radical treatment of metastatic PNETs, although few case series have been published.<sup>4,5</sup> Since 2000, 5-year post-operative rates of hepatic resection for PNETs metastases have ranged from 74% to 100%, with disease-free survival rates ranging from 29% to 96%.<sup>6</sup>

Surgery for advanced metastatic PNETs seems to play a role and is recommended by international guidelines<sup>7,8</sup>. Patients may choose from a variety of palliative treatment options, including radiofrequency ablation, chemotherapy, hepatic artery embolization or pharmacological treatment with octreotide or lanreotide. In addition, primary tumor resection has been recommended to alleviate symptoms related to the tumor burden or functional tumors<sup>8</sup>, but its prognostic effect is controversial. On the other hand, some studies have shown that primary pNETs removal could increase disease control.<sup>9,10</sup>

The aim of this systematic review was to assess whether or not patients who underwent palliative PNET resection (pPanNEN-R) had an improved overall survival (OS) compared to those patients who did not undergo resection PanNEN-nR.

## Methods

### Search strategy

PubMed, Web of Knowledge, Medline, Ovid's database were searched from January 2005 to May 2024 with English language. The search terms used were "pancreatic neuroendocrine tumor," "liver metastases," "resection" and "survival rate." The reference lists of relevant studies were checked manually to locate any missing studies.

### Study selection

Identified full papers were assessed for eligibility for inclusion in the review by scanning the titles, abstracts,

and keywords of every record retrieved. Clinical studies concerning comparisons of outcomes between the pPanNEN-R group and PanNEN-nR group were included regardless of randomized controlled trials (RCTs) or non RCTs (NRCTs). Studies were restricted to those published in English.

### Data extraction

Three coauthors (JZ, WW and YZ) independently selected studies for inclusion and exclusion and reached consensus when they did not agree in the initial assignment. The following variables were recorded: authors, journal and year of publication, number of patients, age, median tumor size, histological type, surgical procedure, and 5-year OS. If necessary, the corresponding authors of studies were contacted to obtain supplementary information. The Methodological Index assessed that of the NRCTs for Nonrandomized Studies.<sup>11</sup>

### Statistical analysis

A formal meta-analysis was carried out for all included studies comparing the results of pPanNEN-R group and PanNEN-nR group. The outcomes in our study were OS. A fixed effects model was used to calculate a pooled odds ratio (OR) with its 95% confidence interval (CI). Heterogeneity was explored using  $I^2$  statistics, a measure of how much the variance between studies, rather than chance, can be attributed to inter-study differences.  $I^2 > 50\%$  was regarded to indicate strong heterogeneity. Begg's and Egger's tests<sup>12,13</sup> were used to estimate the publication bias. Meta-analysis was conducted using STATA software, version 14.0.

## Results

### Study selection

A total of 87 potentially relevant titles and abstracts were obtained (Fig. 1). After exclusion of duplicate references, non-relevant literature, and those that did not satisfy the inclusion criteria, 21 candidate articles were considered for the meta-analysis. After careful review of the full text of these articles, 10 studies (Table 1)<sup>4,10,14-21</sup> fulfilled the eligibility criteria. These 10 papers were retrospective clinical trials. The publication dates

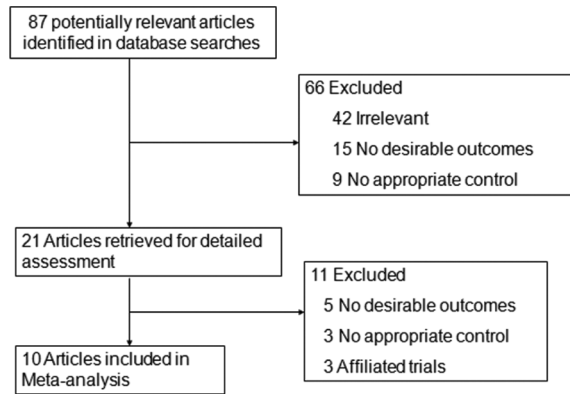


Figure 1. Flowchart of the results of the literature search.

ranged from January 2001 to December 2018. Study sizes ranged from 36 to 442 patients.

### Outcome measures

A total of 373 patients who underwent primary tumor resection and 779 patients who allow non-surgical management were analyzed. The 5-year OS was 48.26% in the pPanNEN-R group compared with 22.34% in the PanNEN-nR group, and the 5-year OS was significantly higher in pPanNEN-R group than in the PanNEN-nR group (OR = 0.32, 95% CI 0.24-0.43,  $p < 0.00001$ ) (Fig. 2). The publication bias confirmed by the Begg's and Egger's tests did not appear significant ( $P > |z| = 1.000$ ,  $P > t = 0.795$ ) (Figs. 3 and 4).

Five studies reported the 30-day post-operative complications in patients who underwent pPanNEN-R, the overall complication rate reached 52.7%. Post-operative complication was mainly related to the formation of pancreatic fistula. Thirty-day readmission, length of stay, or quality of life data were not reported by any of the ten studies.

### Discussion

Studies exploring the role of pPanNEN-R were considered in this review, but these studies have some limitations. These studies were not randomized trials, and almost all series were retrospective with limited sample sizes.

Surgical resection of the primary tumor site in patients with metastatic PNET is a controversial practice, especially in patients with advanced disease. In regard of primary resection, international guidelines distinguish tumor arising from the small intestine and those arising from pancreas.<sup>22,23</sup> Resection of primary

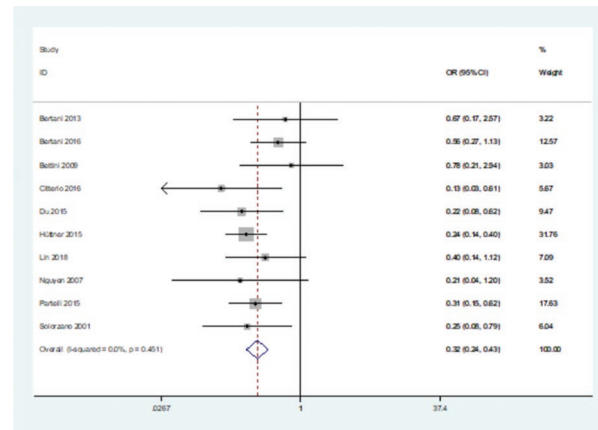


Figure 2. Meta-analysis of 5-year overall survival for palliative pancreatic neuroendocrine tumor resection group versus PanNEN-non-surgical management group.

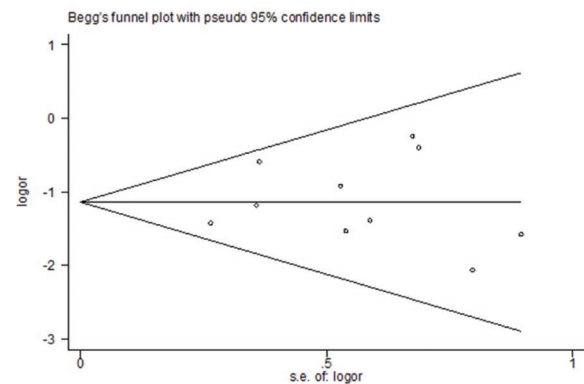


Figure 3. Begg's funnel plot for visual assessment of no publication bias for 5-year overall survival.

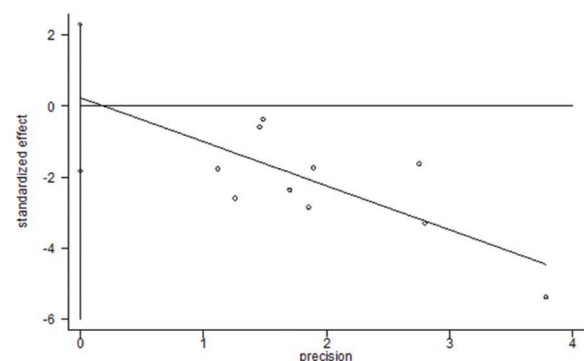


Figure 4. Egger's publication bias plot showed no publication bias for 5-year overall survival.

tumor is strongly recommended for intestinal tumors, whilst the resection of the primary tumor in metastatic PNETs is not recommended.<sup>22-24</sup> This distinction is mainly related to the high risk of post-operative morbidity after pancreatic surgery.

Table 1. Overview on surgical and oncological outcomes reported or retrieved from included studies

| Author, Year                       | Country | Study design  | No. of patients | Sex (male/female) | Mean age (Years)                   | Median primary Tumor size (cm)   | Type of surgery on primary tumor |    |             | Complications | Follow-up (months)                 | Quality score <sup>a</sup> |
|------------------------------------|---------|---------------|-----------------|-------------------|------------------------------------|----------------------------------|----------------------------------|----|-------------|---------------|------------------------------------|----------------------------|
|                                    |         |               |                 |                   |                                    |                                  | PD                               | DP | Enucleation |               |                                    |                            |
| Bertani et al. 2013 <sup>14</sup>  | Italy   | Retrospective | 43              | 20/23             | -                                  | -                                | -                                | -  | -           | 3/12          | 60                                 | 7/9                        |
| Bertani et al. 2016 <sup>15</sup>  | Italy   | Retrospective | 124             | 66/58             | 54.6                               | 6.0                              | 0                                | 63 | 0           | 10/63         | 96                                 | 7/9                        |
| Bettini et al. 2009 <sup>10</sup>  | Italy   | Retrospective | 51              | 24/27             | 55                                 | 4.5                              | 5                                | 14 | 0           | 8/19          | 26                                 | 7/9                        |
| Citterio et al. 2016 <sup>16</sup> | Italy   | Retrospective | 36              | -                 | -                                  | -                                | -                                | -  | -           | -             | 127                                | 6/9                        |
| Du et al. 2015 <sup>17</sup>       | China   | Retrospective | 98              | -                 | -                                  | -                                | -                                | -  | -           | -             | -                                  | 5/9                        |
| Hüttner et al. 2015 <sup>18</sup>  | Germany | Retrospective | 442             | 247/195           | pPanNEN-R: 52.9<br>PanNEN-nR: 59.6 | -                                | -                                | -  | -           | -             | pPanNEN-R: 32.5<br>PanNEN-nR: 17.6 | 7/9                        |
| Lin et al. 2018 <sup>19</sup>      | China   | Retrospective | 63              | 28/35             | pPanNEN-R: 49.1<br>PanNEN-nR: 49.0 | 4.0                              | 8                                | 25 | 2           | -             | 37                                 | 7/9                        |
| Nguyen et al. 2007 <sup>20</sup>   | Italy   | Retrospective | 51              | -                 | -                                  | -                                | -                                | -  | -           | 5/20          | 41                                 | 6/9                        |
| Partelli et al. 2015 <sup>21</sup> | Italy   | Retrospective | 148             | 83/65             | pPanNEN-R: 73<br>PanNEN-nR: 75     | pPanNEN-R: 4.8<br>PanNEN-nR: 4.4 | 19                               | 52 | 2           | 112/148       | 40.5                               | 7/9                        |
| Solorzano et al. 2001 <sup>4</sup> | USA     | Retrospective | 96              | -                 | -                                  | -                                | 4                                | 12 | 0           | -             | -                                  | 6/9                        |

<sup>a</sup>Quality scores of the included studies were assessed using the Newcastle–Ottawa Scale (NOS), with scores expressed as \*actual score/maximum possible score<sup>9</sup>. PD: distal pancreatectomy; pPanNEN-R: palliative pancreatic neuroendocrine tumor resection; PanNEN-nR: PanNEN-non-surgical management.

However, a positive impact on prognosis after resection of the primary tumor has also been reported for PNETs. Zheng et al.<sup>25</sup> reported resection of the primary tumor was associated with prolonged survival in all patients with gastric, small intestinal, colorectal, and pancreatic neuroendocrine neoplasms with liver metastases. Tao et al.<sup>26</sup> reveals that local treatment on the primary benefits OS in PNETs patients with liver metastases. Chen et al.<sup>27</sup> illustrated primary tumor resection led to improved survival for gastrointestinal neuroendocrine carcinoma patients with non-resected liver metastases regardless of primary tumor site, tumor grade, and N stage. Our meta-analysis showed that primary tumor resection provided a significant benefit for 5-year OS in PNETs patients with liver metastases.

There are two possible explanations for the survival-prolonging effect of primary tumor resection. First, a reduction in immunosuppressive tumor burden may prolong prognosis by minimizing the chance that the tumor will lead to disease progression and further metastasis. Second, resection of the primary lesion helps to relieve symptoms of the tumor, such as bleeding, obstruction, and symptoms of tumor compression, control symptoms caused by functional tumors, and helps to focus subsequent therapy on liver metastases treatment. The actual mechanism of how primary tumor resection contributes to improved prognosis remains unclear. In the era of personalized therapy, primary tumor resection should be viewed as part of an integrated multidisciplinary approach to optimize the treatment of patients with Stage IV pancreatic neuroendocrine neoplasm.

Despite the fact that more than half of patients faced a post-operative complication, the majority of resections involved the tail of the pancreas, and surgical sequelae can usually be managed safely.

There are some limitations in our study. First, most of the included studies were retrospective chart reviews with inherent limitations such as selection bias and inaccurate or missing data reports. Second, our analysis only included published studies in English. Hence, our findings must be interpreted with caution.

## Conclusions

The present study provides a meta-analysis of palliative surgical approach to patients with PNETs associated with liver metastasis, exhibiting an obvious survival benefit of primary tumor resection over time. However, the included studies were subject to selection bias. A RCTs comparing pPanNEN-R associated

with non-surgical treatment versus non-surgical treatments alone is urgently needed.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

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

**Confidentiality, informed consent, and ethical approval.** This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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# A novel free functional muscle transfer model for animal experiments: rat triceps brachii muscle flap

*Un novedoso modelo de transferencia muscular funcional libre para experimentación animal: colgajo muscular del tríceps braquial de rata*

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## Abstract

**Objective:** Although free functional muscle transfer (FFMT) has been used in clinical practice for many years, there is no experimental model for FFMT. We aimed to describe a novel experimental muscle flap model and define the triceps brachii free muscle flap as an FFMT model in rats. **Methods:** A total of 10 Wistar-Albino rats were used. The rats were divided into two groups with five rats in each. Animals in Group 1 were used for the identification of the triceps brachii muscle flap, whereas rats in Group 2 were used for the FFMT model. After 3 months, all the flaps were examined electrophysiologically, and biopsy samples were obtained from the muscles and nerves. **Results:** The presence of reinnervation was confirmed electrophysiologically in all of the flaps. Histological examination findings were compatible with neural healing, which was seen in all of the flaps. Myelination was found significantly more in Group 1. **Conclusions:** The rat triceps brachii muscle flap can be used as a pedicled flap or FFMT model. By describing a novel muscle flap in the upper extremity, we hope that it will contribute to the experimental microsurgical training, providing a new donor area.

**Keywords:** Experimental flap. Experimental microsurgery. Rat triceps brachii muscle flap. Rat-free muscle transfer model.

## Resumen

**Objetivo:** Aunque la transferencia muscular funcional libre (TMFL) se ha utilizado en la práctica clínica durante muchos años, no existe un modelo experimental para ella. Nos propusimos describir un nuevo modelo experimental de colgajo muscular y definir el colgajo muscular libre del tríceps braquial como modelo de TMFL en ratas. **Métodos:** Se utilizaron 10 ratas Wistar-Albino. Los animales del grupo 1 se usaron para la identificación del colgajo muscular del tríceps braquial, mientras que los del grupo 2 se usaron para el modelo TMFL. Al cabo de 3 meses se examinaron electrofisiológicamente todos los colgajos y se obtuvieron muestras de biopsia de los músculos y los nervios. **Resultados:** La presencia de reinervación se confirmó electrofisiológicamente en todos los colgajos. Los hallazgos del examen histológico fueron compatibles con la curación neural que se observó en todos los colgajos. La mielinización fue significativamente mayor en el grupo 1. **Conclusiones:** El colgajo muscular de tríceps braquial de rata puede utilizarse como colgajo pediculado o modelo TMFL. Al describir un nuevo colgajo muscular en la extremidad superior, esperamos que contribuya a la formación microquirúrgica experimental proporcionando una nueva zona donante.

**Palabras clave:** Colgajo experimental. Microcirugía experimental. Colgajo de músculo tríceps braquial de rata. Modelo de transferencia muscular libre en rata.

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## Introduction

Free functional muscle transfer (FFMT) has been used in clinical practice for more than 30 years.<sup>1</sup> Unlike classical free flaps, FFMT allows the transferred muscle mass to function by coaptation of the muscle's nerve with an appropriate and sacrificial nerve in its new location.

During microsurgery training, research conducted on rats is invaluable. Besides neurovascular repairs, the free transfer of flaps forms a significant portion of advanced microsurgery courses. The identification of a large number of flaps on rats during these trainings is crucial for cost-effective utilization of experimental animals and for enabling a greater number of course participants to benefit simultaneously.

Plenty of rat muscle flaps, such as rectus abdominis, latissimus dorsi, cutaneous maximus, pectoralis major and gluteus maximus, have been previously used in experimental studies.<sup>2</sup> Since there is no free muscle flap previously described in the upper extremity of rats, experimental muscle flap education is carried out in the other body parts. On the other hand, although it has been successfully applied in clinical applications targeting motor function, such as functional reconstructions of the upper limb<sup>3</sup> or lower limb,<sup>4</sup> fascial reanimation<sup>5</sup> and tongue reconstruction,<sup>6</sup> a FFMT model designed in rats is not available in the literature.

In this study, we aimed to introduce the triceps brachii free muscle flap and its use as an FFMT model in rats.

## Methods

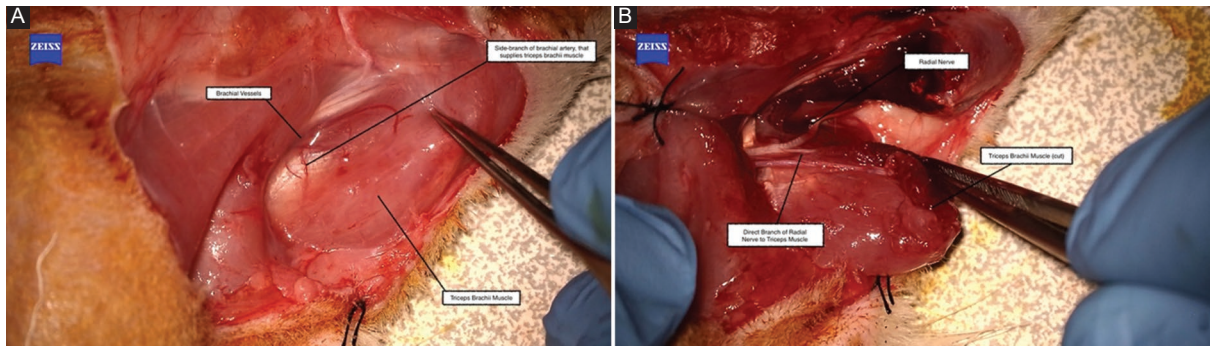
Ethical approval from the local animal experiments committee was obtained before the study was started, and the entire study was conducted according to the principles for the care of research animals (Ethical Appr. No.: 2021-058). A total of 10 male Wistar-Albino rats weighing 250-300 g were used throughout the study. The rats were divided into two groups of five animals each. Animals in Group 1 were used for the identification of the triceps brachii muscle flap and determination of its neurovascular pedicle, whereas rats in Group 2 were used for modeling the transfer of the triceps brachii muscle flap in the form of FFMT.

## *Anatomy of the rat triceps brachii muscle*

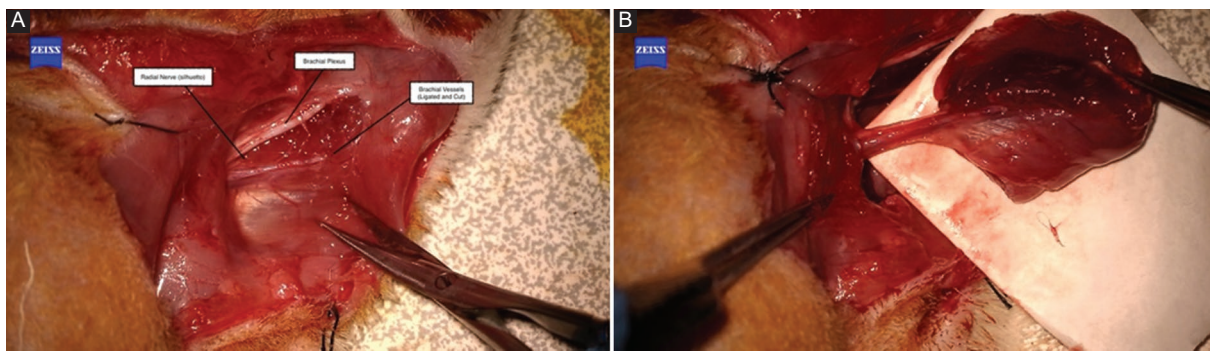
In the rat body, the triceps brachii muscle is located in the posterior part of the arm and consists of three heads called the medial, lateral and long head, just like in humans. It briefly originates from the bones of the scapula and humerus and inserts on the ulna in the forearm. The lateral head is wide and originates from the tricipital line of the humerus, and inserts on the tuberosity of the olecranon. The long head is a large muscle taking its origin from the level of the infraglenoid tubercle of the scapula. This head inserts on the caudal part of the tuberosity of the olecranon. Unlike the previous two heads, the medial head originates from the medial side of the humerus and inserts on the caudal part of the olecranon tuberosity together with the long head. The main function of the triceps brachii muscle is the extension of the forearm.<sup>7</sup> Several side branches from the brachial artery and vein provide muscle perfusion by entering directly into the muscle (Fig. 1A). The muscle is innervated by a nerve bundle that directly branches from the radial nerve (Fig. 1B).

## *Surgical technique of flap harvesting*

Before surgery, sedoanalgesia is achieved by administering 10 mg/kg xylazine and 90 mg/kg ketamine to the rat. After the rat is placed in the supine position and the other three extremities that will not be used are fixed by surgical tapes, the extremity from which the muscle flap will be harvested is abducted, and an incision is made through the medial intermuscular sulcus in the arm. Then, the brachial artery, vein and brachial plexus are explored between the biceps brachii and triceps brachii muscles (Fig. 1A). Afterward, the direct segmental branches from the brachial artery and vein to the triceps muscle are explored and protected. The triceps muscle is separated from the surrounding tissue by securing the integrity of the pedicle. Subsequently, the distal end of the brachial artery and vein are ligated, leaving the segmental branches supplying the muscle intact on the muscle, thus the radial nerve behind the vessels could be seen clearly (Fig. 2A). After exposure of the nerve, the insertion of the muscle is cut and released distally, thus the direct branch of the radial nerve to the muscle become exposed (Fig. 1B). The length of the nerve is increased by releasing it from the radial nerve by intra-neural neurolysis. The



**Figure 1.** A: intraoperative view of the triceps muscle and the insertion of the supplying side branches of the brachial vessels into the muscle tissue. B: view of the triceps muscle with the distal end cut surgically, the radial nerve and the branch of the radial nerve that innervates the muscle.



**Figure 2.** A: intraoperative view during the harvesting of the flap, the distal ends of the brachial vessels were ligated and the direct branches of the vessels to the muscle were preserved. B: TRICEPS brachii muscle flap prepared as an island flap based on its artery, vein and nerve.

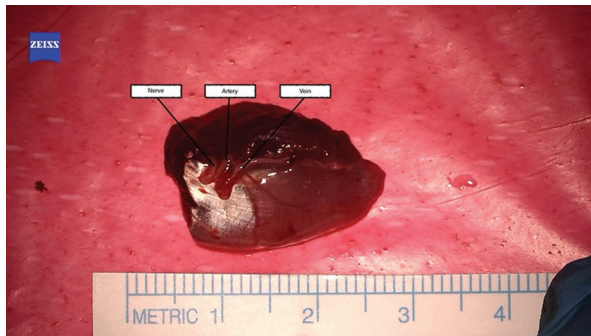
proximal end of the muscle is cut to obtain an innervated muscle flap (Fig. 2B). After this dissection is achieved, the muscle flap can be used as a pedicled flap or as an FFMT model by separating the pedicle and nerve (Fig. 3), depending on the purpose of the experiment.

### Experimental groups

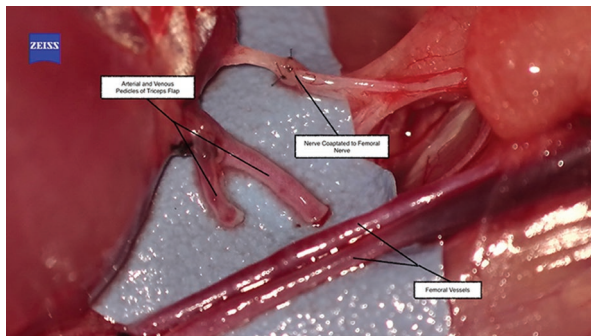
In our study, the left forelimb triceps brachii muscle flaps of rats in Group 1 were harvested as a pedicled flap. Then, the nerve branches innervating the muscle were cut at a distance of 3 mm from the muscle and coaptated to its original stump using 10-0 nylon suture material. The mean diameter of the nerve was found to be 0.58 mm, and the epineural neurorrhaphy technique was applied with five stitches. The distal and proximal ends of the isolated triceps muscle were sutured back to their anatomical position with 4-0 absorbable suture and kept strained.

In group 2, the triceps brachii muscle flaps of the left forelimb were harvested as a free flap, including

the nerve. Then, femoral vessels and a side branch of the femoral nerve were prepared in the right groin area as the flap recipient area, and the flap inset was completed by performing end-to-end vessel anastomosis and nerve coaptation using 10-0 nylon sutures (Fig. 4). The mean diameter of vessels was measured 0.63 mm for artery and 0.66 mm for vein. Six stitches were placed for each artery anastomosis, while five stitches were applied for vein anastomosis. Then, the triceps muscle was sutured to the anterior abdominal wall and the femoral muscle with 4-0 absorbable suture for fixation and kept strained. After the surgical procedures, the incision lines were closed with 4-0 non-absorbable suture. At the end of surgery, heparin at a dose of 200 U/kg was injected subcutaneously once in the free flap group.<sup>8</sup> All procedures were performed by the same surgeon. The animals were kept at a temperature of 21-23°C on a 12/12 h light/dark cycle (lights on at 8:00 am, lights off at 8:00 pm.). They were fed normal rodent chow in their isolated cages (600 mm × 400 mm × 200 mm). Post-operative analgesia was provided with 100 mg/kg paracetamol



**Figure 3.** The triceps brachii muscle flap was harvested as a free functional muscle flap.



**Figure 4.** An intraoperative view during free flap transfer, nerve coaptation has been completed, and artery and vein anastomoses will be done.

mixed in drinking water for 5 days. All rats were kept single in cages for 3 months.

### **Outcome evaluations**

At the end of 3 months of follow-up period, all animals underwent the operation under sedoanalgesia, and the triceps brachii muscle flaps and nerves that were located in the posterior arm in Group 1 and in the groin area in Group 2 were dissected from the surrounding tissue and revealed. For electromyography examination, a recording electrode was inserted into the muscle, and a ground electrode was inserted into the surrounding tissues. A standard stimulating electrode delivered current to the nerve. Pulse duration was fixed at 1 ms at a constant current from 10  $\mu$ A up to 10 mA. A single shock was delivered for each trial, and muscle action potentials (MAP's) were recorded.<sup>9</sup> The presence or absence of reinnervation was determined with the MAP's obtained in the muscles.

After electrophysiologic evaluation, animals were sacrificed, and biopsy samples were obtained from muscles and nerves for histopathologic analysis. The samples were fixed in 10% neutral formalin solution for 24-48 h, and then sample pieces were taken macroscopically from the muscles and microscopically from the distal part of the coaptation line for the nerves. After embedding, paraffin blocks were sectioned at 4-5  $\mu$ m thickness with a microtome for Hemotoxylin and Eosin, Masson trichrome (MTC), and Luxol fast blue (LFB). MTC and LFB staining were performed with the Dako Artisan Link Pro fully automated histochemistry device. H&E and histochemical-stained slides were evaluated under a light microscope by a single pathologist.

In the microscopic examination, the inflammation density, vascularization, fibrosis, edema, fascicular organization dysfunction, axonal degeneration, myelination and axonal density were evaluated for nerves. In addition, axons in the peripheral nerve were counted in each mm<sup>2</sup> area. In the evaluation of muscle specimens, inflammation density, vascularization, fibrosis, muscle atrophy, necrosis and edema were evaluated.

### **Statistical analysis**

Statistical analysis was performed using the Statistical Package for the Social Sciences 24.0 (USA). Data were evaluated for eligibility for normal distribution analysis. An analysis of variance test was used for the analysis of normal variables. Chi-squared, Fisher's exact and Mann-Whitney U tests were used for binary comparisons and  $p < 0.05$  was considered a significance level.

### **Results**

At the end of 3 months period, no animal loss was observed. Wound healing was favorable in each of them, and no self-injury was seen either. Flexion contracture and limitation of extension of the left forelimb were common in the rats due to the loss of the triceps muscle. Because the muscle was restitched to its original localization, findings related to the functional disability were presented as milder in Group 1. However, it did not affect their walking and reaching for food in both groups.

According to the results of electrophysiologic evaluation, MAPs, which show the viability and contractibility of the muscles and neural healing, were recorded in the muscles with a single stimulus applied to the nerve in Groups 1 and 2. The mean MAP obtained in Group 1 was 12.475 mV, whereas this number was 12.964 mV in Group 2. There was no statistically significant comparison regarding nerve recovery.

In the histological examination, neural and muscle tissues were evaluated separately (Table 1). Vascular structures and nerve fibers (axonal density) were counted at  $\times 200$  magnification: +1, +2, and +3 indicated the presence of 0-5, 6-10, and  $> 10$  structures, respectively. For uncountable parameters of nerve tissue (edema, disorganization, myelination, fibrosis, and inflammation) and muscle tissue (inflammation, fibrosis, muscle atrophy, and edema): +1 indicated mild, +2 indicated moderate, and +3 indicated severe. The parameters of axonal degeneration and myelination in nerve tissue, and necrosis in muscle tissue, were evaluated as "1" for existence and "0" for absence.

The signs of neural regeneration were obvious in both of the groups. The comparisons of axonal degeneration, axonal density and fascicular organizational dysfunction between the groups were not found statistically significant ( $p = 0.524$ ;  $p = 0.401$  and  $p = 0.100$ , respectively). However, myelination was found significantly more in Group 1 by the Pearson's Chi-squared test ( $p = 0.038$ ). Moreover, the other histological evaluation parameters, such as inflammation density, vascularization, fibrosis and edema, were parallel with neural healing in both of the groups (Fig. 5).

Muscle atrophy, one of the main parameters for functionality, was not found significantly different in the tests ( $p = 0.054$ ) (Fig. 6). There was no flap failure, so that necrosis observed in the histopathological evaluation was at the cellular level rather than macroscopic. Inflammation was revealed more in Group 2, and the difference between groups was statistically significant ( $p = 0.005$ ).

## Discussion

Experimental flap models are usually defined by adapting the flaps used in the clinics to animals.<sup>10</sup> On the other hand, the human triceps brachii muscle flap is not a commonly used flap due to the functional deficits it may cause.<sup>11</sup> For this reason, the use of the rat triceps brachii muscle flap model defined in our

**Table 1. Results demonstrate the comparison of histological examinations between the groups in both the nerve and muscle tissues**

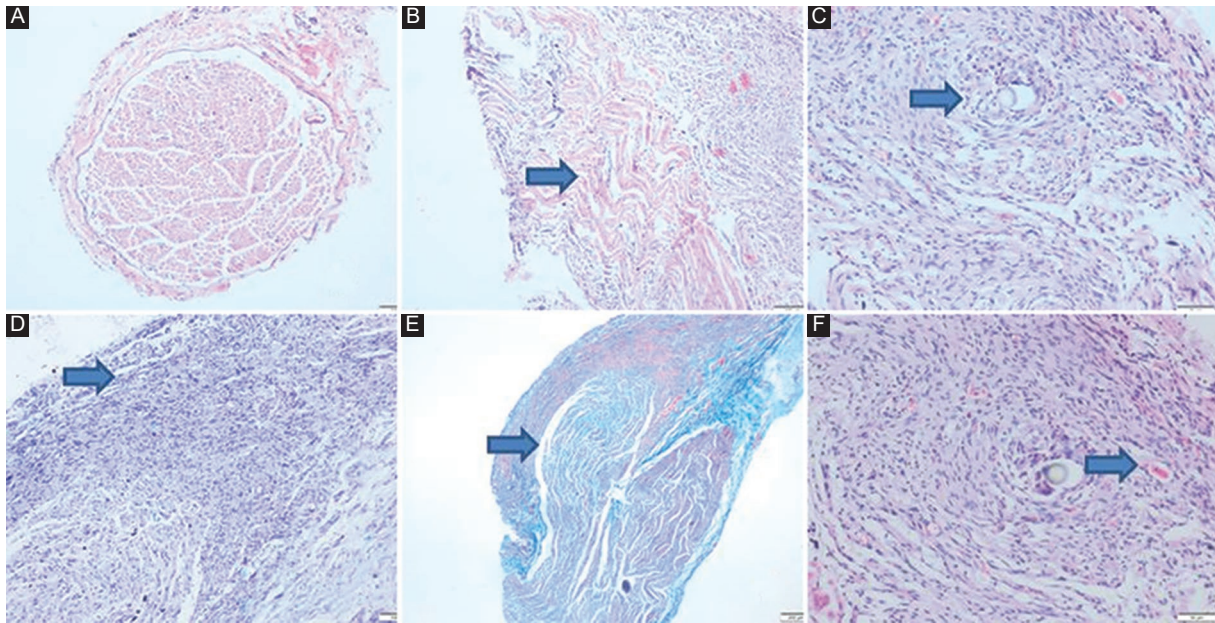
| Histological evaluation                 | Group 1 | Group 2 | p      |
|-----------------------------------------|---------|---------|--------|
| Neural tissue                           |         |         |        |
| Inflammation                            | 1.2     | 1       | 0.317  |
| Vascularization                         | 1.2     | 1.6     | 0.221  |
| Fibrosis                                | 0.6     | 1.2     | 0.212  |
| Edema                                   | 0.6     | 0.6     | 0.152  |
| Fascicular organizational dysfunction   | 0.8     | 1.8     | 0.100  |
| Axonal degeneration                     | 0.2     | 0.6     | 0.524  |
| Myelination                             | 0.6     | 0       | 0.038* |
| Axonal density ( $\times 100$ in a HPF) | 100     | 112     | 0.401  |
| Muscle tissue                           |         |         |        |
| Inflammation                            | 0.4     | 0.8     | 0.005* |
| Vascularization                         | 1.2     | 1.6     | 0.07   |
| Fibrosis                                | 0.6     | 1.2     | 0.214  |
| Muscle atrophy                          | 0.8     | 1.8     | 0.054  |
| Necrosis                                | 0.2     | 0.6     | 0.916  |
| Edema                                   | 0.6     | 0.6     | 0.476  |

\*Indicates the statistically significant results.  $p < 0.05$  was considered a significance level.

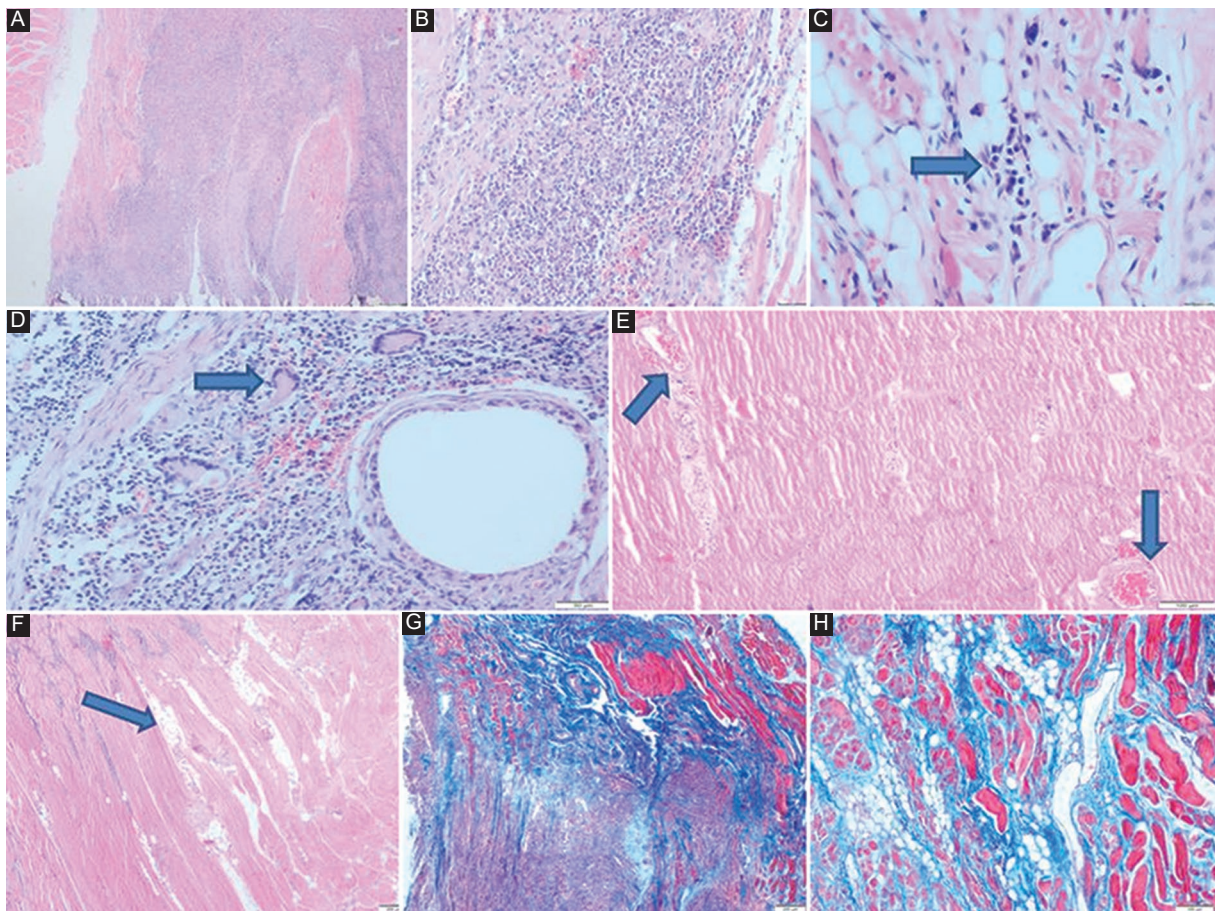
study is unusual for researchers. However, it can be considered a good choice for the reconstruction of the defects in selected cases, such as covering of amputation stumps. It can also be preferred as a free fillet flap in patients with high-level upper extremity amputations.

Microsurgical training of muscle flaps is one of the crucial parts of advanced microsurgery courses. The artery, vein and nerve should be repaired meticulously to obtain viable and functional muscle after microsurgical transfer, which makes muscle flap transfer more challenging. In this study, we described a novel muscle flap in the upper extremity of the rats, which was not considered one of the muscle flap donor areas before. During the microsurgical training, increasing the number of donor areas will contribute to the use of the rats in different ways. Besides, novel injury models can be created with further studies according to the application methods of the triceps muscle flap.

Triceps brachii muscle flap harvesting causes the sacrifice of the brachial artery and vein during the procedure. Although this might suggest that the perfusion of the limb would be disturbed and a process of necrosis or autophagy would be initiated, none of the animals showed any complications related to the disruption of perfusion of the upper limb. Therefore, it can be suggested that the brachial artery can be sacrificed without disrupting limb perfusion in rats. In previously described free flaps and transplantation



**Figure 5.** Microscopic examination of neural tissue. **A:** normal neural section and myelination (Hematoxylin and Eosin [H&E]-  $\times 100$ ). **B:** edema (H&E-  $\times 100$ ). **C:** inflammation (H&E-  $\times 200$ ). **D:** fascicular disorganization of the peripheral nerve (Luxol fast blue-  $\times 100$ ). **E:** fibrosis (MTK-  $\times 40$ ). **F:** vascularization (H&E-  $\times 200$ ).



**Figure 6.** Microscopic examination of muscular tissue. **A:** focus of intense inflammation in muscle tissue (Hematoxylin and Eosin [H&E]-  $\times 40$ ). **B:** abscess area in muscle tissue (H&E-  $\times 200$ ). **C:** intense inflammation, focus of plasma cells (H&E-  $\times 400$ ). **D:** foreign body reaction (H&E-  $\times 200$ ). **E:** vascularization (H&E-  $\times 100$ ). **F:** lipomatous atrophy (H&E-  $\times 40$ ). **G:** fibrosis and atrophic changes (MTK-  $\times 40$ ). **H:** fibrosis, lipomatous changes and atrophy (MTK-  $\times 40$ ).

models, it was determined that ligating the main artery and vein of the extremity does not cause circulatory disturbance. This may be associated with the fact that collateral circulation provides effective perfusion in rats.<sup>12</sup>

Transfer of the muscles as a functional unit is not one of the frequently applied microsurgical training methods because of the complexity and requirement for supermicrosurgery. Usually, training programs of both basic and advanced microsurgical courses do not include the FFMT. The rat gracilis flap was used as an FFMT transfer model in a previous study. However, the flap was not separated from the main supplying vessel, and only the nerve was cut and repaired in that study.<sup>9</sup> It was not possible to transport the flap to a distant body site because the flap was not separated from its vessels. In our study, the triceps flap was transported to function as both a pedicled and a free flap. With this contribution to the literature, the triceps muscle flap emerges as an FFMT model to be used in future studies. Besides, comparison between the groups was not statistically significant regarding electromyographic results, which increases the success rate of the FFMT procedure. It was also compatible with the result of mild/moderate muscle atrophy, which was seen in both of the groups.

During experimental studies, it was observed that the triceps muscle is supplied segmentally by multiple branches from the brachial vessels. If we classify this newly defined muscle flap according to the Mathes-Nahai classification, it is compatible with a Type 4 muscle flap category, which is the most difficult and unreliable type to harvest and use. This problem was overcome by harvesting the flap based on the main vessel supplying the segmental branches. On the other hand, researchers can also elevate this muscle over a single segmental vessel as a segmental muscle flap.

The fact that no necrosis was observed in any animal that underwent flap elevation and that there was no vascular variation that would affect flap harvesting during surgery can be interpreted in favor of the flap having a reliable and constant anatomy. Similarly, the absence of any complications in the donor area that prevented the continuation of the experiment is a sign that the flap is reliable as an experimental model. Besides the free flap concept, it enables functional muscle transfer, which should also be kept in mind during high-level upper extremity injuries. The reposition of the triceps muscle can be considered in patients with severe contractions in extensors and/or

dysfunctional flexors, especially those who have accompanied injury in the thoracodorsal root (latissimus dorsi muscle is unavailable).

In Group 1, it was demonstrated that the triceps flap was elevated as an island flap, and this flap was supplied by the brachial artery. Moreover, in Group 2, it was shown that this flap could also be used as a free flap. According to the results obtained in the subsequent evaluations, no histopathologic and electrophysiologic difference was found between the two groups in terms of nerve healing and integrity and function of the muscle flap. Accordingly, the flap showed similar survival and functional integrity when used both as a free flap and as a pedicled flap.

## Conclusions

We suggest that the rat triceps brachii muscle flap can be used as a muscle flap model. The flap can be harvested either as a pedicled flap or a free flap. Moreover, it can be used in functional muscle transfer by including the nerve if the design of the study requires. By describing a novel muscle flap in the upper extremity, we hope that it will contribute to the experimental microsurgical training, providing a new donor area. Clinical applicability of the free/pedicled triceps brachii muscle flap can be considered in selective cases.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

**Protection of humans and animals.** The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The

procedures were approved by the institutional Ethics Committee.

**Confidentiality, informed consent, and ethical approval.** The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

All procedures performed in studies involving animals were in accordance with the ethical standards of the institution at which the studies were conducted, and ethical approval was obtained from Necmettin Erbakan University, KONUDAM Experimental Medicine Research Center, with the number 2021-058.

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# Three-dimensional visualization systems for laparoscopic surgery training: a peg transfer exercise study

*Sistemas de visualización tridimensional para entrenamiento en cirugía laparoscópica: estudio basado en el ejercicio de transferencia de aros*

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## Abstract

**Objective:** Minimally invasive surgery (MIS) offers significant benefits, including short-term recovery and few complications. However, surgeons face challenges, particularly with two-dimensional (2D) visualization systems. Recent advancements in three-dimensional (3D) technologies can enhance depth perception and improve the training process. This study compares three 3D visualization systems in laparoscopic peg transfer training: (1) head-mounted displays, (2) passive 3D glasses, and (3) active 3D glasses. **Methods:** A randomized controlled trial was conducted with 24 participants performing a peg transfer task under the three 3D systems. Performance metrics included task completion time, number of errors, and subjective ratings of image quality and ergonomics. **Results:** Participants using active glasses completed the task faster (median = 4.1 min, interquartile range [IQR] = 2.1 min) and with fewer errors (median = 6, IQR = 7) compared to the other systems ( $p < 0.01$ ). Subjective ratings also favored active glasses for image quality and ergonomics, though there were no significant differences in visual fatigue across the systems. **Conclusions:** Active 3D glasses proved to be the most effective system for laparoscopic training in terms of both performance and user satisfaction. Integrating them into MIS training could enhance surgical precision and reduce learning curves.

**Keywords:** Laparoscopic surgery training. Peg transfer exercise. Three-dimensional image. Head-mounted displays. Passive three-dimensional glasses. Active three-dimensional glasses.

## Resumen

**Objetivo:** La cirugía mínimamente invasiva ofrece beneficios como una rápida recuperación y pocas complicaciones. Sin embargo, los cirujanos enfrentan desafíos con los sistemas de visualización 2D. Avances recientes en tecnologías 3D pueden mejorar la percepción de profundidad y el proceso de entrenamiento. Este estudio compara tres sistemas de visualización 3D (gafas con pantallas, gafas 3D pasivas y gafas 3D activas) usando el ejercicio de entrenamiento para laparoscopia llamado transferencia de aros. **Métodos:** Los 24 participantes del experimento controlado aleatorizado realizaron el ejercicio con los tres sistemas de visualización. Las métricas de desempeño evaluadas incluyeron el tiempo de finalización de la tarea, la cantidad de errores y la percepción subjetiva de la calidad de la imagen y la ergonomía. **Resultados:** Los participantes que usaron gafas activas completaron la tarea más rápido (mediana: 4.1 min) y con menos errores (mediana: 6) en comparación

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con los que usaron los otros sistemas ( $p < 0.01$ ). Además, la evaluación subjetiva también favoreció a estas gafas. No hubo diferencias significativas en fatiga visual. **Conclusiones:** Las gafas 3D activas demostraron ser el sistema más eficaz en términos de rendimiento y satisfacción del usuario. Su integración en la formación en cirugía laparoscópica podría mejorar la precisión quirúrgica y reducir las curvas de aprendizaje.

**Palabras clave:** Formación en cirugía laparoscópica. Ejercicio de transferencia de aros. Visualización tridimensional. Gafas con pantallas de proyección. Gafas 3D pasivas. Gafas 3D activas.

## Introduction

Minimally invasive surgery (MIS) is a technique that allows surgical procedures to be performed using natural pathways or small incisions in the skin to access the human body organs. This technique requires the surgeons to use a special visualization system.<sup>1</sup> MIS procedures are increasingly important to the scientific and medical community due to their advantages in reducing complications, enabling quick patient recovery, resulting in less painful post-operative periods, and leaving fewer esthetic marks, compared to other surgical treatments.<sup>1,2</sup> However, they require a demanding training process for surgeons.<sup>3</sup>

In many MIS procedures, observation is done on a high-resolution two-dimensional (2D) flat monitor. This is achieved by inserting an endoscope with a special arrangement of lenses and optical fiber, which transmits light generated by an external source to illuminate the cavity where the procedure is performed (abdominal, thoracic, joint, etc.).<sup>2,4</sup> Since the projected image is in 2D, the surgeon loses the sense of depth, which complicates some operational tasks.<sup>4</sup> Therefore, long training periods are necessary for surgeons to infer the depth of the operative field.<sup>4-6</sup>

Advances in three-dimensional (3D) visualization systems represent an opportunity to improve operative processes. This technology has been applied in surgical procedures,<sup>7</sup> with evidence of advantages over traditional 2D visualization.<sup>4,8,9</sup> Thus, to regain the sense of depth in MIS, comparative studies of 2D and 3D vision systems in laparoscopic training have been conducted,<sup>4,10-12</sup> concluding that the depth vision system allows shorter learning times and greater comfort during surgery.<sup>10,13</sup> Moreover, depth perception helps perform laparoscopic tasks more precisely,<sup>12</sup> which could prevent post-operative complications.

Tests have been conducted with stereoscopic and autostereoscopic visualization systems,<sup>14</sup> focusing on the technology's usage mode. Stereoscopic displays require the user to wear or put on an element on their head, such as glasses, whereas autostereoscopic

systems do not require any aids for 3D visualization.<sup>15</sup> However, stereoscopic systems have greater commercial application, generally incorporating image capture with a dual-lens system<sup>16,17</sup> and subsequently processing and displaying it on a monitor capable of reproducing this type of video signal.<sup>18</sup>

Significant benefits have been found in 3D visualization systems in various medical areas, such as stereopsis for MIS surgical training.<sup>19</sup> In addition, comparative advantages have been identified in surgeon training with 3D visualization systems over 2D systems, including improved image quality, shorter average operative time, and reduced stress.<sup>20-22</sup>

Among the companies offering stereoscopic solutions for laparoscopy is Olympus, which claims that using a 3D visualization system improves the surgical experience for medical staff, increases surgeon precision, and shortens learning time.<sup>23</sup> Other companies offer 3D monitors that enhance depth perception using active or passive glasses, such as Sony,<sup>24</sup> Panasonic,<sup>25</sup> Philips,<sup>26</sup> and Eizo.<sup>27</sup> Furthermore, manufacturers of head-mounted displays (HMDs) applicable to MIS, such as eMagin, provide an immersive 3D experience.<sup>28</sup>

In summary, and based on the literature, there is evidence that using 3D visual feedback in surgeon training at different experience levels has advantages over 2D visual feedback, along with the complement of commercial applications for professional practice in MIS. However, there is a lack of more definitive comparative studies, specifically between stereoscopic 3D visualization systems for training in laparoscopic surgery (abdominal MIS). Therefore, this study aimed to determine which 3D visualization system, among passive 3D glasses, active 3D glasses, and HMD, would achieve better results in an MIS training exercise named peg transfer. The variables used to compare the systems were: time elapsed to complete the exercise, the number of errors made during the exercise, and a subjective evaluation of image quality and ergonomics of the visualization device.

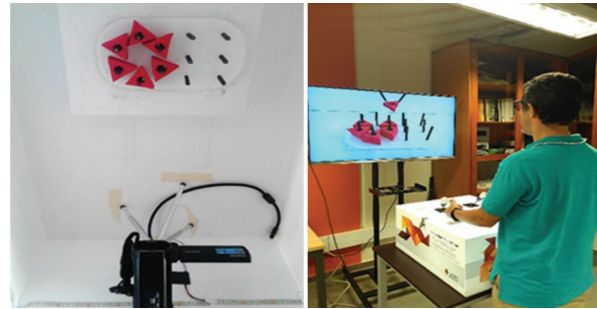
## Methods

### Description of the systems

To compare the 3D visualization systems, the peg transfer exercise was chosen from the fundamentals of laparoscopic surgery (FLS) training standard. This exercise allows for working in multiple spatial planes and performing ambidextrous coordination, enabling analysis of the effect of depth perception. The peg transfer task involves moving six rings from an arrangement of bars on the left side to bars on the right side, transferring them from one hand to the other while elevated, and then returning the six rings to the left side, regardless of the transfer order. As shown in figure 1, a custom Pelvitainer box was designed to be large enough to contain a Sony 3D video camera with dual full HD lenses, a white LED lighting system, and the training exercise. Two Johnson and Johnson laparoscopic forceps were introduced by the upper access points of the Pelvitainer for the participants to perform the exercise, following FLS recommendations. The video camera was selected to ensure that the objects to be projected would be close to the camera lenses, guaranteeing the capture of the Pelvitainer's workspace without needing calibration for each test subject.

The 3D video camera was compatible with all of the following 3D stereoscopic systems that were evaluated and subsequently compared:

- HMD. This technology is based on a multiplexed location approach, in which images are projected independently into each eye through separate channels (lenses, mirrors, and fiber optics). Vuzix900 virtual reality glasses were used in this study. These glasses have a Video Graphics Array (VGA) video input and simulate a 67" 3D screen at 9.8 feet away.
- Passive glasses. It uses polarized multiplexing technology that divides 3D images into two images, one for each eye, by orthogonally oriented filters (linear or circular). They are known for being widely used in cinemas. For this system, a 47" LG SMART TV 3D LM67 with a high-definition multimedia interface input was used.
- Active glasses. In this case, the "persistence of vision" effect (50 ms) is utilized to alternately and synchronously block and unblock the eyes at the same speed as the image changes, creating the sensation of continuous 3D vision. The two



**Figure 1.** Upper view of the peg transfer exercise implemented in a pelvitainer (left). Participant performing the exercise (right).

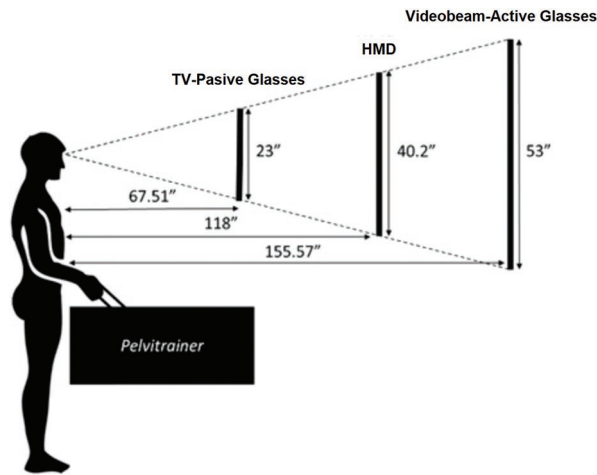
images for the eyes are shown at different times, at a frequency of 120 Hz or more. The device used for this system was the BenQ 3D MX666+ projector.<sup>29</sup>

During the trials, the user was ensured to perceive screens of the same size regardless of the visualization system used. To achieve this, the visualization systems were placed at different distances from the user, according to the size of the image projected by each, while maintaining the same projection ratio. As shown in figure 2, the image projected by the active system is the largest, at 53" high; the television image is the smallest, at 23" high; and the HMD image has a projection of 40.2" high, as if viewed from 118" away. Based on this last value, the location distances for the other two visualization systems were calculated. Therefore, the television was placed 67.51" from the user and the projector at 155.57."

### Protocol

The study was conducted using a randomized controlled trial to reduce cognitive biases and ensure that the different treatment groups were statistically equivalent. Since the goal was to compare three stereoscopic visualization systems (HMD, passive glasses, and active glasses) and each subject performed the peg transfer exercise with each system in a random sequence, a randomized complete block design (RCBD) was conducted.<sup>30</sup>

Following the RCBD methodology, the person performing the exercise is referred to as the subject, and each of the three visualization systems is a factor level. Randomization was applied to the order in which each test subject used each factor level, reducing the impact of confounding variables such as the person's learning curve and fatigue level when using a particular visualization system. Controllable confounding



**Figure 2.** Distance from the participant to each of the display systems.

variables in environmental conditions, such as noise, lighting, and the presence of people around the test subject, were also minimized to be consistent for each observation.

The protocol for the experiment was executed after obtaining informed consent, and each session lasted approximately 1 h. Subjects were first introduced to the exercise with a direct view of the Pelvitrainer; then, subjects performed the same training exercise but with the Pelvitrainer closed, so they did not have a direct view of the peg transfer platform. This approach helped them better understand the task and the basic handling of the laparoscopic forceps. Afterward, they performed the same exercise using 3D visualization systems: Active glasses, passive glasses, and HMDs in random order. Before and after every system (while the subject rested for 5 min), a survey of ocular systems based on the convergence insufficiency symptom survey (CISS)<sup>31,32</sup> was performed. Visual performance data, including errors and completion times, were recorded. In addition, after completing the exercises, participants rated their experience, which included ease of use and ergonomics.

During each exercise, data on depth perception errors (missed grip, transport, or ring placement) and completion time were recorded manually and verified later using recorded videos. Parameters for comparing stereoscopic systems included:

- The number of errors: mistakes made during the exercise were counted by reviewing video footage, following the standard method
- Time taken to complete the FLS exercise: measured from start to finish using a stopwatch, following the FLS methodology (maximum time: 5 min)

- Visual fatigue from using the visualization system: before and after each exercise, the CISS survey was used to assess fatigue, discomfort, double vision, eye pain, headache, drowsiness, dizziness, and blurred vision on a scale of 0-4, using a 9-question survey. A score over 13 indicates convergence issues
- Subjective perception of image quality and ergonomics: participants rated image quality across five factors, including image blending, depth perception, image sharpness (brightness, contrast), color quality, and comfort of the glasses on a scale from 1 (Poor) to 7 (Excellent). Total scores ranged from 5 to 35.

### Statistical analysis

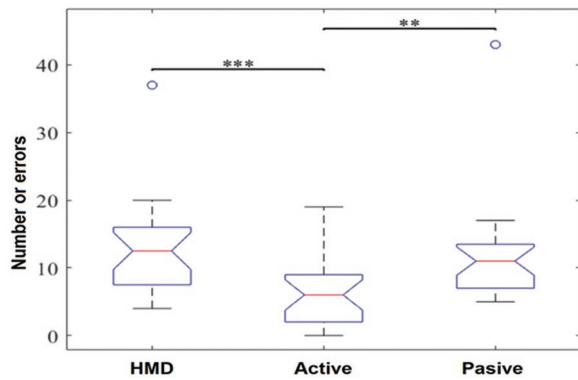
For statistical analysis, normality tests were performed using the Shapiro-Wilk method due to its power to detect non-normality in the data and the sample size. For non-parametric analysis, the Kruskal-Wallis test for independent samples was used. Significance values were adjusted using the Bonferroni correction for multiple tests. The significant difference level considered was  $p < 0.05$ . The entire process was carried out using the Statistical Package for the Social Sciences software.

### Results

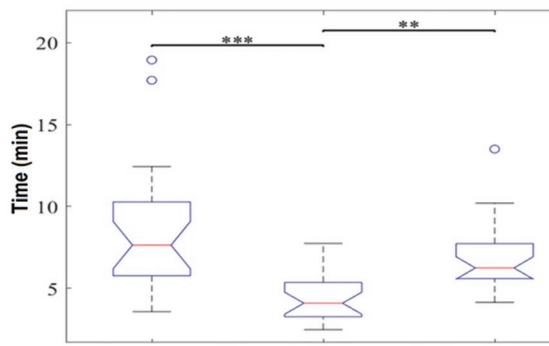
Twenty-four participants without experience in the peg transfer exercise took part in the comparative test. They were aged between 18 and 35, with a mean age of 23, including 6 women and 18 men.

The results for the number of errors made by participants are shown in figure 3. A significant difference was found between the use of active glasses (median = 6, interquartile range [IQR] = 7) and the other two systems; with a  $p < 0.01$  compared to passive glasses (median = 11, IQR = 6.5) and a  $p < 0.001$  compared to HMD (median = 12.5, IQR = 8.5).

On the other hand, the results for the time taken by participants to complete the peg transfer exercise are displayed in figure 4. Similar to the error variable, a significant difference was observed between the use of active glasses (median = 4.1 min, IQR = 2.1 min) and the other two systems; with a  $p < 0.01$  compared to passive glasses (median = 6.25 min, IQR = 2.1 min) and a  $p < 0.001$  compared to HMD (median = 7.64 min, IQR = 4.5 min).



**Figure 3.** Comparison of the number of errors while using the visualization systems. HMD: head-mounted display. \*\* $p < 0.01$  and \*\*\* $p < 0.001$ .



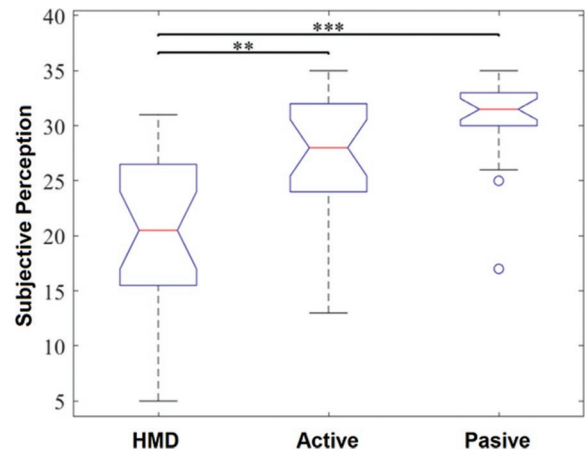
**Figure 4.** Comparison of the time factor according to the visualization systems when performing the exercise. HMD: head-mounted display. \*\* $p < 0.01$  and \*\*\* $p < 0.001$ .

The results of the survey on the participants' subjective perception regarding the image quality and the ergonomics of each system (Fig. 5) show that the active glasses systems (median = 28, IQR = 8) and passive glasses systems (median = 31.5, IQR = 3) were comparable, with no significant difference ( $p = 0.077$ ). However, the HMD system was perceived as lower quality (median = 20.5, IQR = 11) with a significant difference from the other two systems.

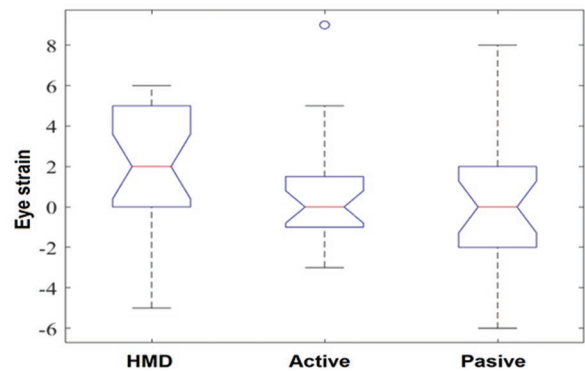
Regarding the eye fatigue variable, no significant differences were observed in the results (Fig. 6). It was also determined that none of the systems caused ocular non-convergence in the users during the tests conducted with the Pelvitainer.

## Discussion

This study demonstrates that, when comparing three 3D visualization systems (HMD, passive glasses, and active glasses), the active glasses were found to be the most effective system for participants performing a basic



**Figure 5.** Comparison of users' subjective perception regarding the visualization systems. HMD: head-mounted display. \*\* $p < 0.01$  and \*\*\* $p < 0.001$ .



**Figure 6.** Comparison of the results obtained regarding eye fatigue generated by the visualization systems. HMD: head-mounted display.

training exercise in the FLS. This is supported by three key findings: (a) Exercises performed with active glasses were completed in less time than those with passive glasses and HMD in the peg transfer exercise of FLS, (b) exercises performed with active glasses resulted in fewer errors than those with HMD in an FLS exercise, although no significant difference was found compared to passive glasses, and (c) exercises performed with active and passive glasses resulted in a better subjective perception of image quality and system ergonomics than those with HMD in an FLS exercise.

## Exercises with active glasses performed in less time

According to the results, the peg transfer exercise was completed significantly faster compared to the time taken with passive glasses and HMD, with no significant differences between the latter two in task execution

time. The analysis suggests that active glasses may contribute to shorter execution times as they provide better image sharpness and depth due to alternating presentation in both eyes. In addition, they utilize the full resolution of the screen, unlike passive glasses, which use only half of it. On the other hand, the HMD used has a lower resolution due to its VGA image format, which performs less effectively compared to the digital technology of the other two systems. The Peg transfer training exercise could benefit from the use of active 3D glasses due to their increased sharpness, visual comfort, and stereoscopic precision, thus potentially improving surgical performance in manipulation tasks.

### ***Fewer errors with active glasses***

The number of errors in FLS exercises with active glasses was lower, although there was no significant difference compared to passive glasses, unlike the significantly higher errors observed with HMD. If the goal is to shorten the learning curve for trainee surgeons, active glasses are considered an appropriate technological support for such practices. Consequently, the reduction in errors with this technology would also imply less physical strain on the surgeon and improved performance in this task. While errors correlate with increased time, as found in previous studies, they are not the sole cause of procedural delays; factors such as eye fatigue, posture, motor skills, etc., must also be considered.

Achieving reduced errors and operative time during training through peg transfer exercises will be enhanced by leveraging the benefits of 3D visualization, such as improved image resolution and depth perception.

### ***Better perception of image quality and ergonomics with active glasses***

When evaluating the perception of image quality and ergonomics in wearing and using the three visualization technologies, variables such as sufficient mixing between right and left images without shadows or double vision, perception of depth, perception of object movement, color quality, and comfort of the glasses were considered critical. Any negative factor in this regard may lead to reluctance to use the system and negatively impact performance during the exercise. Results may differ, tending toward better outcomes, when performed by personnel with experience in

laparoscopic surgery with 2D visualization. In addition, the effects of using high-resolution screens with 4K and 8K technologies (in both 2D and 3D, if applicable) on performance should be evaluated.

In this context, for a more comprehensive analysis regarding the performance of HMD and the other two systems, a larger number of participants is required to generalize the findings, along with longer practice times and guidance from an expert to assist in the use and resolution of learning difficulties. Furthermore, studies should be designed to estimate any retinal effects of using these new technologies to understand their impact on ocular health. Variables were assessed in users not belonging to the surgical medical field and were measured in an exercise conducted in a controlled environment rather than in a real surgical setting.

## **Conclusions**

In the execution of the exercises, the shortest time and the lowest number of errors were obtained with active glasses, and users also benefited from perceiving depth in the image with clarity. The user's skill, combined with the various factors evaluated, influenced the occurrence of errors in exercise execution. For the study population, the time to complete the test, the number of errors, and the system's ergonomics were more relevant in the results than demographic variables, eye disease, or experience in using video games.

For long periods of exercise execution in this study, the weight of the vision device and the lack of peripheral vision, combined with discomfort in wearing the device, hinder the training process. Therefore, the HMD system is the least recommended for this purpose, while active glasses are the ones that yield better results.

Active glasses may allow for less fatigue in their use, better eye-hand coordination, an acceptable degree of sharpness-realism, less energy expenditure, less fatigue, and, in their analysis, the results obtained in the study reflect fewer errors, less time in task completion, and a better perception of the environment and ergonomics. Therefore, they are identified as the best option among the three devices evaluated.

As part of future tests, other FLS exercises should be covered. In addition, consideration should be given to evaluating the performance of other FLS exercises and including personnel with experience in laparoscopic surgery at different levels of expertise in the test.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

**Protection of humans and animals.** The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

**Confidentiality, informed consent, and ethical approval.** The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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# The effect of depression on bone fusion in a rabbit posterolateral bone fusion model

*El efecto de la depresión en la fusión ósea en un modelo de fusión posterolateral en conejos*

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## Abstract

**Objective:** The objective of this study was to evaluate the effect of depression on bone fusion in the rabbit spine using Katz's unpredictable chronic mild stress (UCMS) model. **Methods:** A total of 12 male New Zealand rabbits were divided randomly into 6 control and 6 experimental groups. Each rabbit underwent the same surgical procedure. An autograft was harvested from the iliac crest and put into the L5-L6 space, where the laminae and facets were decorticated. The animals of the control group were followed up for 8 weeks under standard laboratory conditions. The ones in the experimental group were put in Katz's UCMS. After 8 weeks, all rabbits were sacrificed, and the vertebra segments were evaluated with manual palpation and X-rays. **Results:** On manual palpation, fusion was detected in 83.34% in the control group compared to just 33.32% in the UCMS group. The model showed that depression had a significant negative effect on fusion on manual palpation ( $p = 0.045$ ). Second, if no fusion was detected on X-rays, 0 points were given; callus formation received 1 point, and sclerosis received 2 points. In the control group, just 16.66% showed non-union, 49.98% had a callus formation, 16.66% showed sclerosis. In the experimental group, the non-fusion rate was 66.68%. **Conclusions:** Depression has a negative effect on the fusion of rabbit vertebrae. However, vertebrae that are evaluated as "fused" on palpation do not show meaningful relation in their radiologic scores. We believe that our model can work as a basis for further experimental trials.

**Keywords:** Unpredictable chronic mild stress. Depression. Fusion.

## Resumen

**Objetivo:** Evaluar el efecto de la depresión en la fusión ósea de la columna vertebral en conejos utilizando el modelo de estrés leve crónico impredecible (UCMS) de Katz. **Métodos:** Se dividieron aleatoriamente 12 conejos machos de la raza New Zealand en dos grupos: seis en el grupo control y seis en el grupo experimental. Cada conejo fue sometido al mismo procedimiento quirúrgico. Se obtuvo un autoinjerto de la cresta iliaca y se colocó en el espacio L5-L6 tras la decorticación de las láminas y las facetes. Los animales del grupo control fueron monitoreados durante 8 semanas en condiciones estándar de laboratorio, mientras que los del grupo experimental fueron sometidos al modelo UCMS de Katz. Después de 8 semanas, todos los conejos fueron sacrificados y los segmentos vertebrales se evaluaron mediante palpación manual y radiografías. **Resultados:** En la palpación manual se detectó fusión en el 83.34% de los conejos del grupo control, en comparación con solo el 33.32% en el grupo UCMS. El modelo mostró que la depresión tuvo un efecto negativo significativo en la fusión según la palpación manual ( $p = 0.045$ ). En segundo lugar, en la evaluación radiográfica se asignaron 0 puntos si no se detectaba

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fusión, 1 punto para la formación de callo y 2 puntos para la esclerosis. En el grupo control, el 16.66% presentaron ausencia de fusión, el 49.98% mostraron formación de callo y el 16.66% presentaron esclerosis: en el grupo experimental, la tasa de no fusión fue del 66.68%. **Conclusiones:** La depresión tiene un efecto negativo en la fusión de las vértebras en conejos. Sin embargo, las vértebras evaluadas como «fusionadas» mediante palpación no mostraron una relación significativa con sus puntuaciones radiológicas. Creemos que nuestro modelo puede servir como base para futuros estudios experimentales.

**Palabras clave:** Estrés leve crónico impredecible. Depresión. Fusión.

## Introduction

Spinal fusion is among the most frequently performed surgical procedures worldwide, particularly by spine surgeons. The Agency for Healthcare Research and Quality estimates that over 488,000 spinal fusion surgeries are performed annually in the United States, accounting for 3.1% of all surgical procedures.<sup>1</sup> Spinal fusion is indicated for various conditions, including degenerative disc disease, disc herniation, vertebral fractures, and spinal deformities. This procedure involves fusing two or more vertebral segments using screw-rod systems, plates, cages, or a combination of these techniques.<sup>2</sup>

To optimize surgical outcomes, extensive research has focused on surgical techniques, fusion materials, and adjunctive therapies such as grafting, electro-magnetic stimulation, and pharmacological agents. Insufficient bone fusion can result in complications such as pseudoarthrosis, non-union, instrumentation failure, and iatrogenic deformities, significantly diminishing patients' quality of life.<sup>3</sup> Bone grafting remains a cornerstone of fusion surgery, with options including autografts, allografts, xenografts, and synthetic materials.<sup>4</sup> In addition, biological agents such as RANKL inhibitors (e.g., denosumab), parathyroid hormone analogs, growth factors (e.g., Insulin-like growth factor, fibroblast growth factor, and B-epidermal growth factor), and sonic hedgehog genes have demonstrated efficacy in promoting bone healing.<sup>5,6</sup>

Equally critical is understanding factors that hinder bone fusion. Metabolic disorders (e.g., diabetes mellitus and osteoporosis), vitamin deficiencies, vascular issues (e.g., anemia and hypoxia), mechanical factors (e.g., inadequate immobilization and instrumentation failure), and lifestyle factors (e.g., tobacco and alcohol use) have been shown to impair bone healing.<sup>7</sup> Furthermore, psychological factors such as depression and distress are known to affect wound healing adversely.<sup>8</sup> However, the impact of depression on spinal fusion remains unexplored.

Katz's unpredictable chronic mild stress (UCMS) model, developed in the 1980s, serves as a widely used model for studying depression.<sup>9</sup> Given that bone fusion is a form of wound healing, this study aims to investigate the effect of psychological distress and depression on spinal fusion using a rabbit posterolateral fusion model.

## Methods

### Setting and ethics committee

This study was conducted in the Department of Experimental Studies at a university hospital with ethics approval was obtained from the same institution (approval number: 776). The experiment was designed to last for a total duration of 8 weeks.

### Selection criteria for the study and grouping of the animals

A total of 12 male New Zealand rabbits, aged 8 months with a mean weight of 3250 g, were selected for the study. Each rabbit was housed individually in separate cages. The animals were randomly divided into two equal groups: an experimental group and a control group, each consisting of six rabbits.

The control group was maintained under standard laboratory conditions, with *ad libitum* feeding, a 12-h light-dark cycle, a controlled room temperature of 20-24°C, and 60% relative humidity. In contrast, the experimental group was subjected to the conditions of UCMS, which will be described in detail later. All rabbits underwent identical surgical procedures as part of the study protocol.

### Exclusion criteria

To ensure adherence to ethical standards and animal welfare while minimizing potential bias in the results, the following exclusion criteria were established:

- Rabbits that died before the completion of the 8-week study period, either preoperatively, intraoperatively, or postoperatively
- Rabbits that failed to eat or drink adequately during the study
- Rabbits that were unresponsive to external stimuli
- Rabbits deemed unsuitable for the study by the attending veterinarian.

Fortunately, no adverse events occurred during the study, and all rabbits met the inclusion criteria, enabling the collection of optimal data.

### **Anesthesia**

In an operating room environment with air exchange every 5 min, a controlled temperature of 22° C, and 60% humidity, pre-anesthesia was administered intramuscularly using 8 mg/kg xylazine (Rompun 2%®, Bayer AG, Germany). Once the animals were sedated, anesthesia was induced with 40 mg/kg ketamine (Ketasol 10%®, Richter Pharma AG, Austria) administered intraperitoneally. Proper anesthetic depth was confirmed by the veterinary team through the absence of a pain response to foot pinching. To prevent corneal dryness during the procedure, eye drops (Viscotears®, Alcon Pharma, Switzerland) were applied.

### **First surgery**

Once anesthesia was confirmed, the rabbits were positioned prone. The surgical field was shaved and thoroughly cleansed with an antiseptic solution. To minimize intraoperative bleeding and post-operative pain, 2 cc of prilocaine hydrochloride (Pricain 2%®, Polifarma İlaç, Turkey) was administered subcutaneously and intramuscularly into the surgical area. The left and right iliac crests were palpated, and a 2 cm skin incision was made parallel to the left iliac crest. The area was exposed through blunt dissection, and 2 g of bone was harvested from the left iliac crest using a rongeur (Fig. 1A).

A midline skin incision was then made from L4 to S2 to access the rabbit spine. The paravertebral muscles were dissected, exposing the posterior spinal elements (Fig. 1B). As no instrumentation was planned, the left L5 and L6 facets and transverse processes were decorticated using a rongeur to create a stable

environment for fusion. The harvested iliac crest bone graft was placed in the prepared area, and the wound was closed with 3/0 silk sutures (Fig. 1C).

Postoperatively, the rabbits were monitored until full recovery from anesthesia. All animals retained normal motor function following the procedure. Wounds were inspected and cleaned daily. For pain management, the rabbits received 2 mg/kg carprofen (Rimadyl XL®, Zoetis, USA) for 5 days.

### **Applying the UCMS model**

The rabbits in the control group were monitored under standard laboratory conditions for 8 weeks. Those in the experimental group were subjected to the UCMS model, implemented as follows:

#### **Day 1**

A tub was filled with tap water at 24° C to a depth of 1 cm. The rabbits in the experimental group were placed in the tub for 4 h (Fig. 2). Afterward, they were removed, dried, warmed under a 37° C heating lamp, and returned to their cages.

#### **Day 2**

The standard 12-h light and dark cycle was altered. The animals were kept in complete darkness for 24 h.

#### **Day 3**

The light-dark cycle was disrupted again, with the lights left on continuously for 24 h.

#### **Day 4**

A 5 cm box was placed under one side of the shelf holding the cages, tilting the cages to create an inclined position. The rabbits remain in this setting for 4 h (Fig. 3).

#### **Day 5**

The rabbits were confined to a cage typically designed for rats, restricting their movement and inducing a claustrophobic environment for 4 h (Fig. 4).



## Second surgery

After 8 weeks, all animals from the experimental and control groups were sedated with 8 mg/kg intramuscular xylazine (Rompun 2%®, Bayer AG, Germany) and euthanized via intracardiac injection of 100 mg/kg potassium chloride. The midline incision was reopened, and macroscopic observations in some rabbits revealed fusion between the harvested bone graft and the facet and transverse processes.

The vertebral segments were carefully dissected free of surrounding soft tissue and removed *en bloc* using a wire saw. The extracted vertebrae were palpated and assessed for evidence of fusion by manually applying flexion and extension maneuvers. The results were categorized as “fusion” or “no fusion” (Fig. 5).

Subsequently, the vertebrae were preserved in formaldehyde and transported to the radiology department. Anterior-posterior images were obtained using a fluoroscopic C-arm (Ziehm Solo®, Ziehm Imaging, Germany). Radiographic evaluation focused on signs of fusion. A scoring system was applied: vertebrae without callus formation or sclerosis, indicating no evidence of fusion, received 0 points. Vertebrae displaying callus formation, an early marker of fusion, were assigned 1 point. Complete fusion, characterized by sclerosis, received 2 points (Fig. 6).

## Results

### Statistical analysis

The results were analyzed using the Z-test to compare categorical measurements between the two independent groups. Numeric and percentage values were applied as complementary statistical tools for categorical variables. Statistical analysis was performed using the Statistical Package for the Social Sciences v.24 (IBM, USA), and  $p < 0.05$  was considered statistically significant.

### Manual palpation results

Bone fusion was evaluated using two methods. The first involved manual flexion-extension maneuvers performed on the *en bloc* extracted vertebral segments. In the experimental group, subjected to the UCMS model, fusion was observed in only 2 out of 6 rabbits (33.3%). In contrast, in the control group,

**Table 1a. Evaluation of fusion after manual palpation. Evaluation of fusion in the experimental group**

| Rabbit number | Fusion |
|---------------|--------|
| 1             | No     |
| 2             | No     |
| 3             | Yes    |
| 4             | No     |
| 5             | No     |
| 6             | Yes    |

**Table 1b. Evaluation of fusion in the control group**

| Rabbit number | Fusion |
|---------------|--------|
| 1             | Yes    |
| 2             | Yes    |
| 3             | No     |
| 4             | Yes    |
| 5             | Yes    |
| 6             | Yes    |

**Table 1c. Comparison of fusion between the experimental and control groups**

|           | Experimental group | Control group | Total       | z     | p     |
|-----------|--------------------|---------------|-------------|-------|-------|
| Fusion    | 2/6 = 0.33         | 5/6 = 0.83    | 7/12 = 0.58 | 2.020 | 0.045 |
| No fusion | 4/6 = 0.67         | 1/6 = 0.17    | 5/12 = 0.42 |       |       |

which was not exposed to stress, 5 out of 6 rabbits (83.3%) exhibited fusion.

The results from the manual palpation method indicated that UCMS had a significant negative effect on bone fusion compared to the control group ( $p = 0.045$ ) (Table 1a-c).

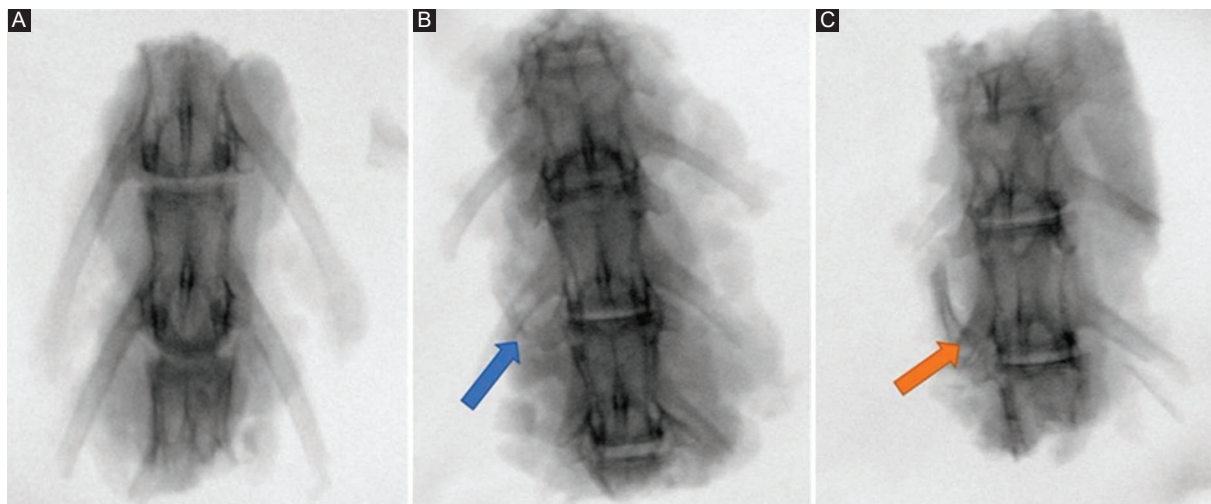
### Radiological evaluation results

The second method involved evaluating the harvested vertebrae under a fluoroscopic C-arm. Vertebrae showing no signs of fusion, such as callus formation or sclerosis, were assigned 0 points. Vertebrae with callus formation were given 1 point, whereas those with sclerosis, indicative of complete fusion, received 2 points.

In the experimental group, only 2 out of 6 rabbits demonstrated fusion. One rabbit exhibited callus



**Figure 5.** Manual palpation and applying flexion-extension movements on the extracted spine segment.



**Figure 6.** Radiological X-ray images of the extracted spine segment. **A:** no sign of fusion = 0 points. **B:** callus formation = 1 point. **C:** sclerosis formation = 2 points.

formation (1 point), and another showed sclerosis formation (2 points). In the control group, only one rabbit displayed no evidence of fusion (0 points), whereas 3 rabbits exhibited callus formation (1 point) and 2 demonstrated sclerosis formation (2 points).

These results suggest that UCMS negatively impacts the overall rate of bone fusion. However, it did not have a statistically significant effect on the degree of fusion, whether callus or sclerosis was present ( $p = 0.180$ ) (Table 2a-c).

## Discussion

In the United States of America, vertebra fusion surgery had increased by 62.3% in total between 2004 and 2015. Especially in the elderly population over 65 years of age, fusion surgery has risen by 138.7%.<sup>10</sup> As this type of surgeries become a part of every spinal surgeon's practice, achieving maximal satisfactory outcomes is extremely important. In 1995, Boden and Sumner, and in 2012, Hudec and Camacho developed a classification of factors that

**Table 2a. Evaluation of fusion after radiodiagnostics. Evaluation of fusion in the experimental group**

| Rabbit number | Rate of fusion |
|---------------|----------------|
| 1             | 0              |
| 2             | 0              |
| 3             | 1              |
| 4             | 0              |
| 5             | 0              |
| 6             | 2              |

**Table 2b. Evaluation of fusion in the control group**

| Rabbit number | Fusion |
|---------------|--------|
| 1             | 1      |
| 2             | 1      |
| 3             | 0      |
| 4             | 1      |
| 5             | 2      |
| 6             | 2      |

Classification of fusion rates. 0 = no fusion, 1 = partial fusion (callus), 2 = complete fusion (sclerosis)

**Table 2c. Comparison of fusion between the experimental and control groups**

| Group        | N | Mean   | Standard deviation | z      | p     |
|--------------|---|--------|--------------------|--------|-------|
| Experimental | 6 | 1.1667 | 0.75277            | -1.450 | 0.180 |
| Control      | 6 | 0.5    | 0.83666            |        |       |

negatively affected bone fusion. They stated that the 4 main elements which interfere with bone fusion: vascular factors, mechanical factors, metabolic factors and other factors. Anemia, hypoxia and infections, part of vascular factors, insufficient immobilization and fixation or abundant soft tissue between the fusion parts were defined as mechanical factors. The metabolic category consisted of osteoporosis, Vitamin C and D deficiency and steroid use. Tobacco and alcohol consumption were accepted as "other" elements slowing down or completely interrupting bone fusion.<sup>7,11</sup> Besides these, lots of many more factors that obstruct bone healing have been published throughout the years. In contrast, using allografts or xenografts, growth hormone derivatives or electrophysiological stimulation were shown to enhance bone fusion<sup>7</sup>. Although there are numerous

publications on how psychological stress has a negative outcome on wound healing, there are no significant reports of how it influences bone healing. In 2013, GBD 2017<sup>12</sup> stated that post-traumatic stress showed negative results in patients after arthrodesis, but a specific paper about how depression affects bone fusion could not be found in any database. The World Health Organization predicts that over 264 million people in the world suffer from depression.<sup>12</sup> We believe that investigation the connection between such a common public health issue and one of the most practiced surgeries of a spinal surgeon would be an interesting topic for further understanding bone healing. To project depression on humans and study their surgical outcome is nearly impossible to accomplish, either due to ethical reasons or to have a homogenous group without any bias or external affecting stimuli. That is why we developed a model to have the best possible results with the minimum number of animals to take part in it. The UCMS model was developed by Katz in the 1980's to induce depression in laboratory animals and was further modified by other authors. For the surgery, we used the standardized posterolateral fusion model, which is commonly chosen by many researchers throughout the years. The duration of the study was limited to 8 weeks because it is the minimum amount of time needed for bone fusion. We wanted to evaluate bone healing in two steps. The first is manual palpation by forcing extension and flexion maneuvers, which is thought to be a simple but subjective way. The other was a more objective way by radiodiagnostics under the C-arm, where we graded the extracted vertebra on its callus and sclerosis formation. The results were rather surprising, in that depression negatively interferes with proper bone fusion but does not affect the degree or quality of it *per se*. These findings were followed by some unanswered further questions. Will the bones without any signs of fusion or with callus formation, so the ones that began the fusion process but did not fully heal, later develop sclerosis despite being under chronic stress? To achieve this, the study time can be prolonged to 12 or maybe 24 weeks. Furthermore, additional diagnostic tests, such as computed tomography and histopathological evaluation, may be used. An interesting topic for another study would be whether this negative effect of depression on bone healing can be reduced by antidepressant agents.

## Key results

Depression mimicked in the UCMS model negatively affects bone fusion.

## Limitations

Prolonged study time and more advanced radiologic and histopathologic evaluations more detailed results might be achieved despite being extortionate.

## Conclusion

Our findings demonstrated that depression significantly impairs bone fusion in rabbits but does not alter the quality or degree of fusion. We believe this model provides a promising foundation for future research. Extending the study duration and incorporating advanced radiologic and histopathologic evaluations could yield more comprehensive results, although these approaches may involve higher costs.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

**Protection of human subjects and animals.** The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of

Helsinki. The procedures were authorized by the Institutional Ethics Committee.

**Confidentiality, informed consent, and ethical approval.** The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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# Minimally invasive approaches in ectopic pregnancy surgery: vaginal natural orifice transluminal endoscopic surgery versus conventional laparoscopy

## Enfoques mínimamente invasivos en cirugía del embarazo ectópico: V-NOTES frente a laparoscopia convencional

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### Abstract

**Objectives:** The objective of the study was to compare the efficacy and safety of vaginal natural orifice transluminal endoscopic surgery (V-NOTES) and conventional laparoscopy in the surgical management of ectopic pregnancy. **Methods:** A retrospective case-control study was conducted, including 40 patients diagnosed with ectopic pregnancy, treated either with V-NOTES (n = 20) or conventional laparoscopy (n = 20). Outcomes assessed included operative time, blood loss, post-operative pain scores, length of hospital stay, and complication rates. **Results:** No significant differences were observed between the two groups in terms of operative time, blood loss, and complication rates. However, V-NOTES resulted in significantly lower post-operative pain scores (Visual Analog Scale:  $2.1 \pm 1.0$  vs.  $4.3 \pm 1.1$ ;  $p = 0.01$ ) and reduced opioid usage compared to conventional laparoscopy. **Conclusions:** V-NOTES appears to be a non-inferior alternative to conventional laparoscopy in ectopic pregnancy surgery, with comparable surgical safety and enhanced post-operative comfort. Further research with larger cohorts is recommended to confirm these findings.

**Keywords:** Ectopic pregnancy. Vaginal natural orifice transluminal endoscopic surgery. Conventional laparoscopy. Minimally invasive surgery. Surgical outcomes.

### Resumen

**Objetivos:** Comparar la eficacia y la seguridad de la cirugía endoscópica transluminal por orificio natural vía vaginal (V-NOTES) y la laparoscopia convencional en el tratamiento quirúrgico del embarazo ectópico. **Métodos:** Se realizó un estudio retrospectivo de casos y controles, incluyendo 40 pacientes diagnosticadas con embarazo ectópico tratadas mediante V-NOTES (n = 20) o laparoscopia convencional (n = 20). Se evaluaron los resultados en términos de tiempo operatorio, pérdida de sangre, puntuaciones de dolor posoperatorio, duración de la estancia hospitalaria y tasas de complicaciones. **Resultados:** No se observaron diferencias significativas entre los dos grupos en cuanto al tiempo operatorio, la pérdida de sangre y las tasas de complicaciones. Sin embargo, V-NOTES resultó en puntuaciones significativamente más bajas de dolor posoperatorio (EVA:  $2.1 \pm 1.0$  vs.  $4.3 \pm 1.1$ ;  $p = 0.01$ ) y menor uso de opiáceos en comparación con la laparoscopia convencional. **Conclusiones:** V-NOTES parece ser una alternativa no inferior a la laparoscopia convencional en la cirugía del embarazo ectópico, con una seguridad quirúrgica comparable y mayor comodidad posoperatoria. Se recomienda realizar investigaciones adicionales con cohortes más grandes para confirmar estos hallazgos.

**Palabras clave:** Embarazo ectópico. V-NOTES. Laparoscopia convencional. Cirugía mínimamente invasiva. Resultados quirúrgicos.

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## Introduction

Ectopic pregnancy is a serious and potentially life-threatening condition that requires prompt surgical intervention. The traditional surgical approach has been open laparotomy, but in recent years, minimally invasive techniques such as laparoscopy have gained significant traction due to their potential benefits, including reduced pain, shorter recovery time, and improved cosmetic outcomes.<sup>1,2</sup> In recent years, a newer approach called vaginal natural orifice transluminal endoscopic surgery (V-NOTES) has emerged as a promising alternative to conventional laparoscopy.<sup>3,4</sup>

V-NOTES is a novel minimally invasive approach that utilizes the vagina as the access point to the peritoneal cavity, offering an alternative to traditional laparoscopic procedures. The use of the vagina as an entry point avoids external incisions, which not only reduces visible scarring but also limits the risk of wound-related complications such as infections and hernias.<sup>5</sup> In the context of ectopic pregnancy, V-NOTES has been explored as a potential option for surgical management, offering the advantage of reduced post-operative pain and quicker recovery. While conventional laparoscopy remains the gold standard for surgical intervention in ectopic pregnancy, the minimally invasive nature of V-NOTES has raised interest in its potential non-inferiority to traditional laparoscopic techniques in terms of surgical outcomes and patient satisfaction.<sup>6</sup> Several studies have indicated that V-NOTES is associated with comparable surgical efficacy and safety to traditional laparoscopy, including similar complication rates and operative times, while also offering enhanced post-operative comfort.<sup>7-9</sup> However, the data on V-NOTES in ectopic pregnancy surgery is limited, and more research is needed to establish its non-inferiority or potential superiority over conventional methods.

The aim of this study is to compare the efficacy and safety of V-NOTES and conventional laparoscopy in the surgical management of ectopic pregnancy. By evaluating the outcomes of both approaches, this research seeks to determine which method offers superior results in terms of surgical effectiveness, complication rates, and post-operative recovery.

## Methods

The study was reviewed by our university's Local Ethics Committee and approved with the date of

January 10, 2025, and number 2025/54. This study was designed as a retrospective case-control analysis involving 40 patients diagnosed with ectopic pregnancy and treated at our institution. The patients were divided into two groups: 20 patients who underwent V-NOTES and 20 patients who underwent conventional laparoscopic surgery. The allocation of patients to either the V-NOTES or conventional laparoscopy group was determined based on the surgeon's preference and clinical judgment at the time of surgery. The patients were identified and reviewed retrospectively using the patient records from our electronic health system.

Inclusion criteria: women aged 18-45 years diagnosed with ectopic pregnancy, patients without any chronic medical conditions, and patients eligible for surgical treatment. Exclusion criteria: a history of severe adhesive disease in the abdominal or pelvic region, patients with serious cardiovascular, pulmonary, or other systemic diseases, conditions unsuitable for surgery (e.g., bleeding disorders), other confounding factors (e.g., patients who are excessively underweight or overweight). Patient management: all patients were initially evaluated by the attending gynecologist following institutional protocols for managing ectopic pregnancy. Women with live ectopic gestations or those presenting with hemodynamic instability were recommended to undergo surgery. Asymptomatic patients with unruptured ectopic pregnancies and  $\beta$ -hCG levels under 5000 IU/L were offered systemic methotrexate therapy. Surgical intervention was recommended for patients with  $\beta$ -hCG levels above 5000 IU/L or those who did not respond to methotrexate treatment. Study group: the V-NOTES and conventional laparoscopic groups consisted of patients who were unsuitable for methotrexate therapy and had no contraindications to the posterior colpotomy approach (e.g., no history of rectal surgery, pelvic radiotherapy, recto-vaginal endometriosis, or active pelvic inflammatory disease) or conventional laparoscopic approach (e.g., severe adhesion, obesity, severe cardiopulmonary conditions, hemodynamic instability or active pelvic inflammatory disease). After receiving counseling, patients who agreed to undergo V-NOTES or conventional laparoscopic surgery were included in the study. The allocation to either approach was based on the surgeon's decision at the time of surgery. Surgical techniques: V-NOTES: The patient was positioned in the dorsal lithotomy position. Following the induction of anesthesia, a standardized antibiotic regimen was administered (Co-Amoxiclav

1.5 g intravenously). If the patient had a cephalosporin allergy, Clindamycin 600 mg and Metronidazole 500 mg were given. A Foley catheter was inserted to empty the bladder, which was removed at the end of the procedure.

A posterior colpotomy was performed using curved Mayo scissors to access the pouch of Douglas. A Gel-POINT V-Path transvaginal access platform was introduced, and the peritoneal cavity was insufflated with carbon dioxide to a pressure of 12 mmHg. The operating table was tilted into a 20° Trendelenburg position. A 10 mm laparoscope was introduced through the vaginal access, and the salpingectomy or salpingostomy was performed using endoscopic instruments (atraumatic graspers and LiGaSure). The specimens were retrieved through the posterior colpotomy incision, and the incision was closed with Vicryl 1 sutures in a continuous fashion. Conventional laparoscopy: the procedure was initiated with the patient in the dorsal lithotomy position. A standard antibiotic regimen was administered as described above. After cleaning and draping, a 10 mm vertical incision was made at the umbilicus. The abdomen was accessed directly using a trocar. A 10 mm trocar was placed, and a 30° laparoscope was introduced. Additional 5 mm and 10 mm accessory trocars were inserted for instrument access. The ectopic pregnancy was identified and removed using endoscopic graspers and a LiGaSure. Hemoperitoneum was evacuated as needed, and the specimen was retrieved in an endoscopic bag through the 10 mm port. The abdominal wall was closed with absorbable sutures. Data collection: data were retrospectively collected from the hospital's electronic medical records, including demographic information (age, body mass index (BMI), parity, gestational age), operative details (surgical time, estimated blood loss, complications), and post-operative outcomes (pain scores at 24 h using the Visual Analog Scale (VAS), length of hospital stay, and post-operative complications).

### **Statistical analysis**

Statistical analysis was performed using the Statistical Package for the Social Sciences software. The Shapiro-Wilk test was applied to assess the normality of the data. For normally distributed data, the independent t-test was used to compare means between the two groups. For non-normally distributed data, the Mann-Whitney U test was employed. Demographic and clinical characteristics, surgical parameters,

post-operative pain scores, analgesic requirements, complication rates, and length of hospital stay were compared between the two groups. The Chi-square test or Fisher's Exact test was used to analyze complication rates. The t-test or Mann-Whitney U test was used to compare post-operative recovery times and cost analysis. A significance level of  $p < 0.05$  was considered statistically significant.

Ethical approval: written consent was collected from all participants along with the questionnaire. The study was reviewed by our university's Local Ethics Committee and approved with the date of January 10, 2025, and number 2025/54.

### **Results**

The comparative analysis between V-NOTES and conventional laparoscopy reveals no statistically significant differences in most measured variables, including demographic parameters, intraoperative data, and complication rates. However, a significant reduction in post-operative pain scores (VAS:  $2.1 \pm 1.0$  vs.  $4.3 \pm 1.1$ ;  $p = 0.01$ ) and the absence of opioid requirement in the V-NOTES group compared to 10% opioid usage in the conventional laparoscopy group ( $p = 0.01$ ) suggest superior post-operative pain management with V-NOTES. Overall, the findings indicate that V-NOTES is non-inferior to conventional laparoscopy with comparable surgical safety, efficacy, and patient outcomes while providing enhanced post-operative comfort. Demographic and surgical outcomes are presented in table 1.

The regression analysis indicates that most perioperative characteristics did not have a statistically significant association with post-operative pain scores. Age, BMI, size of ectopic pregnancy, and blood loss all yielded p-values above 0.05, indicating no strong relationship with post-operative pain. The surgical approach variable (V-NOTES) showed a trend toward lower pain scores (Coefficient:  $-0.10$ ;  $p = 0.09$ ), suggesting a potential clinical benefit, though not statistically significant. The only significant predictors were post-operative pain score itself (VAS:  $p = 0.01$ ) and opioid requirement ( $p = 0.01$ ), which were lower in the V-NOTES group. This further supports the non-inferiority and possible superiority of V-NOTES in pain management compared to conventional laparoscopy. The association between post-operative pain score (VAS) and perioperative characteristics is presented in table 2.

**Table 1. Comparison of V-NOTES and conventional laparoscopy in ectopic pregnancy surgery**

| Variable                                                  | V-NOTES  | Conventional laparoscopy | p    |
|-----------------------------------------------------------|----------|--------------------------|------|
| Age* (mean±SD)                                            | 31.2±5.4 | 32.1±5.7                 | 0.76 |
| BMI* (kg/m <sup>2</sup> )                                 | 24.8±3.1 | 25.0±3.2                 | 0.84 |
| Previous abdominal surgery** (n, %)                       | 5 (25)   | 5 (25)                   | 0.99 |
| Previous laparotomy***                                    | 2 (10)   | 2 (10)                   | 1.00 |
| Previous laparoscopy***                                   | 3 (15)   | 3 (15)                   | 1.00 |
| Previous history of ectopic pregnancy** (n, %)            | 4 (20)   | 4 (20)                   | 1.00 |
| Gestation week*                                           | 7.5±1.1  | 7.6±1.2                  | 0.92 |
| Size of ectopic* (mm, mean±SD)                            | 27.4±4.8 | 28.1±4.7                 | 0.78 |
| bhCG* (mIU/mL)                                            | 2345±780 | 2390±800                 | 0.82 |
| Type of surgery (n, %)                                    |          |                          |      |
| Salpingectomy**                                           | 18 (90)  | 16 (80)                  | 0.78 |
| Salpingostomy***                                          | 2 (10)   | 4 (20)                   | 0.89 |
| Emergency surgery** (n, %)                                | 2 (10)   | 3 (15)                   | 0.79 |
| Surgical conversion*** (n, %)                             | 1 (5)    | 1 (5)                    | 1.00 |
| Duration of surgery* (min, mean±SD)                       | 58±12    | 60±13                    | 0.80 |
| Blood loss* (mL, mean±SD)                                 | 110±25   | 115±28                   | 0.77 |
| Post-operative day 1 hemoglobin decrease* (g/dL, mean±SD) | 1.2±0.3  | 1.3±0.4                  | 0.85 |
| Hospital stay* (days)                                     | 1.2±0.5  | 1.3±0.6                  | 0.88 |
| Post-operative pain score (VAS)*                          | 2.1±1.0  | 4.3±1.1                  | 0.01 |
| Post-operative opioid requirement*** (n, %)               | -        | 2 (10)                   | 0.01 |
| Complication rate*** (n, %)                               |          |                          |      |
| Infection                                                 | 1 (5)    | 1 (5)                    | 1.00 |
| Hemorrhage                                                | 0 (0)    | 0 (0)                    | 1.00 |
| Reoperation                                               | 0 (0)    | 0 (0)                    | 1.00 |
| Bowel injury                                              | 0 (0)    | 0 (0)                    | 1.00 |
| Readmission to hospital** (n, %)                          | 2 (10)   | 2 (10)                   | 1.00 |
| Return to work/Normal activity* (days)                    | 7.5±1.2  | 7.7±1.3                  | 0.82 |
| Surgeon experience* (years)                               | 2±4      | 14±5                     | 0.01 |

\*Independent t-test.

\*\*Chi-square test.

\*\*\*Fisher's exact test.

BMI: body mass index; v-NOTES: vaginal natural orifice transluminal endoscopic surgery; VAS: Visual Analog Scale; SD: standard deviation.

## Discussion

In the current study, the comparison between V-NOTES and conventional laparoscopy for the management of ectopic pregnancy was evaluated. Our findings suggest that both techniques offer similar surgical outcomes, but V-NOTES appears to provide some advantages, particularly in terms of post-operative pain and recovery times.

The results align with previous studies that have explored the benefits of minimally invasive techniques in gynecological surgery. For example, a study by Tierney et al. demonstrated that V-NOTES was associated with less post-operative pain and shorter recovery times compared to conventional laparoscopic approaches in various gynecological procedures, including ectopic pregnancy surgery.<sup>10</sup> In addition, similar findings were reported by Yoong et al., who

**Table 2. Association between post-operative pain score (VAS) and perioperative characteristics**

| Variable                      | Coefficient (B) | Standard error | 95% CI     | p*   |
|-------------------------------|-----------------|----------------|------------|------|
| Age (year)                    | 0.02            | 0.01           | −0.01-0.05 | 0.18 |
| BMI (kg/m <sup>2</sup> )      | 0.03            | 0.02           | −0.01-0.06 | 0.12 |
| Surgical approach (vNOTES)    | −0.10           | 0.08           | −0.25-0.05 | 0.09 |
| Surgical type (Salpingostomy) | 0.05            | 0.09           | −0.12-0.22 | 0.55 |
| Previous abdominal surgery    | 0.06            | 0.07           | −0.08-0.20 | 0.42 |
| Size of ectopic               | 0.01            | 0.01           | −0.01-0.03 | 0.25 |
| Emergency surgery             | 0.07            | 0.06           | −0.05-0.19 | 0.29 |
| Blood loss                    | 0.01            | 0.01           | −0.01-0.03 | 0.22 |
| Hospital stay                 | 0.09            | 0.07           | −0.05-0.23 | 0.20 |
| Surgeon experience (years)    | −0.02           | 0.01           | −0.04-0.01 | 0.13 |

\*Linear regression.

BMI: body mass index; v-NOTES: vaginal natural orifice transluminal endoscopic surgery; VAS: Visual Analog Scale.

observed that patients undergoing V-NOTES had significantly lower VAS pain scores and required fewer analgesics in the post-operative period.<sup>8</sup>

In our study, the reduced post-operative pain observed in the V-NOTES group may be attributed to the lack of external incisions, which helps minimize the risk of wound-related complications, such as infection and hernias. The use of a natural orifice, such as the vagina, for access in V-NOTES eliminates the need for abdominal wall incisions, thus avoiding the discomfort often associated with conventional laparoscopic port sites.

While V-NOTES is considered a promising alternative to traditional laparoscopy, it is important to note that its use is not without challenges. Studies by Raquet et al.<sup>11</sup> and Ferro et al.<sup>12</sup> have highlighted the technical complexities of the V-NOTES approach, including the need for specialized training and equipment. Despite these challenges, our findings are consistent with previous research indicating that V-NOTES may offer comparable, if not superior, outcomes to conventional laparoscopy, especially in terms of post-operative recovery and cosmetic outcomes.

Some limitations of our study are as follows: First, the study design is retrospective, and the lack of randomization may introduce bias, which could influence the results. The choice of V-NOTES or conventional laparoscopy was based on the surgeon's preference, which may have impacted the outcomes. In addition, our sample size is relatively small, limiting the generalizability of the findings. Larger, multicenter studies are needed to validate the results and provide a more comprehensive understanding of the benefits of V-NOTES

compared to conventional laparoscopy. Another limitation is the learning curve associated with V-NOTES, as the success of the technique depends on the surgeon's experience and expertise. Furthermore, the follow-up period in our study was short, and we were unable to capture long-term outcomes such as recurrence rates or chronic pain. There is also a potential risk of selection bias, as surgeons may have used different criteria when deciding which technique to apply to patients based on their conditions. Lastly, while we briefly mentioned cost analysis, a more detailed economic evaluation comparing V-NOTES and conventional laparoscopy was not performed.

## Conclusions

V-NOTES shows promise as a minimally invasive technique for the management of ectopic pregnancy, with potential advantages in post-operative pain control and recovery. However, more extensive research is required to fully assess its non-inferiority or potential superiority over conventional laparoscopy in terms of surgical outcomes and long-term patient satisfaction.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

**Protection of humans and animals.** The authors declare that no experiments involving humans or animals were conducted for this research.

**Confidentiality, informed consent, and ethical approval.** The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed. All participants signed informed written consent before being enrolled in the study. The study was reviewed by our university's Local Ethics Committee and approved with the date of January 10, 2025, and number 2025/54. It was carried out according to the Declaration of Helsinki.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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# Effects of breast milk nutrition on chronic adenoiditis, chronic tonsillitis and allergy

## *Efectos de la nutrición con leche materna sobre la adenoiditis crónica, la amigdalitis crónica y la alergia*

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### Abstract

**Objective:** It is aimed to reveal whether breast milk has an effect against recurrent upper respiratory tract infections and allergies. **Methods:** The study group consisted of 300 children aged 0-15 years who applied to the Ear, Nose, and Throat Outpatient Clinic with complaints of frequent throat infections, snoring, sleeping with an open mouth, and decreased hearing. The control group consisted of 300 randomly selected healthy children between the ages of 0-15 whose routine controls were terminated. Both groups were compared in terms of age, gender, birth weight, duration of breast milk and formula use, eosinophil count in complete blood count, and time of transition to solid food. **Results:** It was observed that more operation (adenotonsillectomy) were performed in children with lower than normal birth weight (< 2500 g), children who had breastfed for < 6 months, and children who received formula for more than 6 months ( $p < 0.001$ ). Eosinophil count was found to be higher in the complete blood count of the children in the study group compared to the children in the control group ( $p < 0.001$ ). **Conclusions:** Children are protected from recurrent adenotonsillar infections and allergies with breast milk.

**Keywords:** Breastmilk. Tonsillitis. Allergy.

### Resumen

**Objetivo:** Investigar si la leche materna tiene efecto sobre las infecciones recurrentes del tracto respiratorio superior y las alergias. **Métodos:** Se incluyeron en el estudio 300 niños de 0 a 15 años que presentaban quejas de frecuentes infecciones de garganta, ronquidos, dormir con la boca abierta y pérdida de audición. El grupo control estuvo constituido por 300 niños sanos de edades comprendidas entre 0 y 15 años. Se compararon ambos grupos en términos de edad, sexo, peso al nacer, duración del uso de leche materna y fórmula, y recuento de eosinófilos en el hemograma completo. **Resultados:** Se observó que se realizaron más intervenciones quirúrgicas (adenoamigdalectomía) en niños con bajo peso al nacer (< 2500 g), en niños que fueron amamantados por menos de 6 meses y en niños que fueron alimentados con fórmula por más de 6 meses ( $p < 0.001$ ). El recuento de eosinófilos en el hemograma completo de los niños del grupo de estudio fue mayor que en el de los niños del grupo control ( $p < 0.001$ ). **Conclusiones:** La leche materna protege a los niños frente a infecciones adenoamigdalares recurrentes y alergias.

**Palabras clave:** Leche materna. Amigdalitis. Alergia.

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## Introduction

Waldeyer lymphatic ring consists of palatine tonsils, pharyngeal tonsil (adenoid), lingual tonsils, lateral pharyngeal bands, and tubal tonsils. Adenotonsillar lymphoid tissues, a component of Waldeyer, are the structures that form the body's first defense mechanism against gastrointestinal and respiratory antigens. Immunological activity in these tissues starts after birth, reaches its maximum level between 3 and 10 years of age, and adenotonsillar tissues are at their greatest size at this age.<sup>1</sup> Local or systemic attacks of infection affect the growth of adenotonsillar lymphoid tissues.

The fact that adenotonsillectomy is one of the most frequently performed surgical procedures in childhood is important in terms of determining adenotonsillectomy indications. Among the indications for adenoidectomy, the most common chronic mouth breathing, adenoid hypertrophy causing snoring and obstructive sleep apnea (OSA), recurrent purulent adenoiditis, and tonsillectomy indications, which are frequently recurrent acute tonsillitis and tonsillar hypertrophy causing OSA.

## Methods

The study was planned a cross-sectional cohort study in the Ear, Nose, Throat, and Pediatrics between August 1, 2020, and February 1, 2022, after the approval of the ethics committee of Karadeniz Technical University Faculty of Medicine (2020/91).

Otomicroscopic examination, audiometry, tympanometry, anterior rhinoscopy, and flexible nasal endoscopy, oropharynx and oral cavity examinations were performed when necessary, in all patients who applied to the Ear, Nose, and Throat clinic with the complaints of frequent throat infections, snoring, sleeping with an open mouth, and decreased hearing. In some cases, a direct lateral cervical radiograph was taken. The study group included 300 children aged 0-15 years, who were indicated for adenoidectomy, tonsillectomy, adenotonsillectomy, and ventilation tube application as a result of anamnesis, physical examination, audiological tests, and direct lateral cervical radiography. The control group consisted of 300 randomly selected healthy children between the ages of 0-15 whose routine controls were terminated. Five children with cleft palate, two with velopharyngeal insufficiency, three with systemic diseases, two with

bleeding diatheses, and 20 with previous adenotonsillectomy were excluded from the study group. Five children with bleeding diatheses and 20 with systemic diseases were excluded from the control group.

## Patient selection flow diagram

Total children evaluated at ENT and Pediatrics clinics (n = 657)

- A. Excluded from study group (n = 32):
  - Submucosal cleft palate (n = 5)
  - Velopharyngeal insufficiency (n = 2)
  - Uncontrolled systemic disease (n = 3)
  - Bleeding diathesis (n = 2)
  - Previous adenotonsillectomy (n = 20).
- B. Excluded from control group (n = 25):
  - Bleeding diathesis (n = 5)
  - Uncontrolled systemic disease (n = 20).

In addition to demographic information such as age and gender, the families of the children included in the study were asked questions about birth weight, duration of breast milk use, use and duration of formula, and transition to complementary foods. Parents of the patients were informed about the study, and written informed consent forms were obtained. Palatine tonsil sizes were noted in both groups, and adenoid size was noted in the study group. Serological tests performed on the patients were evaluated; the presence of eosinophilia and abnormal values was noted.

In the patients who accepted to participate in the study and had the necessary indications, operations were planned. During the operation, the neck was extended in the supine position under general anesthesia, and the tongue was pressed with a Crowe-Davis mouth opener, and the inside of the mouth was exposed. Adenoidectomy with the help of a curette, tonsillectomy with cold dissection, adenotonsillectomy, and ventilation tube application were performed when necessary. Demographic data such as age, birth weight, gender, breastfeeding status and duration, status and duration of formula feeding, eosinophil counts in serological tests, and transition time to solid food were compared between the children in the study group and the control group.

## Statistical analysis

While evaluating the findings obtained in the study, IBM Statistical Package for the Social Sciences for Windows 23.0 program was used for statistical

analysis. Categorical data are number (n) and percentage (%); metric data were presented with mean, standard deviation, median, minimum, and maximum values. Chi-square test was used to compare categorical data. Cases with a  $p < 0.05$  were considered significant. The power of the research was calculated as 91.5% using Open Epi version 3.0 software with a 95% confidence interval.

Multivariate logistic regression analysis was used to determine the factors affecting the presence of disease. The dependent variable was the presence of adenotonsillectomy, and the independent variables were gender, birth weight, duration of breastfeeding, and formula feeding. The reference categories were "girl" for gender, "normal" for birth weight, and "> 12 months" for duration of breastfeeding and formula feeding. The model was constructed using the enter method, and the results were evaluated at a 95% confidence interval.

## Results

### Gender

The study included 296 (49.3%) girls and 304 (50.7%) boys aged between 1 and 15 (mean 5,193). The control group included 166 (55.3%) girls and 134 (44.7%) boys, while the study group included 130 (43.3%) girls and 170 (56.7%) boys. When the applications to the outpatient clinics were evaluated in both groups, it was seen that adenoidectomy, tonsillectomy, adenotonsillectomy, and ventilation tube application when necessary were performed at a higher rate in boys ( $p = 0.003$ ) (Table 1).

### Birth weight

Of the 600 children participating in the study, 36 (6%) had a low birth weight, 536 (89.3%) had a normal birth weight, and 28 (4.6%) had a high birth weight. Of the 36 children with low birth weight, 7 (19.4%) were in the control group, and 29 (80.6%) were in the study group. Of the 536 children with normal birth weight, 283 (52.8%) were in the control group, and 253 (47.2%) were in the study group. Of the 28 children with high birth weight, 10 (35.7%) were in the control group, and 18 (64.3%) were in the study group. It was observed that more adenoidectomy, tonsillectomy, adenotonsillectomy and ventilation tube application when necessary were performed in

**Table 1. Comparison of control and study groups by gender**

| Gender     | Control | Study | Total | p     |
|------------|---------|-------|-------|-------|
| Girl       |         |       |       | 0.003 |
| Number (n) | 166     | 130   | 296   |       |
| Ratio (%)  | 56.1    | 43.9  | 49.3  |       |
| Boy        |         |       |       |       |
| Number (n) | 134     | 170   | 304   |       |
| Ratio (%)  | 44.1    | 55.9  | 50.7  |       |
| Total      |         |       |       |       |
| Number (n) | 300     | 300   | 600   |       |

children with lower than normal birth weight ( $< 2500$  g) ( $p < 0.001$ ) (Table 2).

### Breast milk

Of the 600 children in our study, 16 (2.7%) were not breastfed at all, while 584 (97.3%) were breastfed. Of the 584 children who were breastfed, 299 (51.2%) were in the control group, and 285 (48.8%) were in the study group; of the 16 children who were not breastfed, 1 (6.2%) was in the control group, and 15 (93.8%) were in the study group. Of the children who were breastfed, 100 (16.7%) were breastfed for 0-6 months, 148 (24.7%) for 7-12 months, and 352 (58.6%) for more than 12 months. Of the 100 children who were breastfed for 0-6 months, 8 (8%) were in the control group, and 92 (92%) were in the study group. Of the 148 children who were breastfed for 7-12 months, 89 (60.1%) were in the control group, and 59 (39.9%) were in the study group. Of the 352 children who were breastfed for more than 12 months, 203 (57.7%) were in the control group, and 149 (42.3%) were in the study group.

It was observed that adenoidectomy, tonsillectomy, adenotonsillectomy, and ventilation tube application when necessary were performed more frequently in children who were breastfed for  $< 6$  months compared to children who were breastfed for more than 6 months ( $p < 0.001$ ) (Table 3).

### Formula feeding

It was observed that more adenoidectomy, tonsillectomy, adenotonsillectomy, and ventilation tube applications when necessary were performed in children who received formula for more than 6 months

**Table 2. Comparison of control and study groups by birth weight**

| Birth weight (g)              | Control | Study | Total | p       |
|-------------------------------|---------|-------|-------|---------|
| Lower than normal (< 2500 g)  |         |       |       | < 0.001 |
| Number (n)                    | 7       | 29    | 36    |         |
| Ratio (%)                     | 19.4    | 80.6  | 6     |         |
| Normal (2500-4000 g)          |         |       |       |         |
| Number (n)                    | 283     | 253   | 536   |         |
| Ratio (%)                     | 52.8    | 47.2  | 89.3  |         |
| Higher than normal (> 4000 g) |         |       |       |         |
| Number (n)                    | 10      | 18    | 28    |         |
| Ratio (%)                     | 35.7    | 64.3  | 4.7   |         |
| Total                         |         |       |       |         |
| Number (n)                    | 300     | 300   | 600   |         |
| Ratio (%)                     | 50      | 50    | 100   |         |

**Table 3. Comparison of control and study groups by time of breastfeeding**

| Time of breastfeeding | Control | Study | Total | p       |
|-----------------------|---------|-------|-------|---------|
| 0-6 month             |         |       |       | < 0.001 |
| Number (n)            | 8       | 92    | 100   |         |
| Ratio (%)             | 8       | 92    | 16.7  |         |
| 7-12 month            |         |       |       |         |
| Number (n)            | 89      | 59    | 148   |         |
| Ratio (%)             | 60.1    | 39.9  | 24.7  |         |
| > 12 month            |         |       |       |         |
| Number (n)            | 203     | 149   | 352   |         |
| Ratio (%)             | 57.7    | 42.3  | 58.6  |         |
| Total                 |         |       |       |         |
| Number (n)            | 300     | 300   | 600   |         |
| Ratio (%)             | 50      | 50    | 100   |         |

**Table 4. Comparison of control and study groups by time period of formula feeding**

| Time period of formula feeding | Control | Study | Total | p       |
|--------------------------------|---------|-------|-------|---------|
| 0-6 months                     |         |       |       | < 0.001 |
| Number (n)                     | 8       | 47    | 55    |         |
| Ratio (%)                      | 14.5    | 85.5  | 30.2  |         |
| 7-12 months                    |         |       |       |         |
| Number (n)                     | 7       | 64    | 71    |         |
| Ratio (%)                      | 9.9     | 90.1  | 11.8  |         |
| > 12 months                    |         |       |       |         |
| Number (n)                     | 0       | 56    | 56    |         |
| Ratio (%)                      | 0       | 56    | 9.4   |         |
| Total                          |         |       |       |         |
| Number (n)                     | 300     | 300   | 600   |         |
| Ratio (%)                      | 50      | 50    | 100   |         |

**Table 5. Comparison of transition time to complementary food in control and study groups**

| Transition time to complementary food | Control | Study | Total | p     |
|---------------------------------------|---------|-------|-------|-------|
| 0-6 months                            |         |       |       | 0.178 |
| Number (n)                            | 259     | 247   | 506   |       |
| Ratio (%)                             | 51.2    | 48.8  | 84.3  |       |
| > 6 months                            |         |       |       |       |
| Number (n)                            | 41      | 53    | 94    |       |
| Ratio (%)                             | 43.6    | 56.4  | 15.7  |       |
| Total                                 |         |       |       |       |
| Number (n)                            | 300     | 300   | 600   |       |
| Ratio (%)                             | 50      | 50    | 100   |       |

compared to children who received formula for 6 months or less ( $p < 0.001$ ) (Table 4).

## Eosinophilia

The eosinophil count was found to be higher in the complete blood count of the children who underwent adenoidectomy, tonsillectomy, adenotonsillectomy, and when necessary, ventilation tube application compared to the children in the control group ( $p < 0.001$ ).

The switching time to additional food in the control and study groups is shown in table 5, and there was no statistically significant difference between the groups ( $p = 0.178$ ). There was no significant relationship between the control and study groups in terms of switching to solid food earlier than 6 months or after 6 months.

When the adenoid sizes of the children in the study group were examined, 7 (1.2%) children had grade 1,

9 (1.5%) children had grade 2, 240 (40%) children had grade 3, and 44 (7.3%) children had Grade 4 adenoids. When the palatine tonsil sizes of the children in our study were examined, 383 (63.8%) children had Grade 1, 83 (13.8%) children had Grade 2, 97 (16.2%) children had Grade 3, and 37 (6.2%) children had Grade 4 tonsils. It was seen that 223 (58.2%) of 383 children with Grade 1 tonsils were in the control group, and 160 (41.8%) were in the study group. 71 (85.5%) of 83 children with Grade 2 tonsils were in the control group, 12 (14.5%) were in the study group. 6 (6.2%) of 97 children with Grade 3 tonsils were in the control group, 91 (93.8%) were in the study group, and 37 (100%) of 37 children with Grade 4 tonsils were in the study group.

Of the children in the study group, 87 (29%) had adenoidectomy, 84 (28%) had adenotonsillectomy, 42 (14%) had adenotonsillectomy with simultaneous

bilateral ventilation tube application, 81 (27%) had adenoidectomy with simultaneous bilateral ventilation tube application, 4 (1.3%) had tonsillectomy, 2 (0.7%) had tonsillectomy and simultaneous bilateral ventilation tube application.

According to regression analysis, the risk of disease was statistically significantly increased in boys compared to girls ( $p = 0.006$ ; odds ratio = 1.69). Low birth weight increased the probability of disease by 3.55 times compared to normal birth weight ( $p = 0.010$ ), and the association between high birth weight and disease risk was not statistically significant ( $p = 0.085$ ). When examined in terms of duration of breastfeeding, a 3.91-fold increase in disease risk was observed in those breastfed for the first 6 months compared to those breastfed for more than 12 months ( $p = 0.002$ ), while no statistically significant association was found for those breastfed for 7-12 months ( $p = 0.060$ ). No significant association was found between duration of formula feeding and disease risk ( $p = 1.000$ ) (Table 6).

## Discussion

Waldeyer lymphatic ring consists of palatine tonsils, pharyngeal tonsil (adenoid), lingual tonsils, lateral pharyngeal bands, and tubal tonsils. Adenotonsillar lymphoid tissues, a component of Waldeyer, are the structures that form the body's first defense mechanism against gastrointestinal and respiratory antigens. With the independent immune system that develops in the mucous membranes, antigens are quickly eliminated, and permanent immunity is provided. This independent immune system is called mucosa-associated lymphoid tissue (MALT).

In adenotonsillar lymphoid tissues, plasma cells are transformed into lymphocytes with weak antigenic stimuli, while high stimuli lead to proliferation of B cells. Immunoglobulin G (IgG) and IgA are produced by the resulting B cell response. Produced IgG is distributed to the nasopharynx, and IgA to MALT.<sup>2</sup> Ogra et al. found that nasopharyngeal IgA levels decreased 3-4 times in children who had undergone adenotonsillectomy.<sup>3</sup> Jeschke and Ströder found that there was a decrease in serum and secretory IgA levels after adenotonsillectomy.<sup>4</sup> D'Amelio et al. They observed a decrease in serum IgA levels in individuals aged 16-24 who had undergone tonsillectomy.<sup>5</sup>

In the intrauterine life, the transmission of immune-active components that protect against infections to the baby is provided by the placenta, and these functions of the placenta can be fulfilled through nutrition after birth. Breast milk is a biologically active food with

**Table 6. Logistic regression analysis results**

| Variable                                                      | p     | OR [Exp (B)] | 95% CI (OR) |
|---------------------------------------------------------------|-------|--------------|-------------|
| Boy (Reference: girl)                                         | 0.006 | 1.69         | 1.16-2.46   |
| Low birth weight (Reference: normal birth weight)             | 0.010 | 3.55         | 1.36-9.29   |
| High birth weight (Reference: normal birth weight)            | 0.085 | 2.16         | 0.90-5.21   |
| Time of breastfeeding (0-6 months) (Reference: >12 months)    | 0.002 | 3.91         | 1.65-9.26   |
| Time of breastfeeding (7-12 months) (Reference: >12 months)   | 0.060 | 0.66         | 0.42-1.02   |
| Time of formula feeding (0-6 months) (Reference: >12 months)  | 1.000 | 0.000        | 0.000       |
| Time of formula feeding (7-12 months) (Reference: >12 months) | 1.000 | 0.000        | 0.000       |

OR: odds ratio; CI: confidence interval

more than 200 compounds in it. Most of the breast milk is water (88%), and other elements are dispersed.<sup>6</sup> Breast milk can protect babies against infections and allergies, with compounds with antimicrobial activity such as immunoglobulins, T and B lymphocytes, macrophages, granulocytes, lysozyme, C3, and C4. Protection against infections with breast milk; it is the classical protection mediated by IgA, IgG, and IgM, or by the direct binding of microorganisms and viruses by some bioactive substances in breast milk, or by accelerating the maturation of the infant's immune system.<sup>7-9</sup> There are immunoglobulins such as IgG, IgM, IgD, and IgE, especially secretory IgA in breast milk. Plasma cells that produce IgA in the mother's intestinal and bronchial system produce antibodies against the microorganisms they encounter, and these antibodies pass to the baby through breast milk.<sup>7-9</sup> The major antibody in breast milk is secretory IgA, preventing viruses and bacteria from adhering to the mucosa. By binding the lactoferrin-free iron in breast milk, lysozyme also protects the baby against infections by acting on the bacterial cell wall. Cytokines, prolactin, ascorbic acid, alpha-tocopherol,  $\beta$ -carotene, antioxidants, and epithelial growth factor in breast milk provide the development of the infant's immune system and protect it from atopic diseases.

Adenoidectomy is one of the most commonly performed surgical procedures in childhood and is important in determining the indications for adenotonsillectomy. Indications for adenoidectomy include one or more of the following: history of nasal airway

obstruction with sleep disturbance for at least 3 months; four or more recurrent episodes of purulent rhinorrhea in the past 12 months in a child < 12 years of age (one episode must be documented by intranasal examination or diagnostic imaging); hyponasal speech; otitis media with effusion for > 3 months; dental malocclusion or orofacial growth disorder; cor pulmonale; pulmonary hypertension; cardiopulmonary complications such as right ventricular hypertrophy associated with upper airway obstruction; otitis media with effusion (age 4 years and older).

The two most common indications for tonsillectomy are sleep-disordered breathing and recurrent throat infection. Recurrent throat infection with a frequency of at least seven episodes in the past year, at least five episodes per year for 2 years, or at least three episodes per year for 3 years with documentation in the medical record for each episode of sore throat and one or more of the following: temperature > 38.3°C or 101°F, cervical adenopathy, tonsillar exudate, or positive test for group A beta hemolytic streptococcus. Additional indications for tonsillectomy include multiple antibiotic allergies/intolerance, periodic fever, aphthous stomatitis, pharyngitis, and adenitis, history of more than one peritonsillar abscess and suspected malignancy.

OSA syndrome is a common disease affecting 2-3% of the pediatric population. OSA is a common condition in which there are recurrent episodes of airflow interruption despite constant effort due to a mechanical obstruction anywhere from the nasopharynx to the larynx during sleep. According to the study by Lim and McKean, if OSA is not treated, it causes neurobehavioral and cardiovascular complications.<sup>10</sup> Apnea episodes lead to hypoxia and hypercapnia, stimulating an increase in sympathetic output that causes an increase in heart rate and blood pressure. This causes subcortical stimulation, which allows the individual to clear the airway obstruction by changing their body position. OSA is seen in adults and children, but the two groups usually have different etiologies.<sup>10</sup> Known risk factors for OSA in children are adenotonsillar hypertrophy, male gender, obesity, allergic rhinitis, premature birth, inadequate breastfeeding, rhinosinusitis, passive smoking, low socioeconomic status, African origin, family history of OSA, and craniofacial anomalies.<sup>10</sup> Considering that the most common cause of OSA in children is adenoid and tonsil hypertrophy; highlighted the importance of adenotonsillar hypertrophy formation mechanisms and risk factors. Factors such as passive smoking exposure, allergies, and intervening respiratory infections have all been recognized by

several epidemiological studies to be associated with temporary or permanent hypertrophy of lymphoid tissues in the upper respiratory tract of snoring children. The main problem in all these risk factors is inflammation in lymphoid tissues.

According to the study of Goldbart et al.<sup>11</sup>, in children exposed to respiratory syncytial virus (RSV) infection in the early period, lymphoid tissue proliferation occurs as a result of neuroimmune changes in the airway, and increased levels of nerve growth factor (NGF), neurokinin (NK1), and substance P (SP) are observed in adenotonsillar tissues. Together with mediators such as P, it causes the continuation of inflammation and hypertrophy as a result of hypoxia and reoxygenation.<sup>11</sup> It has been observed that NGF, NK1, and SP increase in the lymphoid tissues of the upper airways of children with sleep apnea.<sup>11</sup> However, adenotonsillar hypertrophy does not develop in every child with RSV infection.<sup>11</sup>

The pathophysiology of pediatric OSA is a complex interaction between neuromuscular compensation that can lead to airway collapse. Anatomical measurements of the airway lumen, soft tissue, and skeleton are important in the treatment of this disease. OSA is most common in children between the ages of 3 and 10 years because of significant lymphoid tissue enlargement around the airway during this time period. According to the study of Kang et al., OSA was found more in boys than girls. Although the exact mechanism of this has not been found, obesity, upper airway anatomy, breath control, and hormones can be counted among the causes.<sup>12</sup> In addition, an increase in soft palate cross-sectional area and an increase in airway volume were found in men compared to women. This study suggests that men's susceptibility to pharyngeal collapse is anatomically based, mainly as a result of increased soft palate size as well as increased sensitive airway length.<sup>13</sup> In our study, there were 166 (55.3%) girls and 134 (44.7%) boys in the control group, whereas 130 (43.3%) girls and 170 (56.7%) boys were found in the study group. Consistent to the previous studies, it was observed in our study that adenoidectomy, tonsillectomy, adenotonsillectomy, and ventilation tube application were performed more frequently in boys than in girls ( $p = 0.003$ ).

According to the study conducted by Joosten et al., the probability of developing OSA in children born prematurely and with low birth weight is 3-5 times higher than in normal children.<sup>14</sup> Facial asymmetry and elongated head shape are common features in preterm infants and may impair the size and growth of the upper airway, resulting in increased upper airway resistance.<sup>14</sup>

Premature or low birth weight children are more likely to be hospitalized for additional problems. Thus, their breast milk intake rates are lower compared to normal children, whereas infection rates are higher due to the immaturity of immunity. Compared to normal children, the effects of enlargement in lymphoid tissue in terms of OSA are more in premature or low birth weight children due to their anatomical structures. Excessive infections lead to enlargement of adenotonsillar tissues, which leads to sleep apnea, and thus, the rate of undergoing adenotonsillectomy is higher in premature or low birth weight children than in children born at normal term or with normal birth weight. In our study, out of 36 children with lower than normal birth weight, 7 (19.4%) were in the control group, and 29 (80.6%) were in the study group. Consistent with the results of previous related studies, children with low birth weight had more indications for surgery ( $p < 0.001$ ).

According to the study of Ponce-Garcia et al., breastfeeding has been suggested as a potential protective factor against childhood sleep apnea and snoring.<sup>15</sup> achieved by immunological mechanisms. The oropharyngeal muscle and palate development of the child may be altered by sucking. Mechanically, bottle feeding causes less oral motor stimulation because it delivers milk through simple tongue depression, eliminating the need for the active, complex sucking and jaw movements required during breastfeeding. Therefore, proper development and coordination of the oropharyngeal musculature, which is necessary for effective swallowing, is provided more effectively with breast sucking. Thus, oral and oronasal respiration is gained effectively. Immunologically, the immunoglobulins (especially IgA) provided by breast milk protect the baby from infection by respiratory viruses and bacteria, prevent potential inflammation, thereby reducing adenotonsillar hypertrophy.<sup>15</sup> Adenotonsillar lymphoid tissues are the primary proliferation point for respiratory viruses. In the long term, neuro-immune modulatory pathways are activated in adenotonsillar tissues and lead to proliferation in tissues.<sup>15</sup> According to the study of Ponce-Garcia et al., more adenotonsillar hypertrophy was observed in children who were breastfed for < 6 months and children who were fed with formula.<sup>15</sup> In our study, 8 (8%) of 100 children who were breastfed for 0-6 months were in the control group, and 92 (92%) were in the study group. 89 (60.1%) of 148 children who were breastfed for 7-12 months were in the control group, and 59 (39.9%) were in the study group. It was seen that 203 (57.7%) of 352 children who were breastfed for more than 12 months

were in the control group, and 149 (42.3%) were in the study group. Consistent with this study,<sup>15</sup> in our study, it was observed that adenoidectomy, tonsillectomy, adenotonsillectomy, and ventilation tube applications were performed more in children who were breastfed for < 6 months compared to children who were breastfed for more than 6 months ( $p < 0.001$ ). In our study, 8 (14.5%) of 55 (30.2%) children who received formula for 6 months or less were in the control group, 47 (85.5%) were in the study group, and 7 out of 71 (39%) children who received formula for 7-12 months. (9.9%) were in the control group, 64 (90.1%) in the study group, and 56 (100%) of the 56 (30.8%) children who received formula for more than 12 months were in the study group. Consistent with this study,<sup>15</sup> in our study, it was observed that more adenoidectomy, tonsillectomy, adenotonsillectomy and ventilation tube applications were performed in children who received formula for more than 6 months compared to children who received formula for < 6 months ( $p < 0.001$ ). We can say that we can contribute to the literature by increasing the duration of breastfeeding, reducing the feeding of formula foods, and reducing the rates of adenotonsillectomy.

Breastfeeding for 4-6 months increases the colonization of bifidobacteria and lactic acid bacteria and creates a strong intestinal microbiota with galactooligosaccharides in breast milk. A wide variety of galactooligosaccharides is found in breast milk and show bifidogenic effects in the infant gut.<sup>16</sup> There are differences in the microbial content of the intestinal flora between breastfed and formula-fed infants. Bifidobacteria and lactobacillus are found in both breast-fed and formula-fed infants, but *Clostridium difficile*, Bacteroides, Enterococci, and Enterobacteriaceae are more abundant in formula-fed infants, while Staphylococci are more abundant in breast-fed infants. Breastfed children have more diverse bacteria in their gut microbiome, and this diversity provides protection from allergic diseases.<sup>17</sup>

Adenotonsillar lymphoid tissues are located at the entrance of the airways and are the first contact points for inhalant allergens. Chronic and recurrent inflammatory events around the adenotonsillar tissues cause adenotonsillar hypertrophy. Allergy is among the most common inflammatory causes for the upper respiratory tract. Allergic diseases can initiate inflammatory processes affecting adenotonsillar tissues, and large numbers of IgE-positive plasma cells/mast cells can cause an increase in allergen-specific IgE and eosinophilic infiltration. As eosinophils are the primary effector cells in allergic diseases, they have often been

found to be increased in serum and related tissues. In the study of Yücel Ekici et al., it was found that children with allergic complaints who underwent adenotonsillectomy due to hypertrophy and/or recurrent infection had a significantly higher eosinophil count both in their tissues and in the serum.<sup>18</sup> Specific IgE produced in tissues may contribute to serum eosinophilia. Thus, it can be said that the allergic response is not limited to local inflammation, and it causes an increase in systemic inflammation too. In the study conducted by Nave et al., it was found that there are more IgE plasma cells in the adenotonsillar tissues and regional lymph nodes of atopic patients compared to non-atopic individuals.<sup>19</sup> In the study by Fokkens et al., when adenoidectomy tissues of allergic and non-allergic children were compared, eosinophils were found to be significantly higher in the allergic group than in the non-allergic group. In other words, this study revealed that eosinophils, which are involved at least in an allergic inflammation, increase in the adenotonsillar tissues of allergic children.<sup>20</sup> As it could be a local response in tissues, it can be detected in the skin test or serological tests as well. However, it is still unknown whether there is an increase in the frequency of tonsillopharyngeal infections in children with allergic diseases. In the study conducted by Griffin et al., no relationship was found between allergy and adenotonsillar disease.<sup>21</sup> In our study, 61 (30.3%) of 201 children with eosinophilia were in the control group, and 140 (69.7%) were in the study group. Compared to the children in the control group, the children in the study group had higher eosinophil counts in the complete blood count ( $p < 0.001$ ). This may support the view that children with allergic diseases may have more tonsillopharyngitis attacks or that inflammation in allergies may cause adenotonsillar hypertrophy. Adenotonsillar lymphoid tissues have immunological properties that may contribute to the inflammation seen in allergy, but more comprehensive studies are needed to explain their role in allergic inflammation. Transforming growth factor  $\beta$ , which is high in breast milk, reduces the possibility of developing allergic diseases in children.<sup>22,23</sup> Children who are breastfed are less likely to have allergic diseases than children fed with formula or cow's milk.<sup>22,23</sup>

Feeding the baby only with breast milk for the first 6 months is called natural feeding. In cases where it is not possible to give breast milk, the use of formula milk, which is produced from cow's milk and compared to breast milk, is called artificial nutrition. If the baby receives other milk besides breast milk, it is defined

as mixed feeding. In line with the recommendations of the World Health Organization, babies should be fed only with breast milk for the first 6 months. The most common type of nutrition in the first 6 months in our country is mixed nutrition. There is growing concern that the current practice of delaying the introduction of solid food until the baby is 6 months old may increase the risk of immune disorders such as eczema and allergic disease. Evidence suggests that proper intestinal colonization through continued breastfeeding can increase tolerance to foods as well as protection when complementary feeding is initiated.<sup>24</sup> New recommendations say that allergenic foods should be given between 4 and 6 months.<sup>25</sup> Prescott et al.'s study suggested that early administration of certain allergenic foods is safe and may create tolerance.<sup>26</sup> In our study, 259 (51.2%) of 506 children aged 0-6 months in the control group, 247 (48.8%) in the study group. It was observed that 41 (43.6%) of 94 children who switched to solid food for more than 6 months were in the control group, and 53 (56.4%) were in the study group. There was no significant relationship between the control and study groups in terms of switching to solid food earlier than 6 months or after 6 months ( $p = 0.178$ ). Further research is required to identify the microbial stimulus for normal development, to investigate the relevant mechanisms, and to confirm the role of microbiota in the prevention of allergic disease, chronic adenotonsillar infection, and adenotonsillar hypertrophy.

### **Limitations in our study**

Since our study was carried out during the Coronavirus Pandemic period, the small number of people participating in the study, not recording the allergic symptoms of the children participating in the study, paying attention only to eosinophilia in the evaluation of allergic parameters in the complete blood count (not checking Ig E), and not noting the birth weeks of the children participating in the study are among the limitations of the study.

### **Conclusions**

Adenotonsillectomy is one of the most common surgical operations in childhood. For this reason, operation indications, risk factors, and attempts to prevent surgery are important for public health.

Breast milk is a very important physiological nutrient source because it contains the nutrients necessary from the birth of the baby, various bioactive substances that provide protection against infections, and is protective

against chronic diseases in the long term. Breast milk ensures the formation of a strong microbiota in the child's intestines, ensures the development of the immune system, and protects it from allergic diseases.

When our cases were evaluated with a literature review in line with our plan, it was found that the patients who underwent adenoidectomy, tonsillectomy, and bilateral ventilation tube operations were mostly male, had a lower birth weight, had higher eosinophilia rates in complete blood counts, breastfed for less time, and formula-fed for longer. There are many variables that can play a role in recurrent upper respiratory tract infections and allergies. In our study, we found that breastfeeding is one of these variables. Based on our findings, breast milk protects the child from infections and allergies. Hence, we contribute to the literature in the favor of breastfeeding, stating that breastfeeding can reduce the number of surgical procedures due to allergies and recurrent adenotonsillar infection.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

**Protection of humans and animals.** The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

**Confidentiality, informed consent, and ethical approval.** The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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# Pre-operative differentiation of atypical parathyroid tumors and parathyroid adenomas: is it possible?

*¿Es posible diferenciar preoperatoriamente los tumores paratiroides atípicos de los adenomas paratiroides?*

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## Abstract

**Objectives:** This study aimed to determine whether atypical parathyroid tumors (APTs) can be differentiated from benign parathyroid adenomas (PAs) preoperatively and to compare their biochemical characteristics, post-operative complications, and long-term outcomes. **Methods:** A retrospective analysis was conducted on patients who underwent parathyroidectomy between 2010 and 2022. Fifty patients with APT and one hundred with PA (control group) were included. Demographic data, biochemical parameters, complications, and follow-up outcomes were compared. **Results:** Pre-operative serum calcium and parathyroid hormone (PTH) levels were significantly higher in APT patients. Receiver operating characteristic analysis identified  $\text{Ca} > 11.5 \text{ mg/dL}$  and  $\text{PTH} > 180 \text{ pg/mL}$  as thresholds for distinguishing APTs. Multivariate analysis confirmed these as independent predictors. APT patients had a higher rate of concurrent thyroid surgery and more frequent complications such as transient nerve injury and hungry bone syndrome. No significant difference was found in persistent disease or recurrence after an average follow-up of 4.8 years. **Conclusions:** Pre-operative Ca and PTH levels may help distinguish APTs from PAs. Patients with APT should be informed about the increased risk of complications and concurrent thyroid surgery, and appropriate preventive strategies should be considered.

**Keywords:** Atypical parathyroid tumor. Parathyroid adenoma. Calcium. Parathyroid hormone nerve paralysis. Hungry bone syndrome.

## Resumen

**Objetivos:** Determinar si los tumores paratiroides atípicos (TPA) pueden diferenciarse de los adenomas paratiroides (AP) en el periodo preoperatorio, y comparar sus características bioquímicas, complicaciones posoperatorias y evolución a largo plazo. **Métodos:** Se realizó un análisis retrospectivo de pacientes sometidos a paratiroidectomía entre 2010 y 2022. Se incluyeron 50 pacientes con TPA y 100 con AP como grupo control. Se compararon datos demográficos, parámetros bioquímicos, complicaciones quirúrgicas y resultados del seguimiento. **Resultados:** Los niveles preoperatorios de calcio sérico y hormona paratiroidea (PTH) fueron significativamente más elevados en los pacientes con TPA. El análisis ROC identificó calcio  $> 11.5 \text{ mg/dL}$  y  $\text{PTH} > 180 \text{ pg/mL}$  como puntos de corte útiles para distinguir los TPA. El análisis multivariado confirmó estos valores como predictores independientes. Los pacientes con TPA presentaron mayor frecuencia de cirugía tiroidea concomitante y complicaciones como lesión nerviosa transitoria y síndrome del hueso hambriento. No se observaron diferencias significativas en enfermedad persistente ni en recurrencia tras un seguimiento promedio de 4.8 años. **Conclusiones:** Los niveles

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0009-7411/© 2025 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

*elevados de calcio y PTH preoperatorios pueden contribuir al diagnóstico diferencial de TPA. Se debe informar a los pacientes sobre el mayor riesgo quirúrgico y considerar estrategias preventivas.*

**Palabras clave:** Tumor paratiroideo atípico. Adenoma paratiroideo. Calcio. Hormona paratiroidea. Parálisis nerviosa. Síndrome del hueso hambriento.

## Introduction

Parathyroid tumors are a relatively homogeneous group of neoplasms, affecting approximately 0.1-0.3% of the population. These tumors are primarily characterized by the dysregulation in the secretion of parathyroid hormone (PTH), resulting in primary hyperparathyroidism (PHPT).<sup>1</sup> Among patients with PHPT, around 10% present with parathyroid hyperplasia, 85% with a single parathyroid adenoma (PA), and 3% with multiple PAs, whereas fewer than 2% of cases involve atypical parathyroid tumors (APT) or parathyroid carcinomas (PC).<sup>2</sup>

APTs represent a distinct clinical entity, a state considered to be in between benign PAs and malignant PCs. These tumors exhibit atypical cytological and/or architectural characteristics but do not demonstrate definitive evidence of capsular, vascular, perineural, or adjacent tissue invasion, nor metastasis. Previously termed atypical PA, the nomenclature has been updated to APT in the 5<sup>th</sup> edition of the World Health Organization (WHO) classification of endocrine tumors.<sup>3</sup>

The classification of APTs has been controversial due to their ambiguous features, both clinically and histopathologically. However, in 2018, the American Joint Committee on Cancer added the “Tis” category to the staging of parathyroid cancers, defining “Tis” as an atypical parathyroid neoplasm with uncertain malignant potential.<sup>4</sup> Similarly, according to the 2022 WHO classification, APTs are categorized as neoplasms of uncertain malignant potential.

Symptoms and findings in APT patients include nephrolithiasis, fatigue, bone pain, brown tumors, and depression. Importantly, these findings are not specific to APTs.<sup>2</sup> Most APTs behave similarly to PAs and do not recur after surgical excision. However, recurrent disease and metastasis have been reported, particularly in cases with parafibromin (PFIB) (a tumor suppressor protein, PFIB) deficiency.<sup>5-8</sup> Therefore, management of APTs is recommended to consist solely of clinical and biochemical follow-up.<sup>3</sup>

The primary aim of this study was to identify distinct morphological and laboratory characteristics of APTs,

beyond histopathological findings, that differentiate them from PAs and to establish pre-operative markers suggestive of APT. The secondary aim was to compare the short- and long-term outcomes of these two parathyroid neoplasms.

## Methods

In this retrospective study, data were collected from patients who underwent surgery for PHPT at our hospital between January 2010 and December 2022. A total of 486 patients underwent surgery during this period. Of these, 77 patients were excluded due to chronic renal failure (n = 12), secondary or tertiary hyperparathyroidism (n = 9), familial syndromes, including MEN1 and MEN2A (n = 4), carcinoma (n = 6), and incomplete medical records (n = 46). Ultimately, 359 patients were diagnosed with PA, and 50 with APT. Fifty patients diagnosed with APT and one hundred patients with PA, who were treated during the same period, were randomly selected for inclusion in the study. To minimize selection bias, the 100 PA patients were selected from the 351 eligible cases using R statistical software. Each patient was assigned a unique identifier, and simple random sampling without replacement was performed with a fixed random seed to ensure reproducibility and maintain methodological rigor.

Demographic data (age, sex), date of surgery, date of the last evaluation (the most recent serum calcium [Ca] and PTH levels and/or neck imaging recorded in the medical files were considered as the date of the last evaluation), concurrent thyroid surgery was documented. Tumor localization, size, volume (parathyroid tumors were considered as ellipsoid objects, and the volume was calculated using the formula  $\frac{4}{3} \pi abc$  (where a, b, and c represent the radii)). Biochemical data included pre-operative serum calcium (Ca, mg/dL) and PTH (pg/mL) levels, which were obtained from the records. For the pre-operative values, the highest measurements within the month preceding surgery were considered. The reference ranges for Ca and PTH were 8.5-10.5 mg/dL and 15-60 pg/mL, respectively. Histopathological features observed in APTs

were documented. Microscopy findings in pathology reports were re-evaluated based on the 2022 WHO classification updates for parathyroid tumors and ranked according to their frequency.

Recurrent laryngeal nerve injury was defined as a known injury occurring during surgery, as documented in the operative report, and/or based on evidence of hypomobility or immobility observed upon post-operative clinical laryngoscopy. No improvement in nerve function within 6 months was considered as permanent nerve damage. The absence of a decrease in PTH and Ca levels in the post-operative period was considered as persistent disease. Disease recurrence was defined as the reappearance of hypercalcemia along with elevated serum PTH levels after a disease-free period (normocalcemia) of at least 6 months. Patients who, within the first seven post-operative days and in the presence of normal or elevated PTH levels, developed hypocalcemia symptoms (e.g., paresthesia or muscle spasms) requiring intravenous Ca supplementation, or exhibited a serum Ca concentration below 7.5 mg/dL, were considered to have hungry bone syndrome (HBS).

This study was approved by the Ethics Committee of Ankara Bilkent City Hospital (Approval number E2-23-3377).

### Statistical analysis

A power analysis was conducted to determine the required sample size for detecting a significant difference between PA and atypical parathyroid adenoma (APT) groups. The effect size was set at 0.50 (moderate effect), with an alpha level of 0.05 and a power of 80% ( $\beta = 0.20$ ). Due to the unequal sample allocation ( $n_2/n_1 = 0.5$ ), the required total sample size was adjusted accordingly. Using G\*Power 3.1, the estimated minimum sample size for an independent samples t-test with this allocation ratio was  $n_1 = 96$  (PA),  $n_2 = 48$  (APT), total = 132. For this reason, this study included 100 PA and 50 APT patients.

All statistical analyses were performed using R (version 4.4.1). Continuous variables were tested for normality using the Shapiro–Wilk test. Normally distributed data were presented as mean  $\pm$  standard deviation and compared using the independent samples t-test. Non-normally distributed data were expressed as median and interquartile range (IQR, 25–75<sup>th</sup> percentile) and compared using the Mann-Whitney U test. Categorical variables were presented as frequencies and percentages (%) and compared using the

Chi-square test or Fisher's exact test, as appropriate. A receiver operating characteristic (ROC) curve analysis was performed to determine the diagnostic performance of pre-operative calcium and PTH levels in distinguishing atypical parathyroid adenoma (APT) from PA. The area under the curve (AUC) was calculated, and optimal cutoff values were determined. Sensitivity, specificity, positive predictive value, and negative predictive value were reported. To identify independent predictors of APT, a multivariate logistic regression analysis was performed, including variables that were statistically significant in univariate analysis ( $p < 0.05$ ). Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). The goodness-of-fit of the final model was assessed using the Hosmer-Lemeshow test.

### Results

A total of 150 patients were included in the study, with 100 diagnosed with PA and 50 with APT. The mean age of patients with PA was significantly higher ( $56 \pm 13$  years) compared to those with APT ( $50 \pm 12$  years,  $p < 0.005$ ). The sex distribution did not differ significantly between the two groups ( $p = 0.899$ ).

The median lesion diameter was larger in APT cases (20 mm, IQR 15–27) compared to PA (17 mm, IQR 13–21), though this difference did not reach statistical significance ( $p = 0.054$ ). The median lesion volume was also higher in APT patients ( $996.5 \text{ mm}^3$ , IQR 563–2612) compared to PA ( $734.34 \text{ mm}^3$ , IQR 370.44–1382.3), but the difference was not statistically significant ( $p = 0.085$ ) as shown in table 1. The distribution of lesion localization differed significantly between groups ( $p < 0.05$ ). APT lesions were most frequently found in the left superior and right inferior positions, while PA lesions showed a more even distribution. Concomitant thyroid surgery was significantly more common in APT patients, with 42% undergoing lobectomy and 32% requiring total thyroidectomy, compared to 20% and 12%, respectively, in PA patients ( $p < 0.005$ ).

Preoperatively, APT patients exhibited significantly higher PTH and Ca levels compared to PA patients. The median pre-operative PTH level in APT cases was  $242.75 \text{ pg/dL}$  (IQR 185–407.5), significantly higher than in PA cases ( $166.3 \text{ pg/dL}$ , IQR 127.5–268.2;  $p < 0.001$ ). Similarly, pre-operative calcium levels were significantly elevated in APT patients ( $11.93 \text{ mg/dL}$ , IQR 11.33–12.2) compared to PA patients ( $11.03 \text{ mg/dL}$ , IQR 10.79–11.72;  $p < 0.001$ ). However,

**Table 1. Patients demographics, adenoma characteristics, and laboratory measurements**

| Variables                     | Parathyroid adenoma (n = 100) | Atypical parathyroid tumor (n = 50) | p       |
|-------------------------------|-------------------------------|-------------------------------------|---------|
| Age*                          | 56 ± 13                       | 50 ± 12                             | < 0.005 |
| Sex†                          | 29 (29)                       | 15 (30)                             | 0.899   |
| Median lesion diameter (mm)‡  | 17 (13-21)                    | 20 (15-27)                          | 0.054   |
| Volume (mm³)‡                 | 734.34 (370.44-1382.3)        | 996.5 (563-2612)                    | 0.085   |
| Localization†                 |                               |                                     |         |
| Left superior                 | 9 (9)                         | 10 (20)                             | < 0.05  |
| Left inferior                 | 45 (45)                       | 12 (24)                             |         |
| Right inferior                | 34 (45)                       | 20 (40)                             |         |
| Right superior                | 12 (12)                       | 8 (16)                              |         |
| Concurrent thyroid surgery†   |                               |                                     |         |
| None                          | 68 (68)                       | 21 (42)                             | < 0.005 |
| Lobectomy                     | 12 (12)                       | 16 (32)                             |         |
| Thyroidectomy                 | 20 (20)                       | 13 (26)                             |         |
| Pre-operative Pth (pg/dL)‡    | 166.3 (127.5-268.2)           | 242.75 (185-407.5)                  | < 0.001 |
| Pre-operative Ca (mg/dL)‡     | 11.03 (10.79-11.72)           | 11.93 (11.33-12.2)                  | < 0.001 |
| Post-operative PTH (pg/dL)‡   | 23 (13-36)                    | 30.15 (12.52-52.10)                 | 0.369   |
| Post-operative Ca (mg/dL)‡    | 9 (8.6-9.39)                  | 8.95 (8.51-9.32)                    | 0.354   |
| Pth > 180 pg/mL‡              | 42 (42)                       | 38 (76)                             | < 0.001 |
| Ca > 11.5 mg/dL‡              | 31 (31)                       | 35 (70)                             | < 0.001 |
| Last PTH measurement (pg/dL)‡ | 44.85 (35.20-54.81)           | 44.35 (34.9-56.3)                   | 0.897   |
| Last Ca measurement (mg/dL)‡  | 9.50 (8.44-9.52)              | 9.40 (8.90-9.62)                    | 0.444   |

\*Values presented as the mean ± standard deviation.

†Values presented as the number of patients (percentage).

‡Values presented as the median days (25-75<sup>th</sup> percentile).

post-operative PTH and Ca levels were not significantly different between the groups ( $p = 0.369$  and  $p = 0.354$ , respectively).

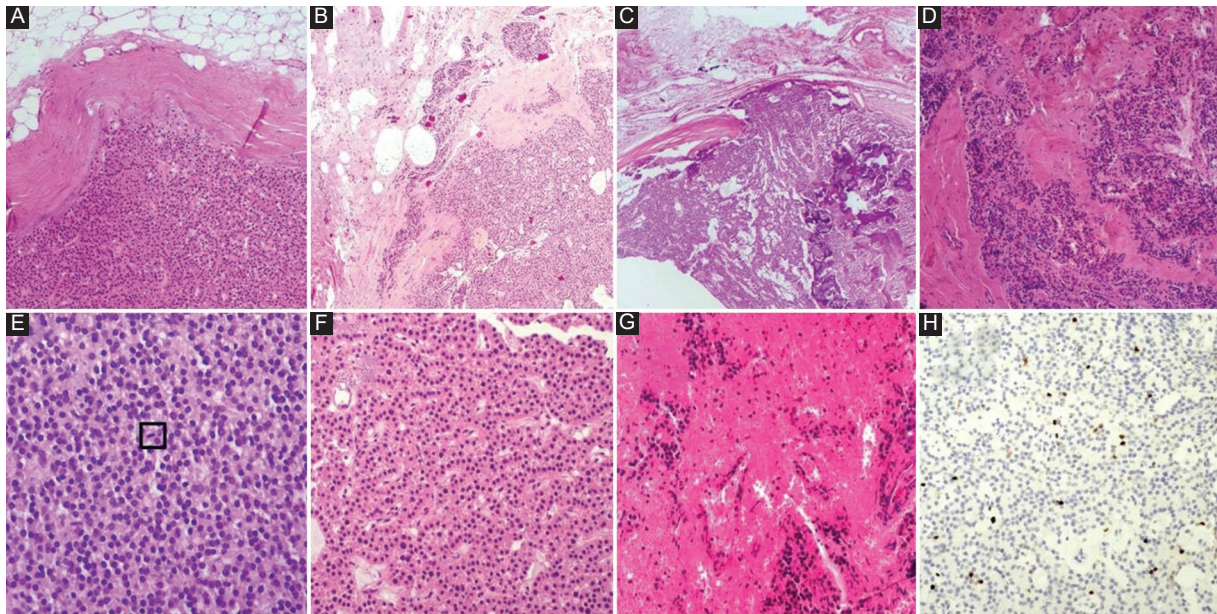
Post-operative complications were more frequent in APT patients. Temporary recurrent nerve paralysis occurred in 16% of APT cases versus 6% of PA cases ( $p < 0.05$ ). The incidence of “hungry bone syndrome” was also significantly higher in APT patients (16% vs. 3%,  $p < 0.005$ ). Permanent recurrent nerve paralysis, post-operative disease persistence, and recurrence rates did not significantly differ between groups as shown in table 2.

Table 3 demonstrates the frequency of histopathological features observed in APT cases. Among APT cases, fibrotic bands were the most frequently observed histopathological feature (84%), followed by tumor cells in the capsule (40%) and atypical mitosis (36%). Trabecular growth was present in 28% of cases, while adhesion and Ki-67 proliferation index > 5% were each observed in 18% of cases. Increased

mitotic activity (> 5/10 mm<sup>2</sup>) and coagulative necrosis were the least common feature (4%) (Fig. 1).

Table 4 provides the details of the ROC curve analysis, and figures 2 and 3 illustrate the ROC curves for pre-operative PTH and Ca, respectively. ROC analysis was performed to determine the optimal cutoff values for distinguishing APT from PA. The AUC for calcium was 0.751 (95% CI: 0.672-0.830,  $p < 0.001$ ), with an optimal cutoff of 11.5 mg/dL, yielding a sensitivity of 70% and specificity of 69%. The AUC for PTH was 0.691 (95% CI: 0.607-0.775,  $p < 0.001$ ), with an optimal cutoff of 180 pg/dL, demonstrating a sensitivity of 76% and specificity of 58%. According to these results, A significantly higher proportion of APT patients had PTH levels exceeding 180 pg/mL (76% vs. 42%,  $p < 0.001$ ) and calcium levels > 11.5 mg/dL (70% vs. 31%,  $p < 0.001$ ).

Multivariate logistic regression analysis identified calcium > 11.5 mg/dL as an independent predictor of APT (OR: 3.571, 95% CI: 1.604-7.950,  $p < 0.005$ ),



**Figure 1.** Histological features of atypical parathyroid tumor. Histological features of atypical parathyroid tumor. **A:** solid growth pattern formed by oncocytic cells and the thick fibrous capsule that develops it ( $\times 100$  hematoxylin and eosin [H&E]). **B and C:** extension into the capsule that does not completely exceed the characteristics of the chief cell ( $\times 40$  H&E). **D:** band-like fibrosis within the tumor ( $\times 100$  H&E). **E:** increased mitotic figure, in square ( $\times 400$  H&E). **F:** trabecular growth pattern and pleomorphism ( $\times 200$  H&E). **G:** coagulative necrosis within the tumor ( $\times 200$  H&E). **H:** growth staining in Ki-67 immunohistochemical test ( $\times 200$ ).

**Table 2.** Post-operative complications and follow-up results

| Complications                                    | Parathyroid adenoma (n = 100) | Atypical parathyroid tumor (n = 50) | p       |
|--------------------------------------------------|-------------------------------|-------------------------------------|---------|
| Temporary recurrent nerve paralysis <sup>†</sup> | 6 (6)                         | 8 (16)                              | < 0.05  |
| Permanent recurrent nerve paralysis <sup>†</sup> | 1 (1)                         | 0 (0)                               | 0.478   |
| Hungry bone syndrome <sup>†</sup>                | 3 (3)                         | 8 (16)                              | < 0.005 |
| Temporary hypoparathyroidy <sup>†</sup>          | 5 (5)                         | 4 (8)                               | 0.466   |
| Permanent hypoparathyroidy <sup>†</sup>          | 1 (1)                         | 1 (1)                               | 0.615   |
| Persistent disease                               | 3                             | 2                                   |         |
| Recurrence disease                               | 0                             | 0                                   |         |

\*Values presented as the mean  $\pm$  standard deviation.

<sup>†</sup>Values presented as the number of patients (percentage).

along with PTH > 180 pg/dL (OR: 1.127, 95% CI: 1.127-6.069,  $p < 0.05$ ). Tumor volume did not show a significant association ( $p = 0.886$ ). Table 5 presents the results of the multivariate analysis.

**Table 3.** Histopathological features of atypical parathyroid tumors

| Histopathological features                           | Frequency n (%) |
|------------------------------------------------------|-----------------|
| Band-like fibrosis                                   | 42 (84)         |
| Tumor cells in capsule                               | 20 (40)         |
| Atypical mitotic figures                             | 18 (36)         |
| Trabecular growth                                    | 14 (28)         |
| Adherence to adjacent structures                     | 9 (18)          |
| Ki-67 labeling index > 5%                            | 9 (18)          |
| Increased mitotic activity (> 5/10 mm <sup>2</sup> ) | 2 (4)           |
| Coagulative necrosis                                 | 2 (4)           |

## Discussion

In this study, our primary aim was to identify distinct morphological and laboratory characteristics of APTs, beyond histopathological findings, that differentiate them from PAs and to establish pre-operative markers suggestive of APT. Our secondary aim was to compare the post-operative complications and long-term follow-up outcomes of these two parathyroid neoplasms.

**Table 4. Areas under curve for biochemical parameters for distinguishing PA from APT**

| Variables | AUC   | 95% CI      | p       | Cut-off | Sensitivity | Specificity | PPV  | NPV  |
|-----------|-------|-------------|---------|---------|-------------|-------------|------|------|
| Ca        | 0.751 | 0.672-0.830 | < 0.001 | > 11.48 | 0.70        | 0.69        | 0.53 | 0.82 |
| PTH       | 0.691 | 0.607-0.775 | < 0.001 | > 182   | 0.76        | 0.58        | 0.48 | 0.83 |

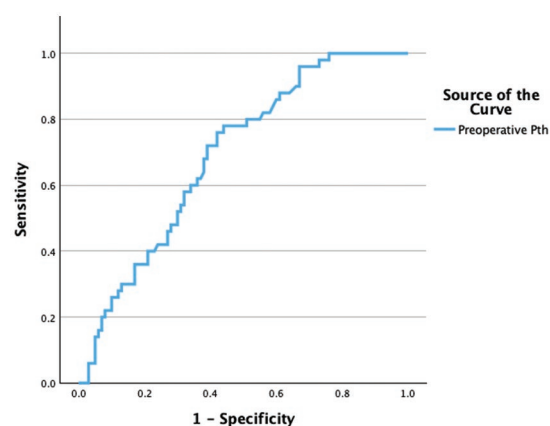
AUC: area under the curve; CI: confidence interval; PA: parathyroid adenoma; APT: atypical parathyroid adenoma; PPV: positive predictive value; NPV: negative predictive value; PTH: parathyroid hormone.

**Table 5. Multivariate analysis of variables independently associated with the presence of APTs**

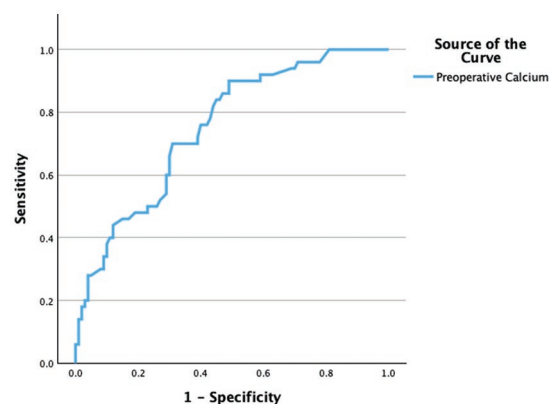
| Variables       | Odds ratio | 95% CI |       | Wald  | p       |
|-----------------|------------|--------|-------|-------|---------|
|                 |            | Lower  | Upper |       |         |
| Ca > 11.5 mg/dL | 3.571      | 1.604  | 7.950 | 9.716 | < 0.005 |
| Pth > 180 pg/dL | 1.127      | 1.127  | 6.069 | 5.007 | < 0.05  |
| Volume          | 1.000      | -      | -     | 0.021 | 0.886   |

Consistent with the literature,<sup>9,10</sup> no significant difference in gender distribution was observed between patients with APT and PA. However, both APTs and PAs were more frequently diagnosed in females. Although some previous studies suggest that APTs and PAs typically occur at similar ages,<sup>9,11</sup> the present study found that APTs manifested at a younger age (median age: 50 ± 12) than PAs. Indeed, Chen et al. evaluated 79 APT patients and reported that APTs were diagnosed at a younger age (median age: 46.9 ± 17.1) than PAs, attributing this to possible germline mutations.<sup>12</sup>

Many studies have compared sizes of parathyroid neoplasms. Although Marini et al. found no significant size difference between atypical tumors and carcinomas,<sup>13</sup> it is generally accepted that PCs are larger than other neoplasms.<sup>12,14-16</sup> Size comparisons in the literature primarily focus on PCs versus APTs, and few studies include PAs in such analyses. One example is the study by Chen et al., which evaluated characteristics of PAs, APTs, and PCs together. They reported significant differences in size among the groups, with APTs occupying an intermediate position between PAs and PCs. In the present study, the median diameter was 17 mm (13-21) for PAs and 20 mm (15-27) for APTs, showing borderline significance ( $p = 0.054$ ). Considering that a single diameter measurement may not always accurately reflect lesion volume, we calculated lesion volumes, unlike prior studies. APTs were found to be larger in volume



**Figure 2.** Receiver operating characteristic curve analysis for pre-operative parathyroid hormone (area under the curve: 0.691, sensitivity: 76%. Specificity: 58%, positive predictive value: 48%, negative predictive value: 83%).



**Figure 3.** Receiver operating characteristic curve analysis for pre-operative calcium (area under the curve: 0.751, Sensitivity: 70%, Specificity: 69%, positive predictive value: 53%, negative predictive value: 82%).

compared to PAs (median: 996.5 mm<sup>3</sup> vs. 734.34 mm<sup>3</sup>), but the difference was not statistically significant ( $p = 0.085$ ). Consistent with the literature, these results suggest that APTs tend to be larger. However, no definitive cutoff values for size or volume could be

established for APTs, indicating that pre-operative differentiation of APTs from PAs based on size alone remains challenging.

PHPT often presents with mild hypercalcemia (serum Ca < 11 mg/dL).<sup>17</sup> Studies comparing Ca and PTH levels in patients with PA, APT, and PC have shown that the increase in Ca and PTH levels in patients with APT is not as high as that in patients with PC.<sup>18-20</sup> Cakir et al. and McCoy et al. compared APTs with PAs and PCs and found significant differences among these three patient groups in terms of PTH and Ca levels.<sup>10,18</sup> Cakir et al. grouped APT and PC under “aggressive tumors” and compared them with PA. Their analysis identified a cutoff value for Ca (12.45 mg/dL), but not for PTH levels. In the present study, significant differences in Ca and PTH levels were observed between patients with APT and those with PA, with cutoff values established as 11.50 mg/dL and 180 pg/mL, respectively. We attribute the higher Ca cutoff reported by Cakir et al. to their inclusion of patients with PC, rendering their cutoff of 12.45 mg/dL less applicable for patients with APTs. To the best of our knowledge, the present study is the first to report cutoff values for distinguishing APTs from PAs.

Data on the most common gland from which PAs originate, and therefore, the most common localization of PAs, are very limited. In the present study, a significant difference was observed between the anatomical localization of APTs and PAs. APTs were predominantly located in the left superior and right inferior poles, whereas PAs showed a homogeneous distribution.

The coexistence of thyroid disease with PHPT has been reported in 22-70% of cases since the 1950s.<sup>21-23</sup> In the present study, concurrent thyroid surgery (lobectomy or total thyroidectomy) was performed in 58% of APT patients versus 32% of PA patients. The difference between these rates was statistically significant. This finding is consistent with the result reported by Chen et al.<sup>12</sup> We hypothesize that the higher rate of thyroid surgery in APT patients may be due to concomitant thyroid pathology as well as tumor adherence to thyroid tissue. Therefore, in patients with a strong suspicion of APT, the potential need for concurrent thyroidectomy should be considered pre-operatively, and patients should be informed accordingly.

In the present study, patients were evaluated postoperatively for transient/permanent nerve injury, transient/permanent hypoparathyroidism, and HBS. No studies have compared nerve injury rates between APT and PA patients thus far. However, Gurrado et al. reported transient nerve injury in 3.16% and permanent nerve

injury in 1.4% of APT patients.<sup>15</sup> Tang et al. documented a nerve injury rate of 14% in APT patients.<sup>24</sup> In the present study, transient nerve injury occurred in 16% of APT patients, with no permanent nerve injury observed. In PA patients, these rates were 6% and 1%, respectively. Transient nerve injury was significantly more common in APT patients compared to that in PA patients. We hypothesize that this higher risk in APT patients may stem from tumor adherence to nerves/adjacent tissues or the higher frequency of concurrent thyroid surgery. Based on these findings, we suggest that intraoperative nerve monitoring and heightened surgical caution should be considered for patients with pre-operative Ca > 11.50 mg/dL and PTH > 180 pg/mL. Gurrado et al. reported transient hypoparathyroidism in 22.3% and permanent hypoparathyroidism in 4.1% of APT patients.<sup>15</sup> In the present study, these rates were 8% and 1%, respectively, with no significant difference compared to these rates in PA patients.

HBS is characterized by post-operative hypocalcemia, hypophosphatemia, and prolonged hypocalcemia.<sup>25</sup> It occurs in 12-25% of cases after parathyroidectomy.<sup>26</sup> Tang et al. observed HBS in 7% of APT patients in the post-operative period.<sup>24</sup> In the present study, these rates were 16% in APT patients and 3% in PA patients, and the difference was statistically significant. Based on these data, we recommend that patients with a strong suspicion of APT should be monitored more closely for the risk of HBS, and pre-operative initiation of calcitriol and oral calcium supplements should be considered to mitigate this risk.

In 2022, the WHO reclassified parathyroid tumors, defining the atypical APT diagnostic criteria as follows: cellular nests in a thickened connective tissue, tumor cells in the capsule, adherence to adjacent structures without frank invasion, band-like fibrosis, trabecular growth, increased mitotic activity (> 5/10 mm<sup>2</sup>), atypical mitotic figures, coagulative necrosis, PFIB loss, and a Ki-67 labeling index > 5%. APT cases were further stratified into PFIB-positive (PFIB+) and PFIB-negative (PFIB-) groups, with PFIB+ tumors classified as very low-risk and PFIB- as low-risk for recurrence.<sup>3</sup> In the present study, histopathological features of APT patients were reassessed against these criteria, confirming all diagnoses. Band-like fibrosis (84%) and tumor cells within the capsule (40%) were most common, while coagulative necrosis and increased mitotic activity (> 5/10 mm<sup>2</sup>) were rare (4%). Other histopathological features were detected at varying frequencies.

To date, there are no specifically established guidelines for the post-operative follow-up of patients with

APT. While some studies, despite the low risk of recurrence, recommend close follow-up of patients independent of immunohistochemical results based on their own experience,<sup>27,28</sup> other researchers advocate for close followup in patients with germline gene mutations and/or complete loss of PFIB expression.<sup>5,8,29</sup> Several studies did not report any recurrence during follow-up;<sup>11,18,24</sup> however, one study reported a recurrence rate of 5.3%.<sup>13</sup> In the present study, median follow-up time was 4.8 years. During this period, no recurrence was observed in either group. However, persistent disease necessitating a second operation was observed in three patients with PA and two patients with APT. In patients with persistent PA, the adenomas were not completely removed during the first operation. In APT patients, persistent disease was attributed to incomplete initial tumor resection or additional adenomas. Although no significant difference was detected between the two groups in terms of persistent disease and recurrence, we recommend closer follow-up for patients with atypical tumors compared to that for those with adenomas; this recommendation is due to the serious histopathological findings observed in the atypical tumor group.

## Conclusions

Pre-operative identification of APTs is critical. Ca > 11.50 mg/dL and PTH > 180 pg/mL values can be used to differentiate APTs from benign adenomas. Patients with these values should be provided with detailed pre-operative counseling regarding possible concomitant thyroid surgery, nerve injury, and HBS complications. No recurrence was observed in our follow-up, we recommend stricter and more vigilant monitoring for APTs compared to adenomas due to their concerning histopathological features.

## Limitation

The limitations of this study include its retrospective nature, which inevitably leads to data loss. Other limitations are that the surgical treatment and histopathological examination were not performed by the same physicians, and the cases could not be grouped according to PFIB status.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

**Protection of human subjects and animals.** The authors declare to have followed the ethical standards of the relevant experimentation committee, according to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

**Confidentiality, informed consent, and ethical approval.** The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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# Evaluation of dentists' knowledge and attitudes regarding ankyloglossia in children

## *Evaluación del nivel de conocimiento y de las actitudes de los dentistas sobre la anquiloglosia en niños*

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### Abstract

**Objective:** Ankyloglossia, known as tongue-tie, is a common congenital malformation that restricts the movement of the tongue. It is seen in 4.8% of newborns and is more prevalent in males compared to females. This study aims to evaluate the knowledge and attitudes of dentists in Turkey regarding ankyloglossia. **Methods:** Our survey was conducted online with dentists in Turkey who examine and treat patients. The data were analyzed using IBM Statistical Package for the Social Sciences V.21 software. Frequency distributions and percentages were examined, and relationships between nominal variables were assessed using the  $\chi^2$  test. A significance level of  $p < 0.05$  was accepted. **Results:** The results showed that 76.14% of the participants could recognize ankyloglossia in children, and 87.14% believed it to be a congenital anomaly. In addition, 91.49% of the participants thought that ankyloglossia negatively affects breastfeeding, and 98.34% believed that it could cause speech disorders. **Conclusions:** Our study emphasizes the importance of increasing awareness of ankyloglossia and the significance of early diagnosis and treatment.

**Keywords:** Ankyloglossia. Online survey study. Dentists' knowledge and attitudes. Congenital malformation.

### Resumen

**Objetivo:** La anquiloglosia, conocida como frenillo lingual, es una malformación congénita común que restringe el movimiento de la lengua. Se observa en el 4.8% de los recién nacidos y es más frecuente en los hombres que en las mujeres. El objetivo de este estudio es evaluar el conocimiento y las actitudes de los dentistas en Turquía con respecto a la anquiloglosia. **Métodos:** Se realizó una encuesta en línea a dentistas de Turquía que examinan y tratan a pacientes. Los datos se analizaron utilizando el software IBM SPSS V.21. Se examinaron las distribuciones de frecuencia y los porcentajes, y las relaciones entre variables nominales se evaluaron utilizando la prueba  $\chi^2$ . Se consideró como nivel de significancia  $p < 0.05$ . **Resultados:** El 76.14% de los participantes podían reconocer la anquiloglosia en los niños y el 87.14% creían que era una anomalía congénita. Además, el 91.49% de los participantes pensaba que la anquiloglosia afecta negativamente la lactancia materna y el 98.34% que podría causar trastornos del habla. **Conclusiones:** Este estudio enfatiza la importancia de aumentar la conciencia sobre la anquiloglosia y la importancia del diagnóstico y el tratamiento tempranos.

**Palabras clave:** Anquiloglosia. Estudio de encuesta en línea. Conocimientos y actitudes de los dentistas. Malformación congénita.

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## Introduction

Ankyloglossia, also known as tongue-tie, is one of the most common congenital developmental malformations that restricts the mobility of the tongue.<sup>1,2</sup> Ankyloglossia has a prevalence of 4.8% in the newborn population and is three times more common in males than females (3:1). In the general population, its prevalence ranges from 4% to 10.7%, based on studies using different diagnostic criteria. The severity of ankyloglossia varies from mild cases, where tongue movement is minimally affected, to complete ankyloglossia, where the tongue is fully attached to the floor of the mouth.<sup>3-5</sup>

Ankyloglossia can occur sporadically or be familial and can be part of rare syndromes such as Moebius syndrome, Beckwith-Wiedemann syndrome, orofaciocigital syndrome, and X-linked cleft palate. Both isolated and syndrome-associated cases of ankyloglossia are thought to have a genetic component.<sup>3,6</sup>

Classifications for ankyloglossia are based on various anatomical and functional criteria; however, there is no universally accepted classification yet. Key criteria for classification include the amount of tongue elevation and protrusion, breastfeeding, feeding, speech, and the development of dental arches.<sup>7</sup>

In the literature, views on the importance of ankyloglossia vary significantly.<sup>8</sup> Some experts argue that it is symptomatic and usually does not require intervention, while others believe that it can lead to various issues such as breastfeeding difficulties, speech disorders, and oral health problems.<sup>9,10</sup>

Based on these studies, ankyloglossia can cause a range of problems, including breastfeeding difficulties and associated poor weight gain, breast pain or mastitis in the mother, speech and feeding disorders, poor oral hygiene, localized gingival recession on the lingual surfaces of mandibular anterior teeth, sleep apnea, and peer bullying during childhood and adolescence.<sup>4,5,7,11</sup>

Therefore, early diagnosis of ankyloglossia forms the basis for surgical or psychological interventions aimed at improving the child's quality of life.<sup>5</sup>

Dentists play a vital role in the early detection and treatment of ankyloglossia, as they frequently encounter this condition during routine patient examinations. The knowledge level of dentists regarding ankyloglossia allows them to accurately assess patients, make correct diagnoses, and develop appropriate treatment plans. In addition, having current and comprehensive

knowledge and skills related to ankyloglossia enables dentists to treat patients with this condition through a multidisciplinary approach and helps patients achieve the best outcomes. This study aims to evaluate the knowledge levels and approaches of dentists regarding ankyloglossia through a survey, raise awareness, and contribute to the literature. The primary objective of the study is to assess dentists' knowledge and attitudes regarding the diagnosis and treatment methods of ankyloglossia, thereby evaluating current education and practice standards. This survey aims to identify knowledge gaps in the diagnosis and treatment processes of ankyloglossia among dentists and develop strategies to improve education and practice standards in this field.

## Methods

### *Study design and population*

Ethical approval was obtained from the Institutional Ethics Committee and Scientific Review Board of Iğdır University with the decision made at the meeting dated February 28, 2024. Informed consent was obtained online from all participants before the study. In this study, a cross-sectional survey titled "Evaluation Of Dentists' Knowledge And Attitudes Regarding Ankyloglossia In Children" consisting of questions proven to be reliable and valid in similar literature studies, was administered to dentists in Turkey who examine and treat patients.<sup>3,5</sup>

### *Inclusion and exclusion criteria*

Inclusion criteria of the study encompass randomly selected dentists who examine and treat patients in clinics. Exclusion criteria include dentists who do not actively treat patients and those who do not wish to participate in the study.

### *Sample size calculation*

This study is a cross-sectional survey conducted among 44,000 registered dentists nationwide. The online survey prepared on the Google Forms platform was sent to participants via Instagram, email, and WhatsApp at the beginning of 2024. Sample size calculation was performed using OpenEpi's sample size calculator (<https://www.openepi.com/SampleSize/SSPropor.htm>). Using a 95% confidence interval and

a 5% margin of error, the minimum sample size was calculated as 381. To compensate for potential participant dropouts, the sample size was increased by 20%, resulting in a final sample size of 457, which was reached using a simple random sampling method.

### **Data collection**

The questionnaire was developed by the authors by reviewing relevant published literature and international guidelines. The survey was designed to cover key aspects of dentists' knowledge and practices regarding ankyloglossia. The survey consists of three sections:

1. The first section, following informed consent, includes basic characteristics of the participants such as age, gender, and years of professional experience
2. The second section aims to measure dentists' knowledge about ankyloglossia and their awareness of its effects on patients
3. The third section includes questions evaluating dentists' attitudes and practices regarding clinical examination and treatment measures. The participation rate of dentists in the study was recorded as 100%.

### **Statistical analysis**

The data obtained in this study were analyzed using the licensed IBM Statistical Package for the Social Sciences V. 21 package program. Frequency distribution tables with counts and percentage values were examined for variables. The  $\chi^2$  test was applied to examine the relationships between groups of nominal variables. Fisher's Exact Test was used in 2x2 tables when the expected values in the cells did not have sufficient volume, and the Pearson  $\chi^2$  analysis was applied with the help of Monte Carlo Simulation in RxC tables. (\* $\chi^2$  analysis was performed with the help of Monte Carlo Simulation because 20% of the expected values in the cells were < 5.) A significance level of 0.05 was used when interpreting the results; a significant relationship was indicated if  $p < 0.05$ , while no significant relationship was indicated if  $p > 0.05$ .

### **Results**

Among the participants, 70.75% were female, and 29.25% were male. The age distribution of the

participants was as follows: 49.59% were aged 23-30, 37.55% were aged 31-40, 10.37% were aged 41-50, and 2.49% were aged 51 and above. Regarding professional experience, 42.32% had 1-5 years, 30.08% had 6-10 years, 14.11% had 11-15 years, and 13.49% had 15 years or more in the profession.

About 76.14% ( $n = 367$ ) of the participants stated that they could recognize ankyloglossia in a child patient who visits their clinic. 87.14% ( $n = 420$ ) believed that ankyloglossia is a congenital anomaly, and 91.49% ( $n = 441$ ) believed that it could negatively affect breastfeeding. 98.34% ( $n = 474$ ) thought that ankyloglossia could cause speech disorders, and 52.7% ( $n = 254$ ) were aware of the treatment options. The proportion of those who had previously encountered a patient with ankyloglossia was 51.87% ( $n = 250$ ), and 25.93% ( $n = 125$ ) routinely checked for ankyloglossia during examinations. 82.16% ( $n = 396$ ) thought that ankyloglossia should be treated at an early age, 88.17% ( $n = 425$ ) believed that untreated patients might experience psychological problems, and 87.76% ( $n = 423$ ) believed that it could cause feeding difficulties. 63.28% ( $n = 305$ ) strongly agreed that anomalies should be routinely checked during clinical oral examinations (Table 1).

A statistically significant relationship was found between gender and encountering a patient with ankyloglossia during a clinical examination ( $p < 0.05$ ). 53.37% of women and 48.23% of men had previously encountered a patient with ankyloglossia during a clinical examination, while 44.57% of women and 45.39% of men had not.

A statistically significant relationship was also found between gender and routinely checking for anomalies during clinical oral examinations ( $p < 0.05$ ). 67.16% of women and 53.9% of men routinely checked for anomalies during clinical oral examinations, while 1.42% of men did not.

There was no statistically significant relationship between gender and other questions related to knowledge about ankyloglossia and its effects on patients ( $p > 0.05$ ).

A statistically significant relationship was found between age group and the belief that ankyloglossia negatively affects breastfeeding ( $p < 0.05$ ). 91.63% of those aged 23-30, 93.92% of those aged 31-40, 86% of those aged 41-50, and 75% of those aged 51 and above believed that ankyloglossia negatively affects breastfeeding, while 4.6% of those aged 23-30, 3.31% of those aged 31-40, 4% of those aged 41-50, and 16.67% of those aged 51 and above did not.

**Table 1. Frequency distribution of questions regarding knowledge of ankyloglossia and its effects on patients**

| Question                                                                                  | Yes | %     | No  | %     | Undecided | %     | Total | %   |
|-------------------------------------------------------------------------------------------|-----|-------|-----|-------|-----------|-------|-------|-----|
| 1. Do you recognize if a child patient has ankyloglossia when they visit your clinic?     | 367 | 76.14 | 43  | 8.92  | 72        | 14.94 | 482   | 100 |
| 2. Do you think ankyloglossia is a congenital anomaly?                                    | 420 | 87.14 | 16  | 3.32  | 46        | 9.54  | 482   | 100 |
| 3. Do you think ankyloglossia can negatively affect breastfeeding?                        | 441 | 91.49 | 19  | 3.94  | 22        | 4.56  | 482   | 100 |
| 4. Do you think ankyloglossia can cause speech disorders?                                 | 474 | 98.34 | 0   | 0     | 8         | 1.66  | 482   | 100 |
| 5. Are you aware of the treatment options for ankyloglossia?                              | 254 | 52.7  | 115 | 23.86 | 113       | 23.44 | 482   | 100 |
| 6. Have you ever encountered a patient with ankyloglossia during a clinical examination?  | 250 | 51.87 | 216 | 44.81 | 16        | 3.32  | 482   | 100 |
| 7. Do you routinely check for ankyloglossia during clinical oral examinations?            | 125 | 25.93 | 308 | 63.9  | 49        | 10.17 | 482   | 100 |
| 8. Do you think ankyloglossia should be treated at an early age?                          | 396 | 82.16 | 16  | 3.32  | 70        | 14.52 | 482   | 100 |
| 9. Do you think untreated ankyloglossia patients might experience psychological problems? | 425 | 88.17 | 10  | 2.07  | 47        | 9.75  | 482   | 100 |
| 10. Do you think ankyloglossia can cause feeding difficulties?                            | 423 | 87.76 | 14  | 2.9   | 45        | 9.34  | 482   | 100 |
| 11. Anomalies should be routinely checked during clinical oral examinations.              |     |       |     |       |           |       |       |     |
| Strongly agree                                                                            |     |       | 305 | 63.28 |           |       |       |     |
| Agree                                                                                     |     |       | 161 | 33.4  |           |       |       |     |
| Undecided                                                                                 |     |       | 14  | 2.9   |           |       |       |     |
| Disagree                                                                                  |     |       | 2   | 0.41  |           |       |       |     |
| Total                                                                                     |     |       | 482 | 100   |           |       |       |     |

A statistically significant relationship was found between age group and knowledge of treatment options for ankyloglossia ( $p < 0.05$ ). 41% of those aged 23-30, 62.98% of those aged 31-40, 68% of those aged 41-50, and 66.67% of those aged 51 and above were aware of the treatment options, while 28.87% of those aged 23-30, 20.99% of those aged 31-40, 14% of those aged 41-50, and 8.33% of those aged 51 and above were not.

A statistically significant relationship was found between age group and encountering a patient with ankyloglossia during a clinical examination ( $p < 0.05$ ). 40.59% of those aged 23-30, 61.33% of those aged 31-40, 66% of those aged 41-50, and 75% of those aged 51 and above had encountered a patient with ankyloglossia during a clinical examination, while 54.39% of those aged 23-30, 37.57% of those aged 31-40, 32% of those aged 41-50, and 16.67% of those aged 51 and above had not.

A statistically significant relationship was found between age group and routinely checking for ankyloglossia during clinical oral examinations ( $p < 0.05$ ). 15.9% of those aged 23-30, 33.7% of those aged

31-40, 40% of those aged 41-50, and 50% of those aged 51 and above routinely checked for ankyloglossia during clinical oral examinations, while 71.97% of those aged 23-30, 56.91% of those aged 31-40, 56% of those aged 41-50, and 41.67% of those aged 51 and above did not.

A statistically significant relationship was found between age group and the belief that ankyloglossia causes feeding difficulties ( $p < 0.05$ ). 90.79% of those aged 23-30, 87.85% of those aged 31-40, 74% of those aged 41-50, and 83.33% of those aged 51 and above believed that ankyloglossia causes feeding difficulties, while 2.09% of those aged 23-30, 2.21% of those aged 31-40, 8% of those aged 41-50, and 8.33% of those aged 51 and above did not.

There was no statistically significant relationship between age group and other questions related to knowledge about ankyloglossia and its effects on patients ( $p > 0.05$ ).

A statistically significant relationship was found between years of professional experience and the ability to recognize ankyloglossia in a child patient visiting the clinic ( $p < 0.05$ ). 69.61% of those with

1-5 years, 75.17% of those with 6-10 years, 92.65% of those with 11-15 years, and 81.54% of those with 15 years or more professional experience could recognize ankyloglossia in a child patient, while 10.29% of those with 1-5 years, 8.97% of those with 6-10 years, 2.94% of those with 11-15 years, and 10.77% of those with 15 years or more professional experience could not.

A statistically significant relationship was found between years of professional experience and knowledge of treatment options for ankyloglossia ( $p < 0.05$ ). 38.24% of those with 1-5 years, 55.17% of those with 6-10 years, 77.94% of those with 11-15 years, and 66.15% of those with 15 years or more professional experience knew the treatment options, while 31.37% of those with 1-5 years, 24.83% of those with 6-10 years, 13.24% of those with 11-15 years, and 9.23% of those with 15 years or more professional experience did not.

A statistically significant relationship was found between years of professional experience and encountering a patient with ankyloglossia during a clinical examination ( $p < 0.05$ ). 37.25% of those with 1-5 years, 51.72% of those with 6-10 years, 75% of those with 11-15 years, and 73.85% of those with 15 years or more professional experience had encountered a patient with ankyloglossia during a clinical examination, while 58.33% of those with 1-5 years, 44.83% of those with 6-10 years, 25% of those with 11-15 years, and 23.08% of those with 15 years or more professional experience had not.

A statistically significant relationship was found between years of professional experience and routinely checking for ankyloglossia during clinical oral examinations ( $p < 0.05$ ). 15.2% of those with 1-5 years, 26.21% of those with 6-10 years, 38.24% of those with 11-15 years, and 46.15% of those with 15 years or more professional experience routinely checked for ankyloglossia during clinical oral examinations, while 71.08% of those with 1-5 years, 64.83% of those with 6-10 years, 54.41% of those with 11-15 years, and 49.23% of those with 15 years or more professional experience did not.

There was no statistically significant relationship between years of professional experience and other questions related to knowledge about ankyloglossia and its effects on patients ( $p > 0.05$ ).

## Discussion

In the literature, tongue-tie is a controversial issue due to its potential effects on children. Dentists,

pediatricians, otolaryngologists, and lactation consultants play a crucial role in the diagnosis and clinical management of tongue-tie. Dentists should have high knowledge and awareness of this condition as they frequently encounter anatomical disorders such as ankyloglossia. Ankyloglossia is often associated with congenital syndromes such as orofaciogigital syndrome, Simpson-Golabi-Behmel syndrome, Opitz syndrome, Beckwith-Wiedemann syndrome, and X-linked cleft palate syndrome. In a study by Oviya et al., 96% of participants stated that they had knowledge of ankyloglossia, and 85% were aware that ankyloglossia is a congenital condition.<sup>1,5</sup> In our study, 76.14% of participants reported knowing ankyloglossia, and 87.14% were aware that it is a congenital anomaly.

Ankyloglossia can cause nipple pain due to the baby's inability to latch properly, leading to poor milk flow and nipple sores, which can result in the termination of breastfeeding, the baby rejecting the breast, and a switch to bottle feeding.<sup>12</sup> In a study by Oviya et al., 87% of participants reported that ankyloglossia negatively affects breastfeeding.<sup>5</sup> Conversely, another study asked participants (excluding speech pathologists) about the relationship between tongue-tie and sucking or feeding dysfunction in infants. While 90% of pediatricians and 70% of ENT specialists indicated that ankyloglossia rarely causes feeding difficulties, 69% of lactation consultants reported that tongue-tie often or always leads to feeding difficulties, and 30% said it sometimes causes these issues.<sup>9</sup> In our study, 91.49% of dentists reported knowing that ankyloglossia negatively affects breastfeeding.

Research by Messner and Lalakea evaluated the effects of ankyloglossia on speech problems among physicians and speech pathologists. While 60% of ENT specialists reported that tongue-tie sometimes causes speech disorders, only 23% of pediatricians shared this view. The same study indicated that speech pathologists had varying opinions on the impact of tongue-tie on speech.<sup>9</sup> In a study by Oviya et al., 85% of participants stated that ankyloglossia negatively affects children's speech.<sup>5</sup> In our study, 98.34% of dentists reported that ankyloglossia negatively affects children's speech.

A study by Jin et al. indicated variability in ankyloglossia treatment among healthcare professionals, attributed to uncertain treatment outcomes and increased complications, particularly damage to anatomical structures. Untreated children may face breastfeeding, speech difficulties, and dental development issues, necessitating orthodontic intervention.<sup>13</sup>

In the study by Oviya et al., 80% of participants reported knowing the treatment methods for ankyloglossia.<sup>5</sup> In our study, 52.7% of dentists reported knowing the treatment options.

Research by Messner and Lalakea found that over 80% of physicians surveyed considered ankyloglossia rare, with fewer than 10 cases seen annually in their practices. 77% of lactation consultants indicated that ankyloglossia rarely occurs and significantly contributes to breastfeeding problems in only 1-5% of cases. Similarly, 70% of speech pathologists reported rarely seeing symptomatic ankyloglossia in their practices.<sup>9</sup> In the study by Oviya et al., 57% of participants had encountered patients with ankyloglossia.<sup>5</sup> Previous studies reported an incidence of encountering patients with ankyloglossia ranging from 0.02% to 5%.<sup>7</sup> In our study, 51.87% of dentists reported having encountered a patient with ankyloglossia during clinical examinations.

In the study by Oviya et al., 70% of participants reported routinely checking for ankyloglossia in every patient, and 85% acknowledged that all anomalies should be routinely checked during examinations.<sup>5</sup> In our study, only 25.93% of dentists reported routinely checking for ankyloglossia during clinical oral examinations.

Research by Messner and Lalakea indicated significant improvement in breastfeeding among children who underwent surgical intervention for ankyloglossia.<sup>9</sup> A study by Walls et al.,<sup>14</sup> reported improvements in speech outcomes and oral motor activities in children who underwent frenectomy as newborns compared to those who did not.<sup>14</sup> In the study by Oviya et al., 85% of participants stated that ankyloglossia should be treated at an early age.<sup>5</sup> In our study, 82.16% of dentists believed that ankyloglossia should be treated at an early age.

In a case study by Baxter et al.,<sup>15</sup> a child with ankyloglossia was reported to be shy and insecure in communication, selectively preferred foods, and gagged when eating certain foods. In the study by Oviya et al., 79% of participants reported that this anomaly causes psychological problems in children.<sup>5</sup> In our study, 88.17% of dentists believed that untreated ankyloglossia could cause psychological problems.

In the study by Oviya et al., 82% of participants indicated that children with ankyloglossia experience feeding difficulties.<sup>5</sup> In our study, 87.76% of dentists believed that ankyloglossia could cause feeding difficulties.

Given the limited data in the literature on ankyloglossia and related problems, access to some sources in the discussion section was limited. In addition, since the survey method used in our study relied on participants' self-reports, the results may be subjective. The selection of participants from a specific geographical region also limits the generalizability of the results. These limitations underscore the importance of future studies with larger sample groups and more comprehensive data collection methods on ankyloglossia.

## Conclusions

This study evaluated dentists' knowledge and attitudes towards ankyloglossia. Our findings indicate that the majority of dentists have knowledge of ankyloglossia and believe that this anomaly should be treated at an early age. In addition, there is a widespread view in our study that untreated ankyloglossia can lead to breastfeeding, feeding, and speech problems. These findings highlight the importance of increasing awareness of ankyloglossia and considering it during routine examinations. Future studies should support these findings with larger sample groups.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

**Protection of humans and animals.** The authors declare that no experiments involving humans or animals were conducted for this research.

**Confidentiality, informed consent, and ethical approval.** The authors have followed their institution's confidentiality protocols. The authors have obtained approval from the Ethics Committee for the analysis

of routinely obtained and anonymized clinical data, so informed consent was not necessary.

### **Declaration on the use of artificial intelligence.**

The authors declare that artificial intelligence was used in the writing of this manuscript specifically "Chatgpt" in the writing of this manuscript and/or in the creation of images, graphics, tables, or their corresponding captions. "ChatGPT has been utilized to enhance the language of the copyright transfer letter.

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# Can 18F-FDG PET/CT $SUV_{max}$ values predict breast and axillary pathological complete response before neoadjuvant chemotherapy in breast cancer?

*Pueden los valores de 18F-FDG PET-CT  $SUV_{max}$  predecir la respuesta patológica completa mamaria y axilar antes de la quimioterapia neoadyuvante en el cáncer de mama?*

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## Abstract

**Objectives:** We aimed to investigate whether maximum standardized uptake value ( $SUV_{max}$ ) values of breast mass and axilla metastatic lymph nodes are effective independent predictive factors for breast and axillary pathological complete response (PCR) before neoadjuvant chemotherapy (NAC). **Methods:** Factors investigated in predicting were age, type of pathology, tumor size, number of axillary pathological lymph nodes, hormone receptor (HR) positivity, human epidermal growth factor receptor 2 (HER2) positivity, triple negativity, Ki-67 level, multifocality,  $SUV_{max}$  of breast and axillary  $SUV_{max}$ . **Results:** Based on regression analysis, tumor size, HR positivity, Ki-67 level, HER2 positivity, and breast  $SUV_{max}$  were independent predictive factors for PCR of breast after NAC, while HR positivity, Ki-67 level  $\geq 14$ , multifocality, and breast  $SUV_{max}$  were independent predictive factors for axillary PCR after NAC. **Conclusions:** Breast  $SUV_{max}$  value before NAC is an independent predictive factor for breast and axillary PCR.

**Keywords:** Breast cancer. 18F-FDG PET/CT. Pathological complete response.

## Resumen

**Objetivo:** Investigar si los valores de  $SUV_{max}$  de la masa mamaria y los ganglios linfáticos metastásicos de la axila son factores predictivos independientes eficaces para la respuesta patológica completa de la mama y la axila antes de la quimioterapia neoadyuvante. **Métodos:** Los factores investigados en la predicción fueron la edad, el tipo de patología, el tamaño del tumor, el número de ganglios linfáticos patológicos axilares, la positividad de HR, la positividad de HER2, la triple negatividad, el nivel de Ki-67, la multifocalidad, el  $SUV_{max}$  de mama y el  $SUV_{max}$  axilar. **Resultados:** Según el análisis de regresión, el tamaño del tumor, la positividad de HR, el nivel de Ki-67, la positividad de HER2 y el  $SUV_{max}$  de la mama fueron factores predictivos independientes para la respuesta patológica completa de la mama después de la NAC, mientras que la positividad de HR, el nivel de Ki-67  $\geq 14$ , la multifocalidad y el  $SUV_{max}$  de la mama fueron factores predictivos independientes para la respuesta patológica completa axilar después de la NAC. **Conclusiones:** El valor  $SUV_{max}$  de la mama antes de la quimioterapia neoadyuvante es un factor predictivo independiente de la respuesta patológica completa de la mama y la axila.

**Palabras-clave:** Cáncer de mama. PET-TC con 18F-FDG. Respuesta patológica completa.

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## Introduction

Breast cancer is the most common type of cancer in women. Neoadjuvant chemotherapy (NAC) has become the initial treatment for locally advanced breast cancer.<sup>1</sup> Its use has expanded after the recommendation for using NAC to T1c-N0 patients with human epidermal growth factor receptor 2 (HER2) positive and triple negative in the 2023 NCCN guideline. With NAC, the stage of breast cancer can be reduced, and it can allow breast-conserving surgery (BCS) to be performed in patients who need a mastectomy.<sup>2</sup> It is prognostic for survival and disease-free survival.<sup>3</sup> When a complete axillary response is achieved, sentinel lymph node biopsy (SLNB) can be performed instead of axillary dissection (AD), avoiding complications caused by the latter. However, not all patients benefit from NAC. For patients who would not benefit from NAC, consequences such as loss of time, chemotherapy toxicity, and increased costs may arise.<sup>4</sup> In this respect, it is important to be able to predict the patients who would benefit from NAC. Positron emission tomography-computed tomography (PET-CT) is a technique that has been increasingly used in recent years. There are many studies investigating the effectiveness of PET-CT in predicting pathological response after NAC.<sup>5-9</sup> However, the majority of these studies are studies conducted with PET-CTs taken after NAC. Most of them were conducted without comparison with other factors that may affect the response to NAC and are few in number. These studies are important and valuable in terms of the usefulness of PET-CT in re-staging. However, they cannot contribute to patient selection for NAC. It is known that the hormone receptor positive (HR+) patient group benefited less from NAC and patients with HER2 positivity, triple negativity and high Ki-67 levels benefit more from NAC.<sup>10</sup> The response of the breast and axilla to NAC is not always the same. We think there are different factors in breast and axillary response. In this study, we aimed to investigate whether maximum standardized uptake value ( $SUV_{max}$ ) values of breast mass and axillary metastatic lymph nodes before NAC are effective independent predictive factors by comparing them statistically with other parameters in predicting both breast and axillary pathological complete response (PCR). After determining the independent parameters that are effective in predicting the response to NAC, nomograms can be created for the breast and axilla with these factors.

These nomograms can provide clinicians with the opportunity to make a more objective assessment when making NAC decisions.

## Methods

The patients who were T1-4, N1, M0, and who underwent surgery after NAC between January 2019 and August 2023 at Tokat Gaziosmanpaşa Medical Faculty Surgery Clinic were included in our study. The study was conducted prospectively. In all patients, both breast cancer and axillary metastasis were diagnosed by trucut biopsy. The patients with missing data and whose follow-ups were carried out in other hospitals were excluded from the study. Factors investigated in predicting NAC response were age, type of pathology (invasive ductal/invasive lobular), tumor size ( $T < 5$  cm/ $T \geq 5$  cm), number of axillary pathological lymph nodes ( $1/\geq 2$ ), HR positivity, HER2 positivity, triple negativity, Ki-67 level ( $< 14/\geq 14$ ), multifocality,  $SUV_{max}$  of breast mass and axillary  $SUV_{max}$ . A 5-score for the mass in the breast according to the Miller Payne System and lack of any metastasis in the lymph node for the axilla was considered PCR. Care was taken to ensure that all of the factors investigated were created from the data obtained before the NAC.

## Statistical analyses

The statistical analyses of the collected data were conducted using the Statistical Package for the Social Sciences (SPSS) software ver. 18.0 (SPSS Inc., Chicago, IL, USA). The categorical data were presented as percentage. The cut-off value for breast and axillary  $SUV_{max}$  was determined by receiver operative curve (ROC). In the univariate analysis, the comparisons of the factors affecting the breast and axillary PCR after NAC were made by the Pearson Chi-square test. Student t test was used for normally distributed continuous variables. The logistic regression was used to detect the independent factors affecting breast and axillary PCR after NAC and to calculate the odds ratios. Two separate nomograms were created to calculate the probability of breast and axillary complete response using formula  $E(Y) = \text{pr}(Y = 1) = 1/(1 + \exp[\beta_0 + \sum \beta_j X_j])$  and independent predictive factors. The effectiveness of the nomograms created was tested by performing ROC curve analysis using the cut off values obtained from the nomograms. Statistical significance was  $p < 0.05$ .

## NAC procedure

### SELECTION OF PATIENTS FOR NAC

The patients included in our study were the cases who had breast cancer with axillary lymph node metastases, regardless of tumor size, including inflammatory breast cancer, without distant metastases (T1-4, N1, M0), therefore receiving NAC.

### PRE-OPERATIVE THERAPY REGIMENS

Patients with HER2-negative breast cancer AC followed by weekly paclitaxel (Doxorubicin 60 mg/m<sup>2</sup>, Cyclophosphamide 600 mg/m<sup>2</sup> cycled every 21 days for 4 cycles followed by paclitaxel 80 mg/m<sup>2</sup> weekly for 12 weeks).

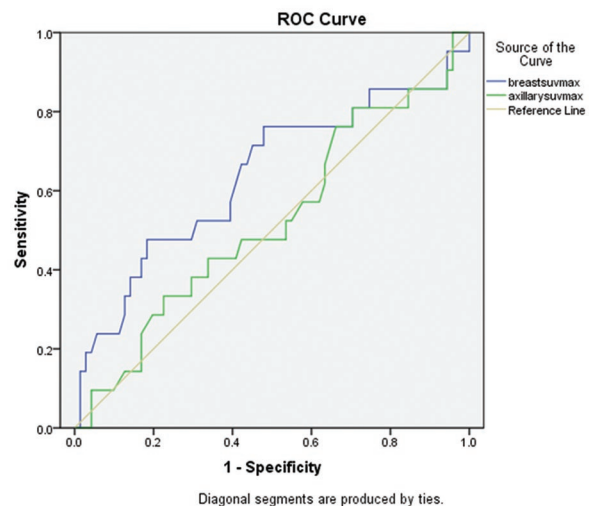
### PATIENTS WITH HER2-POSITIVE BREAST CANCER

AC followed by docetaxel + trastuzumab + pertuzumab (Doxorubicin 60 mg/m<sup>2</sup>, Cyclophosphamide 600 mg/m<sup>2</sup> cycled every 21 days for 4 cycles followed by pertuzumab 840 mg day 1 followed by 420 mg, trastuzumab 8 mg/kg day 1 followed by 6 mg/kg, and docetaxel 75-100 mg/m<sup>2</sup> cycled every 21 days for 4 cycles).

## Results

A total of 184 female patients with locally advanced breast cancer and a median age of 54 (range: 25-88) years were included in our study. The general characteristics of the patients and the results of univariate analysis are given in table 1. Of the patients, 51 underwent BCS + SLNB, 32 underwent BCS + SLNB + AD, 25 underwent BCS + AD, 28 underwent mastectomy + SLNB, 15 underwent mastectomy + SLNB + AD, and 33 underwent modified radical mastectomy. According to the post-operative pathology examinations, PCR rates after NAC were 22.8% for breast mass and 36.9% for axilla.

ROC analysis was performed based on PCR, and separate SUV<sub>max</sub> values were for calculated breast and axilla. In our patient series, the cut-off value was 9.9 for breast tumor and 10.1 for axillary metastasis. In the ROC analysis performed with both SUV<sub>max</sub> values to predict PCR in the breast, it was found that the breast SUV<sub>max</sub> was usable (area under the curve [AUC]: 0.636,  $p = 0.007$ , sensitivity: 66.7%, specificity: 72.4%, cutoff: 9.9) while axillary SUV<sub>max</sub> was not (AUC:



**Figure 1.** Maximum standardized uptake value (SUV<sub>max</sub>) evaluation for breast complete response. Breast SUV<sub>max</sub>: Area under the curve (AUC): 0.636,  $p = 0.007$ , sensitivity: 66.7%, specificity: 72.4%, cutoff: 9.9. Axillary SUV<sub>max</sub>: AUC: 0.531,  $p = 0.678$ .

0.531,  $p = 0.678$ ) (Fig. 1). In the ROC analysis performed with both SUV<sub>max</sub> values to predict axillary PCR, it was revealed that the breast SUV<sub>max</sub> was usable (AUC: 0.731,  $p = 0.000$ , sensitivity: 67.8%, specificity: 73.6%, cutoff: 10.1) while axillary SUV<sub>max</sub> (AUC: 0.578,  $p = 0.078$ ) was not (Fig. 2).

As a result of univariate analyses, age ( $p = 0.519$ ), pathology type ( $p = 0.263$ ), pathological LN number in the axilla before NAC ( $p = 0.586$ ), triple negativity ( $p = 0.974$ ) and axillary SUV<sub>max</sub> ( $p = 0.307$ ) were not significant while tumor size ( $p = 0.021$ ), HR+ ( $p < 0.001$ ), HER2 positivity ( $p < 0.001$ ), Ki-67 level ( $p < 0.001$ ), multifocality ( $p = 0.014$ ) and breast SUV<sub>max</sub> ( $p = 0.029$ ) were significant. As a result of logistic regression analysis using factors found significant in univariate analysis, tumor size ( $p = 0.013$ ), HR+ ( $p = 0.011$ ), Ki-67 level  $\geq 14$  ( $p = 0.02$ ), HER2 positivity ( $p = 0.006$ ), and breast SUV<sub>max</sub> ( $p = 0.038$ ) were independent factors in predicting PCR after NAC (Table 2).

With the nomogram created with the factors obtained, the probability levels of breast PCR were calculated according to the treatment groups. The results showed that the significant cut-off was at the level of 40.5 points. When the calculated value was over 40.5, the probability of PCR increased. In ROC curve analysis, sensitivity was 76.2%, specificity 80.3%, and AUC 0.814 (Fig. 3).

In univariate analyses performed for axillary PCR, age ( $p = 0.731$ ), pathology type ( $p = 0.493$ ), tumor size ( $p = 0.228$ ), pathological LN count in the axilla before NAC ( $p = 0.073$ ), triple negativity ( $p = 0.294$ ) and

**Table 1. General characteristics of the patients and the univariate analysis results**

| Characteristics                              | Breast complete response, n (%) |            | p       | Axillary complete response, n (%) |               | p       |
|----------------------------------------------|---------------------------------|------------|---------|-----------------------------------|---------------|---------|
|                                              | Yes                             | No         |         | Yes                               | No            |         |
| Age (mean±SD)                                | 55.42 ± 14.23                   | 53.94 ± 12 | 0.519   | 54.64 ± 14.72                     | 54.06 ± 12.01 | 0.731   |
| Pathology                                    |                                 |            |         |                                   |               |         |
| Idc                                          | 41 (23.6)                       | 132 (76.4) | 0.263   | 65 (37.5)                         | 108 (62.5)    | 0.493   |
| Ilc                                          | 1 (9)                           | 10 (91)    |         | 3 (27.2)                          | 8 (72.3)      |         |
| Size (cm)                                    |                                 |            |         |                                   |               |         |
| T < 5                                        | 40 (25.9)                       | 114 (74.1) | 0.021   | 54 (35)                           | 100 (65)      | 0.228   |
| T ≥ 5                                        | 2 (6.6)                         | 28 (93.4)  |         | 14 (46.6)                         | 16 (53.4)     |         |
| Number of pathological lymph node before NAC |                                 |            |         |                                   |               |         |
| 1                                            | 24 (24.5)                       | 74 (75.5)  | 0.586   | 42 (43.7)                         | 56 (56.3)     | 0.073   |
| ≥ 2                                          | 18 (21)                         | 68 (79)    |         | 26 (30.2)                         | 60 (69.8)     |         |
| HR status                                    |                                 |            |         |                                   |               |         |
| Positive                                     | 18 (14.4)                       | 106 (95.6) | < 0.001 | 32 (25.8)                         | 92 (74.2)     | < 0.001 |
| Negative                                     | 24 (40.6)                       | 36 (59.4)  |         | 24 (40.6)                         | 36 (59.4)     |         |
| HER2 status                                  |                                 |            |         |                                   |               |         |
| Positive                                     | 30 (39.4)                       | 46 (59.6)  | < 0.001 | 38 (50)                           | 38 (50)       | 0.002   |
| Negative                                     | 12 (11.1)                       | 96 (88.9)  |         | 30 (27.7)                         | 78 (72.3)     |         |
| Triple negative                              |                                 |            |         |                                   |               |         |
| Yes                                          | 6 (23)                          | 20 (77)    | 0.974   | 12 (46.1)                         | 14 (53.9)     | 0.294   |
| No                                           | 36 (23)                         | 122 (77)   |         | 56 (35.4)                         | 102 (64.6)    |         |
| Ki-67 level                                  |                                 |            |         |                                   |               |         |
| < 14                                         | 8 (8.8)                         | 82 (91.2)  | < 0.001 | 10 (11.1)                         | 80 (88.9)     | < 0.001 |
| ≥ 14                                         | 34 (36.1)                       | 60 (53.9)  |         | 58 (61.7)                         | 36 (38.3)     |         |
| Multifocality                                |                                 |            |         |                                   |               |         |
| Yes                                          | 2 (6.6)                         | 30 (93.4)  | 0.014   | 2 (6.6)                           | 30 (93.4)     | < 0.001 |
| No                                           | 40 (24.7)                       | 122 (75.3) |         | 66 (40.7)                         | 86 (59.3)     |         |
| Breast SUV <sub>max</sub> -cut off           |                                 |            |         |                                   |               |         |
| Group 1 (< 9.9)                              | 20 (17.5)                       | 94 (82.5)  | 0.029   | 30 (26.3)                         | 84 (73.7)     | < 0.001 |
| Group 2 (≥ 9.9)                              | 22 (31.4)                       | 48 (68.6)  |         | 38 (76)                           | 12 (24)       |         |
| Axillary SUV <sub>max</sub> -cut off         |                                 |            |         |                                   |               |         |
| Group 1 (< 10.1)                             | 28 (20.8)                       | 106 (79.2) | 0.307   | 46 (34.3)                         | 88 (65.7)     | 0.235   |
| Group 2 (≥ 10.1)                             | 14 (28)                         | 36 (72)    |         | 22 (44)                           | 28 (66)       |         |

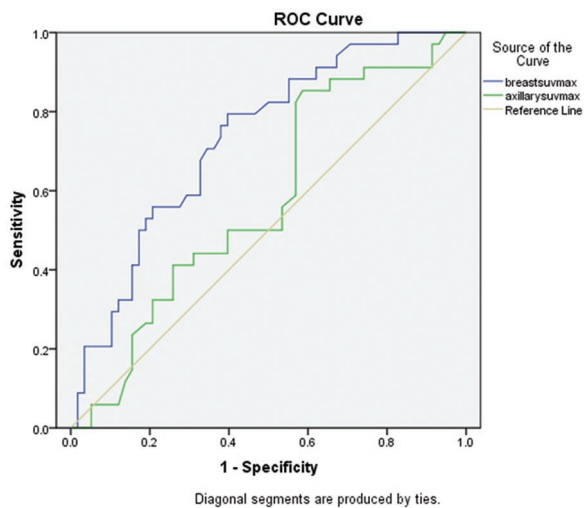
NAC: neoadjuvant chemotherapy; HR: hormone receptor; HER2: human epidermal growth factor receptor 2; SUV<sub>max</sub>: maximum standardized uptake value.**Table 2. Logistic regression analysis**

| Logistic regression              | p       | OR   | 95% CI for EXP.(B) |
|----------------------------------|---------|------|--------------------|
| Breast complete response         |         |      |                    |
| T < 5-T ≥ 5                      | 0.013   | 4.9  | 1.53-36.7          |
| HR positive                      | 0.011   | 2.53 | 1.28-7             |
| Ki-67 level ≥ 14                 | 0.02    | 5.8  | 1.24-8.34          |
| HER2 positive                    | 0.006   | 5.2  | 1.27-7.06          |
| Breast SUV <sub>max</sub> ≥ 9.9  | 0.038   | 2.16 | 1.81-9.54          |
| Axillary complete response       |         |      |                    |
| HR positive                      | 0.007   | 4.93 | 1.49-7.39          |
| Ki-67 level ≥ 14                 | < 0.001 | 3.37 | 1.69-3.6           |
| Multifocality                    | 0.016   | 8.6  | 1.44-32.3          |
| Breast SUV <sub>max</sub> ≥ 10.1 | 0.003   | 8.86 | 1.49-7.2           |

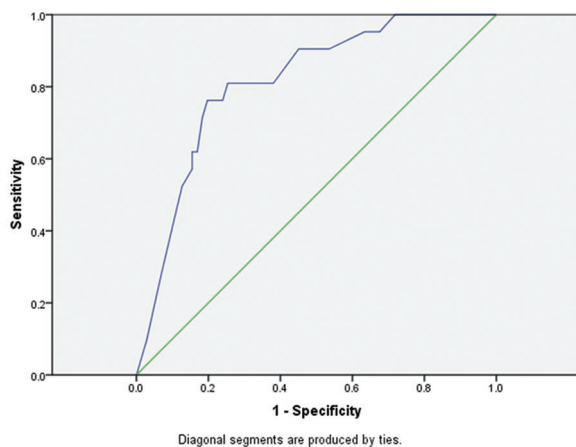
OR: Odds ratios; CI: Confidence interval; HR: hormone receptor; HER2: human epidermal growth factor receptor 2; SUV<sub>max</sub>: maximum standardized uptake value.

axillary SUV<sub>max</sub> (p = 0.235) were not significant while HR positivity (p < 0.001), HER2 positivity (p = 0.002), Ki-67 level (p < 0.001), Multifocality (p = 0.014) and breast SUV<sub>max</sub> (p = 0.029) were significant. As a result of logistic regression analysis performed using factors that turned out to be significant in univariate analysis, HR positivity (p = 0.007), Ki-67 level ≥ 14 (p < 0.001), multifocality (p = 0.016) and breast SUV<sub>max</sub> (p = 0.003) were independent factors in predicting axillary PCR after NAC (Table 2).

It was shown in the logistic regression analysis that in order to increase the probability of axillary complete response, HR should not be positive and multifocality



**Figure 2.** Maximum standardized uptake value ( $SUV_{max}$ ) evaluation for axillary complete response. Breast  $SUV_{max}$ : Area under the curve (AUC): 0.731,  $p = 0.000$ , sensitivity: 67.8%, specificity: 73.6%, cutoff: 10.1. Axillary  $SUV_{max}$ : AUC: 0.578,  $p = 0.078$ .

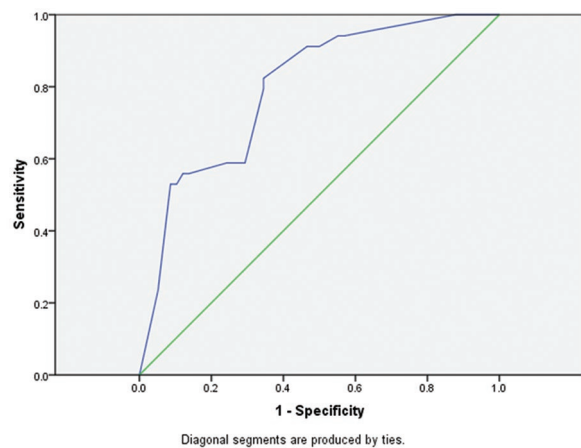


**Figure 3.** Nomogram receiver operative curve analysis for breast complete response: Area under the curve: 0.81,  $p < 0.001$ , sensitivity: 76.2%, specificity: 80.3%, cut of: 40.5.

should not exist, Ki-67 should be  $\geq 14$ , and breast  $SUV_{max}$  should be higher than 10.1. With the nomogram created with the factors obtained, the probability levels of axillary PCR were calculated according to the treatment groups. According to the results, it was found that the significant cut-off point was 24.5. When the calculated value was over 24.5, the probability of axillary PCR increased. In the ROC curve analysis, sensitivity was 71%, specificity 84.24%, and AUC 0.795 (Fig. 4).

## Discussion

$SUV_{max}$  is defined as the ratio of the maximum intensity of activity in the lesion to the fluorodeoxyglucose



**Figure 4.** Nomogram receiver operative curve analysis for axillary complete response: Area under the curve: 0.795,  $p < 0.001$ , sensitivity: 71%, specificity: 84.24%, cut off: 24.05.

(FDG) dose injected per kilogram.<sup>11</sup> The SUV value of the primary tumor is directly associated with the subgroups of the tumor, histological grade, proliferation index, and early recurrence.<sup>11</sup> FDG uptake may also be affected by the phenotype and mitotic index of the primary tumor.<sup>12</sup> It was also shown that  $SUV_{max}$  is associated with tumor mutational burden and the total number of oncogenic anomalies in tissue biopsy.<sup>13</sup> Kwon et al.<sup>14</sup> reported a correlation between the increase in Ki-67 level and the increase in FDG uptake. According to a meta-analysis of 22 studies and 1630 patients, 18F-FDG PET was found to have a predictive value in the evaluation of response to NAC.<sup>15</sup> However, Tian et al. initially reported that the use of 18F-FDG PET/CT to evaluate PCR in tumors with low glucose metabolism was not significant.<sup>16</sup> In the light of all these scientific data, it is possible to assume that the  $SUV_{max}$  values obtained before NAC can predict the response to NAC.

The majority of the studies in the literature are 18F-FDG PET/CT studies performed in the early period after NAC initiation or after treatment is completed. In our review of English literature, we identified four studies planned according to the results of 18F-FDG PET/CT before NAC in parallel with our study.<sup>17-20</sup> In their study involving 73 patients, Ha et al. reported that PCR could be estimated using radiomics in 18F-FDG PET/CT before NAC and tissue characteristics of the tumor.<sup>17</sup> However, contrary to the literature, they concluded that HER2 positivity had no effect on PCR.<sup>17</sup> In their study involving 163 patients, Li et al.<sup>18</sup> created a model that predicts PCR by combining radiomics and age. Lim et al.<sup>19</sup> studied 100 patients and reported

that radiomics and HER2 positivity were predictive for PCR and created a model that calculates the probability. In addition to radiomics, Chen et al.<sup>20</sup> reported that estrogen receptor, progesterone receptor, HER2, and Ki-67 status were correlated with the results of NAC, and the AUC of the model they created was 0.72. All these four studies involved the use of special software and complex data. In our study, we created two separate models to predict PCR for the breast and axilla using the data of the tumor and the  $SUV_{max}$ , which should be available when the patient is diagnosed.

For PCR in breast, tumor size ( $p = 0.013$ ), HR+ ( $p = 0.011$ ), Ki-67 level  $\geq 14$  ( $p = 0.02$ ), HER2 positivity ( $p = 0.006$ ) and breast  $SUV_{max}$  ( $p = 0.038$ ) were independent factors in predicting PCR after NAC. HR+ ( $p = 0.007$ ), Ki-67 level  $\geq 14$  ( $p < 0.001$ ), multifocality ( $p = 0.016$ ), and breast  $SUV_{max}$  ( $p = 0.003$ ) were independent predictive factors for axillary PCR. We confirmed that two separate nomograms established using these factors were effective in predicting PCR for breast and axilla.

The fact that we obtained different predictive factors for breast and axillary PCR could be clinically valuable since this finding implied that differences may occur in the response of the breast and axilla to NAC. Thanks to the formulas and factors we used, we believe that we have created models that can be easily used by clinicians without the need for special software, unlike other studies. Using these models, more objective NAC decisions could be made. The prospective nature of our study and the relatively higher number of patients in the present study compared to similar studies strengthens our results.

## Conclusions

The factors affecting the response to NAC were not the same for the breast mass and the axilla. While the breast  $SUV_{max}$  value in the 18F-FDG PET/CT before NAC is an independent predictive factor for both breast and axillary PCR, axillary  $SUV_{max}$  is not an effective factor.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

**Protection of humans and animals.** The authors declare that no experiments involving humans or animals were conducted for this research.

**Confidentiality, informed consent, and ethical approval.** The study does not involve patient personal data. The SAGER guidelines were followed according to the nature of the study.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

All procedures in studies involving human participants were conducted by the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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# Sensibilidad y validación de la biopsia de ganglio centinela en el cáncer cervicouterino de etapa temprana en una institución de oncología

## *Sensitivity and validity of sentinel node biopsy in early-stage cervical cancer at an oncology institution*

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### Resumen

**Objetivo:** Determinar la validez de la biopsia de ganglio centinela (BGC) en mujeres con cáncer cervicouterino (CaCu) en etapa temprana. **Métodos:** Se realizó un estudio de 46 pacientes con CaCu en etapas FIGO IA1c-IB2 tratada con cirugía radical uterina. La técnica para la identificación de la BGC fue con colorante azul patente y tecnecio-99m. Para su validación se realizó linfadenectomía pélvica bilateral (LPB) y a todos los ganglios centinela se les realizó ultraestadificación patológica. Se determinaron las tasas de detección de BGC, la bilateralidad, la sensibilidad, la especificidad y los valores predictivos negativo y positivo. **Resultados:** La sensibilidad de la BGC fue del 100%, la especificidad del 95%, el valor predictivo positivo del 75% y el valor predictivo negativo del 100%, con una precisión diagnóstica del 93% y una tasa de falsos negativos del 0%. **Conclusiones:** La técnica de BGC en pacientes con CaCu en etapa temprana que son sometidas a histerectomía radical es un método factible y seguro en el Instituto Nacional de Cancerología. La importancia de este método es que puede evitarse la LPB cuando migra de forma bilateral, disminuyendo la morbilidad del procedimiento.

**Palabras clave:** Ganglio centinela. Cáncer de cérvix. Linfadenectomía.

### Abstract

**Objective:** To determine the validity of sentinel lymph node biopsy (SNB) in women with early-stage cervical cancer (CeCa). **Methods:** We carried out a study of 46 patients with CeCa of FIGO stages IA1c-IB2 treated with radical uterine surgery. The technique for the identification of BGC was performed with patent blue dye and technetium-99m. For its validation, a bilateral pelvic lymphadenectomy (BPL) was performed, and all sentinel lymph nodes underwent pathological ultra-staging. We determined the detection rates of SNB, bilaterality, sensitivity, specificity, and negative and positive predictive values. **Results:** The sensitivity of the SNB was 100%, specificity was 95%, positive predictive value was 75%, negative predictive value was 100%, diagnostic accuracy was 93%, and the false negative rate was 0%. **Conclusions:** The BGC technique in patients with CeCa in the early stages who undergo radical hysterectomy is a feasible and safe method at Instituto Nacional de Cancerología. The importance of this method is that BPL can be avoided when it migrates bilaterally, reducing the morbidity of the procedure.

**Keywords:** Sentinel lymph node. Cervix cancer. Lymphadenectomy.

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## Introducción

El factor pronóstico más importante de supervivencia en el cáncer cervicouterino (CaCu) en etapa temprana (IA1-IB2) de la clasificación de la Federación Internacional de Ginecología y Obstetricia (FIGO) de 2018 es la metástasis ganglionar, que en un 15-20% de los casos ocurre en los ganglios pélvicos<sup>1-4</sup>. La histerectomía radical y la linfadenectomía pélvica bilateral (LPB) son el estándar de manejo en estas pacientes. Sin embargo, la LPB se ha asociado a un riesgo más alto de complicaciones durante la cirugía, tales como mayor pérdida sanguínea y lesión ureteral, nerviosa o vascular, y en el posoperatorio tardío, tales como linfquistes y linfedema de miembro inferior (LMI); este último probablemente sea la complicación más importante y grave a largo plazo, y su incidencia es variable. En el estudio prospectivo GOG-244, Carlson et al. documentaron que hasta el 65.2% de las pacientes con cáncer de cuello uterino tratadas quirúrgicamente desarrollaron síntomas relacionados con linfedema, subrayando el impacto de la linfadenectomía y la extensión del tratamiento en su aparición<sup>5</sup>. Cibula et al.<sup>6</sup> evaluaron de forma prospectiva el LMI en pacientes con ganglio centinela (GC) y encontraron una incidencia acumulada de LMI a los 24 meses del 17.3% para LMI leve, del 9.2% para LMI moderado y del 0.7% para LMI grave.

La biopsia de ganglio centinela (BGC) ha demostrado ser un procedimiento muy seguro que evalúa el primer o primeros GC por los que drenan las células tumorales del cáncer primario<sup>7</sup>. Estos ganglios representan el estado regional de afectación linfática ganglionar. Dicho procedimiento ha sido ampliamente validado en otras neoplasias y es el estándar de manejo para el cáncer de mama y el melanoma<sup>1,2</sup>.

Los primeros resultados de BGC en CaCu fueron publicados en los años 1990 y posteriormente se han evaluado los resultados de numerosos estudios en diferentes centros oncológicos. Han sido muchos los estudios que han demostrado una alta sensibilidad de la BGC para predecir metástasis ganglionares<sup>3-10</sup>.

En la actualidad, el tratamiento estándar del CaCu en etapa temprana IA1 con permeación linfovascular, IA2 e IB1 de la clasificación de la FIGO de 2018 es la histerectomía radical con LPB, y la BGC es una opción factible y segura recomendada en las guías internacionales<sup>11</sup>.

Este estudio presenta la experiencia de un instituto de oncología de tercer nivel de atención en México en el uso de la técnica de BGC en pacientes con

CaCu en etapa temprana con el objetivo de determinar la validez de la BGC.

## Métodos

Se realizó una revisión retrospectiva en el departamento de ginecología oncológica del Instituto Nacional de Cancerología, entre 2010 y 2020, de pacientes con diagnóstico de CaCu en etapa temprana a quienes se les realizó BGC. Para el estudio se adaptó la clasificación FIGO 2018 y se incluyeron las pacientes con CaCu en etapas IA1 con permeación linfovascular, IA2-IB2 con histología epidermoide, adenocarcinoma y adenoescamoso, y se les realizó histerectomía radical, BGC y LPB. La técnica de trazador usada fue con colorante azul patente y tecnecio-99m (Tc-99). Como parte de la validación del estudio se realizaron ambos procedimientos, BGC seguida de LPB, para identificar falsos positivos y negativos de la BGC en comparación con la evaluación del procedimiento estándar. Las cirugías se realizaron por laparotomía. En el departamento de patología, a todos los GC se les realizó tinción de hematoxilina-eosina y cuando fueron negativos para macrometástasis se les sometió a ultraestadificación.

Se excluyeron las pacientes que tuvieron ganglios con macrometástasis en el transoperatorio y aquellas a las que no se les realizó LPB complementaria.

### Procedimiento preoperatorio

Con la paciente anestesiada, colocada en posición ginecológica con las extremidades pélvicas en abducción, se inyectaron el radiotrazador sulfuro de renio marcado con Tc-99 y colorante azul patente al 1% en el cuello uterino en el radio de las 3 y las 9 de las manecillas del reloj. La inyección se realizó superficial y profundo en el estroma cervical, a 1-2 mm y 10 mm, respectivamente.

### Procedimiento operatorio

Se realizó apertura peritoneal para identificar las estructuras retroperitoneales pélvicas, ambos uréteres y los vasos ilíacos externos e internos. Realizando espacios pélvicos laterales y medios, se identificaron los conductos y los GC guiados con visualización del colorante azul patente y la utilización de una gamma sonda (Gamma probe®). Una vez identificados los ganglios «azules o calientes», fueron extraídos para su análisis definitivo de patología.

## **Evaluación de patología y ultraestadificación**

Los GC fueron procesados en el departamento de patología. Cada GC se seccionó a intervalos de 2 mm a lo largo del eje mayor de la muestra y se incluyó completamente la cantidad necesaria de casetes. Se obtuvo un portaobjetos para tinción con hematoxilina-eosina, y si este era negativo para metástasis, se hacían dos cortes más con una diferencia de 50  $\mu$ m. Un portaobjetos se tiñó con hematoxilina-eosina (Fig. 1) y el otro se reservó para estudios de inmunohistoquímica con citoqueratinas CKAE1/AE3 (Fig. 2) en caso de que no se identificaran células neoplásicas en el corte de hematoxilina y eosina. Se informó el tamaño de metástasis, clasificándolo como macrometástasis si el tamaño era  $> 2$  mm, micrometástasis si era  $< 2$  mm y más de 200 células aisladas, y células aisladas cuando hubo menos de 200 células presentes. En caso de más de un GC, cada uno de los ganglios se procesó y reportó por separado.

## **Análisis estadístico**

Se realizó un análisis descriptivo en el cual se presentaron con frecuencias y porcentajes las variables categóricas, mientras que para las continuas se reportaron la mediana y el rango intercuartílico (RIC). Se determinaron las tasas de detección, la bilateralidad, la sensibilidad, la especificidad y los valores predictivos negativo y positivo.

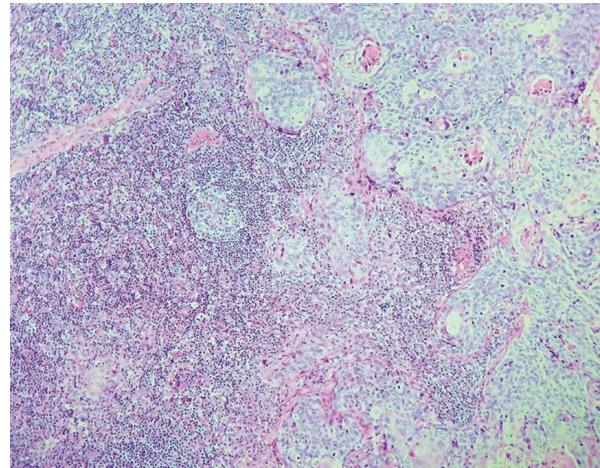
## **Resultados**

Se incluyeron 46 pacientes tratadas quirúrgicamente en el periodo de 2010 a 2020. La edad mediana fue de 47 años (RIC: 39-53 años). El tipo histológico epidermoide se identificó en 34 (73.9%), siendo el más frecuente, seguido por el adenocarcinoma en 11 (23.9%). En cuanto al tipo de histerectomía radical, fue de tipo B en 40 (87.0%) y de tipo C en 6 (13%). La etapa clínica más frecuente fue IB1, en 41 (89.1%) (Tabla 1).

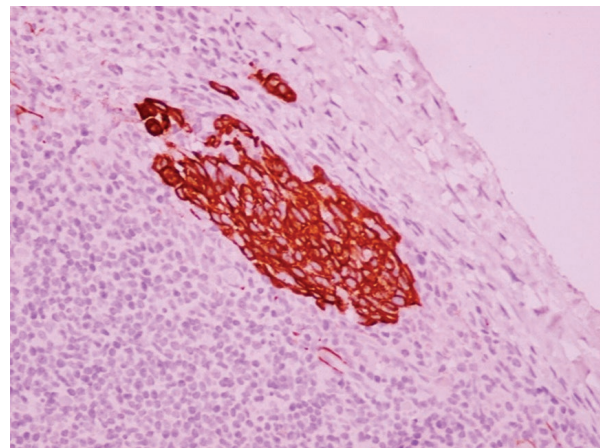
En relación con el tamaño tumoral, 29 (63%) fueron categorizados como  $\leq 2$  cm y 17 (37%)  $> 2.1$  cm. Fueron disecados 1-3 GC en 41 (89.1%) y 3-6 GC en 5 (10.9%)

Respecto a la bilateralidad, 27 (58.7%) fueron bilaterales y 19 (41.3%) unilaterales.

El resultado de la evaluación de patología de los GC solo con hematoxilina-eosina fue 42 (91.3%) negativos



**Figura 1.** Tinción de hematoxilina-eosina: macrometástasis.



**Figura 2.** Inmunohistoquímica con CKAE1/AE3: ganglio obturador con metástasis de 5 mm y focos de 1 mm.

y 4 (8.7%) positivos. Con la técnica de ultraestadificación con inmunohistoquímica, fueron positivos 8 (17.4%), con macrometástasis 6 (13.0%), con micrometástasis 2 (4.3%) y células aisladas 0 (0.0%) (Tabla 2).

La evaluación de la validez de la BGC frente a la evaluación de ganglios de la LPB se muestra en la tabla 3. Se identificó metástasis en 8 GC de 6 pacientes. Los GC fueron correctamente localizados con radiocoloide y azul patente. La sensibilidad de la BGC fue del 100%, la especificidad del 95%, el valor predictivo positivo del 75% y el valor predictivo negativo del 100%, con una precisión diagnóstica del 93% y una tasa de falsos negativos del 0%.

## **Discusión**

El procedimiento de BGC ha sido ampliamente utilizado en pacientes con cáncer de pene, mama, vulva y

**Tabla 1. Datos demográficos (n = 46)**

| Variables                    | n (%)      |
|------------------------------|------------|
| Edad, mediana (RIC)          | 47 (39-53) |
| Histología                   |            |
| Carcinoma epidermoide        | 34 (73.9)  |
| Adenocarcinoma               | 11 (23.9)  |
| Adenoescamoso                | 1 (2.2)    |
| Etapas clínicas              |            |
| IA1                          | 3 (6.5)    |
| IB1                          | 41 (89.1)  |
| IIA1                         | 2 (4.3)    |
| Cirugía                      |            |
| Histerectomía radical tipo B | 40 (87.0)  |
| Histerectomía radical tipo C | 6 (13.0)   |

RIC: rango intercuartílico.

**Tabla 2. Datos del procedimiento de biopsia del ganglio centinela (n = 46)**

| Variables                   | n (%)     |
|-----------------------------|-----------|
| Tamaño del tumor            |           |
| > 2 cm                      | 29 (63.0) |
| < 2 cm                      | 17 (37.0) |
| Total de ganglios centinela |           |
| 1-3                         | 41 (89.1) |
| 4-6                         | 5 (10.9)  |
| Bilateralidad               |           |
| Unilateral                  | 19 (41.3) |
| Bilateral                   | 27 (58.7) |
| Hematoxilina-eosina         |           |
| Negativo                    | 42 (91.3) |
| Positivo                    | 4 (8.7)   |
| Inmunohistoquímica          |           |
| Positivo                    | 8 (17.4)  |
| Micrometástasis             | 2 (4.3)   |
| Macrometástasis             | 6 (13.0)  |
| Células aisladas            | 0 (0.0)   |
| Negativo                    | 38 (82.6) |

melanoma, con buenos resultados en la evaluación ganglionar<sup>7,8</sup>. Los beneficios específicos en el CaCu incluyen una disminución de las lesiones nerviosas, menor pérdida de sangre, reducción del tiempo quirúrgico y mejor identificación de los verdaderos ganglios linfáticos metastásicos mediante ultraestadificación. De acuerdo con los resultados de nuestro estudio, la ultraestadificación incrementó al doble la identificación de metástasis; la evaluación inicial mediante hematoxilina-eosina identificó metástasis en 4 casos (8.7%). Con la aplicación de ultraestadificación, el número de casos

positivos se incrementó a 8 (17.4%), incluyendo 2 micrometástasis (4.3%) y 6 macrometástasis (13.0%). En consecuencia, la ultraestadificación permitió aumentar la detección de enfermedad metastásica en un 8.7% adicional.

La histerectomía radical con LPB es el estándar de tratamiento para las etapas clínicas IA1 con permeación linfovascular, IA2 e IB1 del CaCu<sup>11</sup>. Existe un algoritmo (Fig. 3), publicado en 2011 por Cormier et al.<sup>12</sup>, que sugiere que para una mejor estadificación con el uso de BGC se realice escisión de los GC, así como de cualquier adenopatía sospechosa, además de encontrarse una falta de identificación de GC en alguna de las zonas linfoportadoras se deberá realizar una linfadenectomía para una adecuada evaluación del estado ganglionar bilateral.

Se ha descrito una prevalencia de metástasis ganglionares de hasta el 15% en pacientes con CaCu en etapa temprana, lo cual indica que al 85% de las pacientes a las que se realiza linfadenectomía no tendrán un beneficio, pero sí tendrán el riesgo de las complicaciones asociadas y la morbilidad a largo plazo de la linfadenectomía<sup>13</sup>.

Las posibles complicaciones de la LPB incluyen lesiones a vasos, nervios pélvicos y uréteres, y complicaciones menos comunes como infecciones, eventos tromboembólicos, fístulas y linfocelos, llegando a afectar la calidad de vida de las pacientes<sup>13,14</sup>. Como parte de la validación de la BGC, a todas nuestras pacientes les realizamos LPB, pero no fueron reportadas en su historial médico complicaciones operatorias o posoperatorias inmediatas ni tardías.

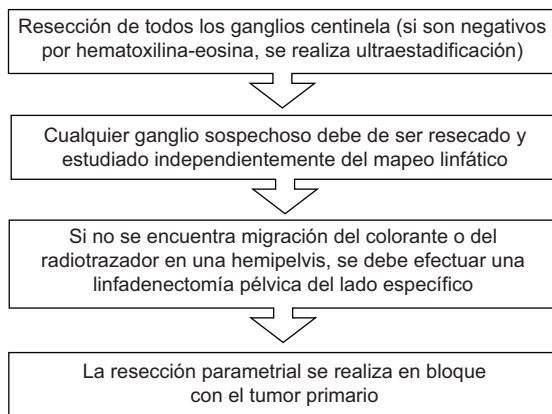
Con la finalidad de disminuir las complicaciones a corto y largo plazo se ha propuesto el uso de la BGC como método de mejor evaluación ganglionar y para detección de micrometástasis y células aisladas<sup>12</sup>. En este estudio se reporta la experiencia del Instituto Nacional de Cancerología del uso de BGC en el cáncer de cuello uterino, con unas adecuadas precisión diagnóstica (93%), sensibilidad (100%) y especificidad (92.6%).

Se han realizado numerosos estudios en diferentes centros oncológicos para evaluar la precisión diagnóstica de la BGC en el CaCu<sup>9,10</sup>. Bats et al.<sup>15</sup> determinaron el valor diagnóstico de la BGC con radiocoloide y colorante en pacientes con CaCu en etapas tempranas, con una tasa de detección del 97.8%. Hubo 17 falsos negativos: 4 con macrometástasis, 4 con micrometástasis y 9 con células tumorales aisladas. Dentro de las recomendaciones derivadas del estudio, se destaca que la detección

**Tabla 3. Validación de la biopsia de ganglio centinela**

| Ultraestadificación | Hematoxilina-eosina |                    |       | Valor predictivo |
|---------------------|---------------------|--------------------|-------|------------------|
|                     | Positivo            | Negativo           | Total |                  |
| Inmunohistoquímica  |                     |                    |       |                  |
| Positivo            | 6                   | 2                  | 8     | VPP: 75%         |
| Negativo            | 0                   | 38                 | 38    | VPN: 100%        |
| Total               | 6                   | 40                 | 46    |                  |
| Sensibilidad: 100%  |                     | Especificidad: 95% |       |                  |

VPN: valor predictivo negativo; VPP: valor predictivo positivo.

**Figura 3. Algoritmo de manejo con biopsia de ganglio centinela para mejorar la estadificación, propuesto por el Memorial Sloan Kettering Cancer Center.**

óptima del ganglio centinela se observa en tumores menores de 2 cm, particularmente cuando se emplea una técnica combinada con colorante y radiotrazador, aplicados mediante inyección en los cuadrantes cervicales<sup>15</sup>.

La técnica de aplicación consiste en la inyección de radiocoloide un día previo o el día del evento quirúrgico, en los cuatro puntos cardinales del cuello uterino, y posteriormente una evaluación quirúrgica por medio de detección del colorante y radiocoloide con gamma cámara<sup>12</sup>.

Frumovitz et al.<sup>16</sup> realizaron un estudio de no inferioridad y de comparación entre pacientes con cáncer de endometrio o CaCu en estadio clínico I sometidas a cirugía curativa, que fueron asignadas aleatoriamente 1:1 a un mapeo linfático con colorante azul de isosulfán (visualizado con luz blanca) seguido de verde de indocianina (visualizado mediante imágenes de infrarrojo cercano) o con verde de indocianina seguido de tinte azul de isosulfán. Concluyeron que el tinte verde de indocianina con imágenes de

fluorescencia en el infrarrojo cercano identificó más GC que el tinte azul de isosulfán en mujeres con CaCu y cáncer de útero, sin diferencias en la confirmación patológica del tejido ganglionar entre las dos sustancias cartográficas<sup>16</sup>.

El ensayo clínico SENTICOL 1 fue un estudio multicéntrico prospectivo que evaluó la sensibilidad y el valor predictivo negativo de la BGC. El mapeo intraoperatorio con colorante azul de radioisótopos detectó al menos un GC en 136 pacientes (97.8%; intervalo de confianza del 95% [IC 95%]: 93.8-99.6), de los cuales 23 tuvieron resultados verdaderamente positivos y 2 tuvieron resultados falsos negativos, con una sensibilidad del 92.0% (23 de 25; IC 95%: 74.0-99.0) y un valor predictivo negativo del 98.2 % (111 de 113; IC 95%: 74.0-99.0) para la detección de metástasis ganglionares, sin falsos negativos. En 104 pacientes (76.5%) se identificó GC bilateralmente. Se concluye que el mapeo de ganglios se asoció con altas tasas de detección de BGC, con elevada sensibilidad y alto valor predictivo negativo para la detección de metástasis. Sin embargo, la BGC solo fue por completo confiable cuando los GC se detectaron bilateralmente<sup>17</sup>. La técnica de aplicación en nuestro estudio fue con Tc-99 y azul patente, se llevó a cabo en todas las pacientes y produjo resultados de bilateralidad del 58.7% y una sensibilidad del 100%.

El ensayo SENTICOL 2 fue un estudio prospectivo aleatorizado en CaCu temprano (estadios IA2 a IIA1 de la FIGO 2009). Las pacientes fueron asignadas aleatoriamente a resección de GC sola (grupo GC) o con disección de ganglios linfáticos pélvicos (grupo GC y LPB)<sup>18</sup>. La resección fue seguida por una cirugía radical del tumor (histerectomía radical o traquelectomía radical). La conclusión del estudio fue que la resección del GC por sí sola se asocia con una disminución temprana de la morbilidad linfática en comparación con GC más LPB en el CaCu temprano<sup>18</sup>.

Se realizó un análisis *post hoc* de las cohortes SENTICOL I y SENTICOL II para comparar los resultados oncológicos de pacientes con CaCu en etapa temprana y ganglios negativos que se sometieron a BGC o LPB<sup>19</sup>. La mediana de seguimiento fue de 47 meses (rango: 4-127). Durante el seguimiento, 21 pacientes (8.1%) experimentaron recurrencias, incluidas 4 (1.9%) recurrencias ganglionares, y 9 pacientes (3.5%) murieron de CaCu. La supervivencia libre de enfermedad y la supervivencia específica de la enfermedad fueron similares en los grupos BGC y LPB: 85.1% vs. 80.4% ( $p = 0.24$ ) y 90.8% vs. 97.2% ( $p = 0.22$ ), respectivamente. Se concluye que omitir la linfadenectomía pélvica completa en pacientes con GC bilateral negativo no parece asociarse con un mayor riesgo de recurrencia. La no inferioridad en cuanto a supervivencia debe ser confirmada por ensayos prospectivos<sup>19</sup>.

Actualmente se están llevando a cabo tres ensayos prospectivos aleatorizados, SENTIX<sup>20</sup>, SENTICOL III<sup>21</sup> y PHENIX/CSEM 010<sup>22</sup>, que evalúan la seguridad oncológica de la BGC frente a la LPB en pacientes con CaCu en etapa temprana. Al disponer de los resultados en los próximos años probablemente tendremos algún cambio de conducta para realizar con seguridad solo BGC o, si no se demuestra la no inferioridad frente a la LPB, dejaremos de realizar un procedimiento de baja morbilidad que es seguro, como lo es ahora la BGC.

Este estudio tiene como fortalezas que se realizó en una institución con un alto volumen de casos de cáncer, que los ganglios fueron todos evaluados por una sola patóloga con gran experiencia en tumores ginecológicos, y que se realizó la ultraestadificación en los GC. Sin embargo, como limitaciones se encuentran las implicaciones que tiene el ser un estudio de naturaleza retrospectiva.

## Conclusiones

La BGC está recomendada en pacientes con CaCu en etapa temprana hasta 4 cm, con una mejor detección y bilateral en menores de 2 cm. El uso de trazador azul patente y Tc-99, con aplicación en al menos dos cuadrantes laterales del cérvix a las 3 y las 9 de las manecillas del reloj, es una técnica segura y eficaz; de acuerdo con la literatura internacional, el uso del trazador verde de indocianina mejora la detección del GC.

En el análisis del GC siempre se deberá considerar la realización de ultraestadificación patológica, ya que

incrementa al doble las tasas de detección de metástasis del ganglio estudiado no identificadas solo por hematoxilina-eosina.

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## Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

## Consideraciones 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, consentimiento informado y aprobación ética.** El estudio no involucra datos personales, historias clínicas ni muestras biológicas humanas, por lo que no requiere aprobación ética. No se aplican las guías SAGER.

**Declaración sobre el uso de inteligencia artificial.** Los autores declaran que no se utilizó ningún tipo de inteligencia artificial generativa para la redacción ni la creación de contenido de este manuscrito.

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# Oral cavity cancer: retrospective analysis of a tertiary level hospital

## *Cáncer de cavidad oral: análisis retrospectivo de un hospital de tercer nivel*

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### Abstract

**Objective:** To describe the clinical characteristics, treatment patterns, and survival outcomes of patients with oral cavity cancer treated at a tertiary care center. **Methods:** A retrospective study was conducted on 224 patients with oral cavity cancer treated between 1988 and 2023. Clinical, pathological, and therapeutic data were collected, evaluating survival through Kaplan-Meier curves and Cox regression models. **Results:** The median overall survival was 92.3 months, with a better prognosis in early stages (111.6 months in stage I) and in patients treated surgically. Non-SCC tumors showed significantly greater survival. The use of induction chemotherapy followed by radiotherapy notably improved survival in advanced disease (203.9 months). Surgery was confirmed as the most effective strategy in the early stages. **Conclusions:** Age, functional status, histology, and clinical stage at diagnosis are relevant prognostic factors. Surgery remains the cornerstone of treatment, and in locally advanced disease, induction chemotherapy is an option.

**Keywords:** Oral cancer. Squamous cell carcinoma. Treatment. Overall survival. Prognosis.

### Resumen

**Objetivo:** Describir las características clínico-patológicas, las estrategias terapéuticas y los resultados de supervivencia de los pacientes con cáncer de cavidad oral tratados en un hospital de tercer nivel. **Métodos:** Estudio retrospectivo de 224 pacientes con cáncer de cavidad oral tratados entre 1988 y 2023. Se recopiló datos clínicos, patológicos y terapéuticos, y se evaluó la supervivencia mediante curvas de Kaplan-Meier y modelos de regresión de Cox. **Resultados:** La mediana de supervivencia global fue de 92.3 meses, con un mejor pronóstico en estadios tempranos (111.6 meses en estadio I) y en pacientes tratados quirúrgicamente. Los tumores distintos del carcinoma de células escamosas presentaron una supervivencia significativamente mayor. El uso de quimioterapia de inducción seguida de radioterapia mejoró notablemente la supervivencia en enfermedad avanzada (203.9 meses). La cirugía se confirmó como la estrategia más eficaz en las etapas iniciales. **Conclusiones:** La edad, el estado funcional, la histología y el estadio clínico en el momento del diagnóstico son factores pronósticos relevantes. La cirugía sigue siendo la piedra angular del tratamiento, y en la enfermedad localmente avanzada la quimioterapia de inducción constituye una opción terapéutica.

**Palabras clave:** Cáncer oral. Carcinoma de células escamosas. Tratamiento. Supervivencia global. Pronóstico.

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## Introduction

Oral cavity cancer is the most frequent site of head and neck tumors, which include the lip, upper and lower alveolar ridge, retromolar trigone, hard palate, the anterior two-thirds of the tongue, floor of the mouth, and buccal mucosa.<sup>1</sup> The incidence of this neoplasm is higher in males.<sup>2</sup> The average age of presentation is 64 years, with different clinical characteristics and prognoses at younger ages.<sup>2-4</sup> The most frequent histology is squamous cell carcinoma (SCC) in more than 90%.<sup>5</sup>

In general, the majority of cases are diagnosed with locoregional disease, making them candidates for radical treatment. In early disease, surgery is the standard treatment followed by radiotherapy, with or without chemotherapy, in high-risk patients.<sup>6</sup> Locally advanced locoregional disease represents a therapeutic challenge, where treatment decisions will depend on multiple factors such as tumor volume, the affected subsite, available therapeutic options or infrastructure, and even patient preference.<sup>7,8</sup> Despite treatment, recurrence rates are close to 50%, and the 5-year life expectancy is < 20%.<sup>9</sup>

Understanding the outcome of therapeutic decisions in patients with oral cavity cancer in our setting will allow us to improve the prognosis of these patients and optimize available resources. The aim of this study is to report the oncological outcomes of patients with oral cavity cancer by clinical stage and treated in a multidisciplinary manner at the Centro Médico Nacional 20 de Noviembre.

## Methods

This study was conducted in accordance with the principles outlined in the Helsinki Declaration. As a retrospective study, ethical approval was not required. We included patients with oral cavity cancer from January 1988 to December 2023. Complete medical records were used for data collection, including the analysis of overall survival, which was defined as the period from diagnosis to the last follow-up visit or the patient's death.

Statistical analysis included the calculation of mean  $\pm$  standard deviation for quantitative variables and relative and absolute frequencies for qualitative variables. Kaplan-Meier curves and log-rank statistics were used to estimate progression-free survival, while Cox regression models were employed for multivariate

analysis and the evaluation of prognostic factors. Statistical analysis was performed using STATA 16.0 software.

## Results

A total of 224 patients with oral cavity cancer were included. The average age was 61.3 years with a standard deviation of 13.8 years. Sex distribution showed a balanced proportion of men and women. 86% of patients had a functional status of 0-1 according to the Eastern Cooperative Oncology Group (ECOG) scale. The tongue was the most frequent anatomical subsite, accounting for 45.5% of cases.

Regarding clinical stage at the time of diagnosis, most patients (56%) presented with advanced disease, corresponding to Stages III and IV, while 34% were in early stages. The predominant histology was SCC, representing 87.9% of cases, while the remaining 12% included other histologies such as adenoid cystic carcinoma, melanoma, sarcomas, and lymphomas. Table 1 summarizes the clinical-pathological characteristics of the patients.

The median overall survival for the cohort was 92.3 months (95% CI: 44.7-147.1 months). Comparing histologies, non-squamous tumors showed significantly greater overall survival compared to SCC, with medians of 280 months and 51.8 months, respectively (HR 2.68, 95% CI: 1.29-5.51,  $p = 0.008$ ).

Subsequent analysis focused on the 197 patients with SCC of the oral cavity. 71.6% of cases received surgical treatment, 61.9% received radiotherapy, and 32.5% received systemic treatment. Table 2 summarizes the treatments received. The median overall survival showed a clear relationship with clinical stage, being 111.6 months in Stage I, 46.7 months in Stage II, 27.4 months in Stage III, 16.2 months in Stage IVA, and 11.9 months for Stage IVB (log-rank  $p = 0.001$ ), as shown in figure 1.

Analysis by initial treatment showed significant differences in median overall survival (log-rank  $p$  adjusted for clinical stage = 0.001). Patients undergoing surgery alone reached 157.2 months, while those who received surgery with adjuvant treatment with radiotherapy or chemoradiotherapy presented 54.9 months. Patients who received induction chemotherapy followed by radiotherapy with or without adjuvant chemotherapy had a survival of 203.9 months, in contrast to those treated with definitive chemoradiotherapy, who achieved 31.4 months, and 15.2 months for patients treated with induction followed by surgery.

**Table 1. Basal characteristics**

| Characteristics         | Patients (n = 224) | Patients with SCC (n = 197) |
|-------------------------|--------------------|-----------------------------|
| Age in years, mean (SD) | 61.3 (± 13.8)      | 62.6 (± 13.7)               |
| Gender, n (%)           |                    |                             |
| Masculine               | 110 (49.1)         | 102 (51.8)                  |
| ECOG, n (%)             |                    |                             |
| 0                       | 29 (13)            | 20 (10.2)                   |
| 1                       | 164 (73.2)         | 149 (75.6)                  |
| 2                       | 23 (10.2)          | 21 (10.7)                   |
| 3                       | 8 (3.6)            | 7 (3.5)                     |
| Site, n (%)             |                    |                             |
| Tongue                  | 102 (45.5)         | 100 (50.8)                  |
| Lower Gums              | 41 (18.3)          | 40 (20.3)                   |
| Palate                  | 31 (13.8)          | 13 (6.6)                    |
| Others                  | 51 (22.8)          | 44 (22.3)                   |
| Histology, n (%)        |                    |                             |
| Epidermoide             | 197 (87.9)         | 197 (100)                   |
| Cystic adenoid          | 10 (4.5)           |                             |
| Others                  | 17 (7.6)           |                             |
| Clinical stage, n (%)   |                    |                             |
| I and II                | 76 (34.1)          | 69 (35.2)                   |
| III                     | 30 (13.4)          | 28 (14.3)                   |
| IVA and IVB             | 117 (42.5)         | 99 (50.5)                   |

SCC: squamous cell carcinoma; ECOG: eastern cooperative oncology group.

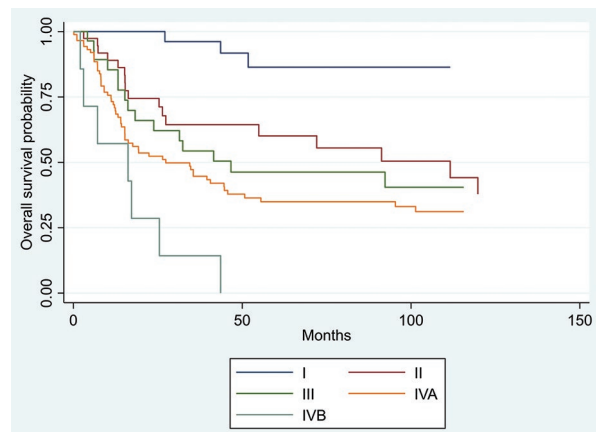
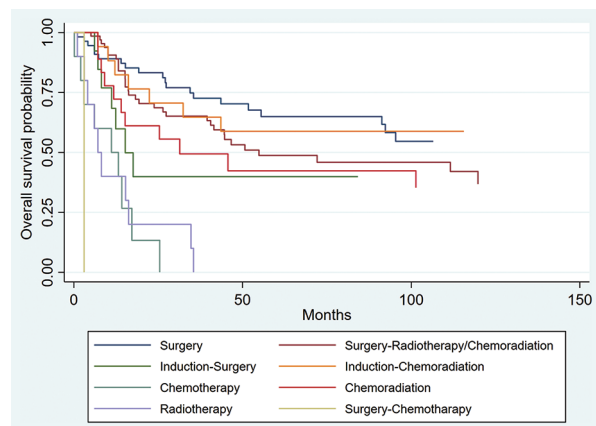
**Table 2. Treatment of patients with oral cavity SCC**

| Treatment, n (%)   | Patients (n = 197) |
|--------------------|--------------------|
| Surgery            | 141 (71.6)         |
| Definitive         | 117 (97.5)         |
| Rescue             | 3 (2.5)            |
| Radiotherapy       | 122 (61.9)         |
| Adjuvant           | 79 (64.7)          |
| Definitive         | 44 (35.3)          |
| Systemic treatment | 64 (32.5)          |
| Induction          | 38 (59.4)          |
| Concomitant        | 42 (65.6)          |

SCC: squamous cell carcinoma.

Patients treated with exclusive radiotherapy or chemotherapy showed median survivals of 7.1 and 11.1 months, respectively. Figure 2 shows Kaplan-Meier curves for overall survival by treatment.

Univariate and multivariate analyses using the Cox model (Table 3) confirmed that age, functional status according to the ECOG scale, clinical stage at diagnosis, and type of treatment received were significant prognostic factors for overall survival, maintaining their relevance in both analyses.

**Figure 1. Kaplan-Meier curves for global survival by clinical stage.****Figure 2. Overall survival by initial treatment sequence.**

## Discussion

In our cohort, SCC represented 87.9% of cases, consistent with reported data. The proportion of advanced stages was 64% in Stages III, IVA, and IVB, which is slightly lower than the described 67-81%.<sup>10,11</sup>

The median overall survival in our cohort was 92.3 months, with marked variation by clinical stage. Our median survival for stage I was 111.6 months, while the median of 21.8 months in Stage IV reflects the limitations of treatment in advanced stages. This finding aligns with studies that also reported progressive decreases in survival with more advanced stages.<sup>12,13</sup>

Regarding treatment, we observed that patients treated solely with surgery had significantly greater survival compared to those who received definitive chemoradiotherapy or palliative treatments. This

**Table 3. Univariate and multivariate analysis for global survival**

| Variable                            | Univariate |             |       | Multivariate |              |       |
|-------------------------------------|------------|-------------|-------|--------------|--------------|-------|
|                                     | HR         | 95% CI      | p     | HR           | 95% CI       | p     |
| Age                                 | 1.02       | 1.01-1.04   | 0.001 | 1.02         | 1.01-1.04    | 0.003 |
| Gender                              | 1.21       | 0.82-1.79   | 0.330 | 0.87         | 0.58-1.31    | 0.509 |
| ECOG                                | 1.74       | 1.31-2.32   | 0.001 | 1.42         | 1.03-1.95    | 0.032 |
| Subsite                             | 1.04       | 0.92-1.16   | 0.531 | 0.99         | 0.92-1.06    | 0.787 |
| Stage                               | 1.60       | 1.32-1.93   | 0.001 | 1.44         | 1.15-1.79    | 0.001 |
| Treatment                           |            |             |       |              |              |       |
| Surgery                             | 1          | 1           | 1     | 1            | 1            | 1     |
| Surgery-Radiotherapy/Chemoradiation | 1.61       | 0.93-2.78   | 0.088 | 1.15         | 0.63-2.07    | 0.651 |
| Induction-Surgery                   | 2.40       | 1.01-5.67   | 0.046 | 1.31         | 0.51-3.33    | 0.570 |
| Induction-Chemoradiation            | 1.16       | 0.51-2.62   | 0.722 | 0.77         | 0.32-1.88    | 0.573 |
| Chemotherapy                        | 9.28       | 4.10-20.98  | 0.001 | 3.75         | 1.43-9.83    | 0.007 |
| Chemoradiation                      | 2.04       | 1.00-4.15   | 0.049 | 1.23         | 0.55-2.77    | 0.608 |
| Radiotherapy                        | 8.55       | 3.94-18.58  | 0.001 | 4.02         | 1.43-11.30   | 0.008 |
| Surgery-Chemotherapy                | 68.43      | 7.87-594.61 | 0.001 | 99.14        | 10.06-976.54 | 0.001 |

ECOG: eastern cooperative oncology group; HR: hazard ratio; CI: confidence interval.

aligns with studies such as that by Wong et al., which highlight surgery as the intervention offering the best prognosis in early stages.<sup>14</sup>

Notably, the survival observed in patients treated with induction chemotherapy followed by radiotherapy (median of 203.9 months) was significantly higher than that reported in other studies, potentially influenced by factors such as patient selection with good functional status or previously mentioned factors.<sup>15,16</sup> Although the use of induction chemotherapy is controversial, in our setting, it remains a therapeutic tool for locally advanced disease due to infrastructure capacity and delays in initiating radiotherapy treatment. However, the survival of patients treated with surgery after induction treatment was much lower, which has been previously reported;<sup>17</sup> this may be explained by the risk of recurrence in the field of cancerization that is not easily delineated and, therefore, not completely resected.<sup>18,19</sup>

The main limitation of our study is its retrospective nature and the heterogeneity of the analyzed subgroups. However, it provides important real-world information regarding the treatment of patients with oral cavity cancer. The reported discrepancies highlight the need for additional studies to evaluate the implications of multiple contextual factors, early detection strategies, and therapeutic approaches that can be used in all regions.

## Conclusions

Age, functional status, histology, and clinical stage at diagnosis are important prognostic factors in oral cavity cancer. Surgery remains the cornerstone of treatment for these patients. In advanced disease, induction chemotherapy followed by chemoradiotherapy is a treatment option.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

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

**Confidentiality, informed consent, and ethical approval.** This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

### Declaration on the use of artificial intelligence.

The authors declare that artificial intelligence was used in the writing of this manuscript. During the preparation of this work, the author(s) used OpenAI. (2024). ChatGPT retrieved from <https://chat.openai.com/to> correct spelling and grammar. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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# Resultados del estudio RAW: revisión narrativa de complicaciones postoperatorias, características del paciente, resección venosa y tratamiento adyuvante

*Findings from the RAW Study: a narrative review of postoperative complications, patient factors, venous resection, and adjuvant treatment*

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## Resumen

Este trabajo sintetiza y analiza los hallazgos de los cuatro estudios derivados del proyecto Recurrence After Whipple's (RAW), enfocados en complicaciones postoperatorias, factores del paciente, técnica quirúrgica y acceso a terapia adyuvante después de pancreatoduodenectomía. La revisión integró la evidencia publicada entre 2023 y 2025 dentro de un marco conceptual orientado a identificar los determinantes del éxito oncológico. Los estudios muestran que la fístula pancreática postoperatoria de grado C y la hemorragia pospancreatectomía representan las complicaciones de mayor impacto en morbilidad y mortalidad, mientras que el retraso en el vaciamiento gástrico tiene una relevancia clínica limitada. La diabetes mellitus no modificó la recurrencia, la supervivencia ni el beneficio de la adyuvancia, en contraste con predictores adversos como márgenes positivos, ganglios metastásicos, tumores mayores de 3 cm y niveles elevados de CA19-9. La resección venosa demostró ser segura y oncológicamente equivalente cuando es realizada en centros con experiencia. Asimismo, las complicaciones mayores reducen la probabilidad de recibir tratamiento adyuvante, comprometiendo la supervivencia. En conjunto, RAW redefine las prioridades clínicas en pancreatoduodenectomía, enfatizando la prevención de complicaciones críticas, la conservación de la ventana terapéutica para adyuvancia y la toma de decisiones guiada por la biología tumoral.

**Palabras clave:** Pancreatoduodenectomía. Complicaciones postoperatorias. Fístula pancreática. Terapia adyuvante. Procedimientos quirúrgicos venosos. Diabetes mellitus.

## Abstract

This review synthesizes the findings of the four studies derived from the Recurrence After Whipple's (RAW) project, which examine postoperative complications, patient-related factors, surgical technique, and access to adjuvant therapy after pancreatoduodenectomy. Published evidence from 2023 to 2025 was integrated into a conceptual framework aimed at identifying the key determinants of oncologic success. The studies show that grade C postoperative pancreatic fistula and post-pancreatectomy hemorrhage are the complications with the greatest impact on morbidity and mortality, whereas delayed gastric emptying has limited clinical relevance. Diabetes mellitus did not influence recurrence, survival, or the benefit of adjuvant therapy, in contrast to independent prognostic predictors such as positive margins, metastatic lymph nodes, tumor size greater than 3 cm, and elevated CA19-9 levels. Venous resection was shown to be safe and oncologically equivalent when performed in experienced

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*centers. Major complications significantly decreased the likelihood of receiving adjuvant treatment, thereby worsening survival. Overall, the RAW project reframes clinical priorities in pancreatoduodenectomy, highlighting the prevention of critical complications, preservation of the therapeutic window for adjuvancy, and decision-making driven by tumor biology.*

**Keywords:** *Pancreaticoduodenectomy. Postoperative complications. Pancreatic fistula. Adjuvant therapy. Venous surgical procedures. Diabetes mellitus.*

## Introducción

El cáncer de páncreas se encuentra entre las principales causas de mortalidad por cáncer en todo el mundo, con un incremento sostenido en el número absoluto de casos reportados en las últimas décadas<sup>1</sup>. La pancreatoduodenectomía (PD) continúa siendo el tratamiento potencialmente curativo para los tumores resecables de la cabeza pancreática, pero es una de las operaciones más complejas de la cirugía abdominal mayor, con tasas de morbilidad que alcanzan entre el 40% y el 60% incluso en centros con alta experiencia<sup>2,3</sup>. Aunque la mortalidad postoperatoria ha disminuido significativamente y en instituciones especializadas suele situarse entre el 1% y el 5%, persiste una variabilidad considerable en los desenlaces entre hospitales, atribuible a diferencias en volumen quirúrgico, experiencia institucional y estandarización de los cuidados perioperatorios<sup>3</sup>. Además, gran parte de la evidencia disponible proviene de series monocéntricas o de cohortes de tamaño limitado, lo que dificulta identificar de manera robusta los factores clínicos y oncológicos que influyen en los resultados posteriores a la PD<sup>4</sup>.

El estudio *Recurrence After Whipple's* (RAW) es una iniciativa multicéntrica internacional desarrollada para superar las limitaciones de la evidencia tradicional sobre la PD, históricamente basada en series unicéntricas y tamaños muestrales reducidos. Su diseño colaborativo, con estandarización de definiciones y recolección sistemática de datos perioperatorios y oncológicos, permite analizar con mayor precisión los factores que influyen en la morbilidad, la recurrencia y la supervivencia tras la cirugía<sup>5</sup>.

A partir de esta cohorte se han publicado cuatro análisis independientes que exploran dimensiones clave del manejo de la PD: el impacto diferencial de las complicaciones postoperatorias, la influencia de características del paciente como la diabetes *mellitus* (DM) en la recurrencia y la supervivencia, los resultados asociados a la resección venosa y el efecto de las complicaciones mayores en el acceso oportuno a la terapia adyuvante<sup>6-9</sup>.

Aunque el estudio RAW ha generado múltiples publicaciones que abordan aspectos específicos de la PD, estos análisis han sido reportados de forma independiente y permanecen dispersos en la literatura. La ausencia de una síntesis que integre los hallazgos limita su interpretación global y dificulta su aplicación en la práctica clínica. Por ello, se requiere una revisión narrativa que reúna y analice los resultados publicados del estudio RAW con el fin de ofrecer una visión unificada y actualizada de los factores que influyen en los desenlaces posteriores a la PD.

## Métodos

Se realizó una revisión narrativa de la literatura basada en los estudios derivados de la base de datos multicéntrica RAW. La búsqueda se llevó a cabo en PubMed, identificando todas las publicaciones originales relacionadas con el estudio RAW desde su registro inicial hasta el año 2025. Se incluyeron artículos que cumplieran los siguientes criterios: estar basados en la cohorte RAW y haber sido publicados en revistas con revisión por pares. Se excluyeron los artículos no derivados directamente de la base RAW.

En total, se analizaron cuatro estudios publicados correspondientes a las principales líneas de investigación generadas a partir del RAW: complicaciones postoperatorias, características del paciente, resección venosa y tratamiento adyuvante.

La síntesis se efectuó mediante una integración narrativa de los hallazgos, debido a la heterogeneidad metodológica de los estudios incluidos y a la ausencia de métricas comparables que permitieran un metaanálisis formal.

## Resultados

Los hallazgos del estudio RAW han sido publicados en cuatro análisis independientes que abordan distintas dimensiones de la PD (Tabla 1). A continuación, se presentan los resultados principales de cada uno de estos trabajos de manera individual. Posteriormente, se integrarán sus implicaciones para ofrecer una visión global y unificada.

**Tabla 1. Publicaciones derivadas del estudio RAW**

| Estudio                         | Tema principal                                                      | Conclusiones                                                                                                                                                                                                                           |
|---------------------------------|---------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Russell et al. <sup>6</sup>     | Complicaciones postoperatorias tras la PD                           | La fístula pancreática postoperatoria de grado C y la hemorragia pospancreatectomía fueron las complicaciones de mayor impacto clínico. El retraso en el vaciamiento gástrico no se asoció con mortalidad ni con complicaciones graves |
| Rajagopalan et al. <sup>7</sup> | Impacto de la DM en la recurrencia y la supervivencia               | La DM preexistente no afectó la recurrencia, la supervivencia global, la supervivencia libre de enfermedad ni la probabilidad de recibir adyuvancia                                                                                    |
| Bellotti et al. <sup>8</sup>    | Seguridad y resultados oncológicos de la resección venosa           | La resección venosa no aumentó la morbilidad ni la mortalidad, y fue equivalente a la PD sin resección venosa                                                                                                                          |
| Russell et al. <sup>9</sup>     | Complicaciones serias y su impacto en el acceso a terapia adyuvante | Las complicaciones mayores (Clavien-Dindo ≥ IIIa) redujeron significativamente el acceso a quimioterapia adyuvante                                                                                                                     |

DM: diabetes mellitus; PD: pancreatoduodenectomía.

### **Complicaciones postoperatorias tras la PD<sup>6</sup>**

Las complicaciones con mayor impacto clínico fueron la fístula pancreática postoperatoria de grado C y la hemorragia pospancreatectomía, ambas asociadas a un aumento significativo de la morbilidad grave y de la mortalidad. En contraste, el retraso en el vaciamiento gástrico, pese a su frecuencia, no se relacionó con mayor mortalidad ni con complicaciones graves. Los factores independientes asociados a complicaciones mayores fueron la edad avanzada, el índice de masa corporal alto, la clasificación de la American Society of Anesthesiologist, la hipoalbuminemia y los tiempos quirúrgicos prolongados.

Mensaje central: no todas las complicaciones pesan igual; la fístula pancreática postoperatoria de grado C y la hemorragia pospancreatectomía son las que realmente determinan el pronóstico.

### **Características del paciente y su impacto en la recurrencia y la supervivencia<sup>7</sup>**

La DM preexistente no tuvo impacto significativo en la recurrencia, la supervivencia global, la probabilidad de recibir terapia adyuvante ni el beneficio derivado de esta. En contraste, los predictores independientes de peor pronóstico fueron las variables relacionadas con la biología tumoral: ganglios positivos, márgenes R1, CA19-9 elevado y tumores mayores de 3 cm.

Mensaje central: el pronóstico está definido por la biología tumoral; la DM no modifica el comportamiento oncológico de la enfermedad.

### **Impacto de la técnica quirúrgica: resección venosa<sup>8</sup>**

La comparación entre PD con y sin resección venosa mostró que esta no aumentó la morbilidad ni la mortalidad, y mantuvo unas tasas similares de complicaciones mayores. Tampoco se observaron diferencias en supervivencia global, supervivencia libre de enfermedad y patrones de recurrencia.

Mensaje central: la resección venosa es segura y oncológicamente equivalente; su éxito depende principalmente de la experiencia institucional.

### **Complicaciones serias y acceso a terapia adyuvante<sup>9</sup>**

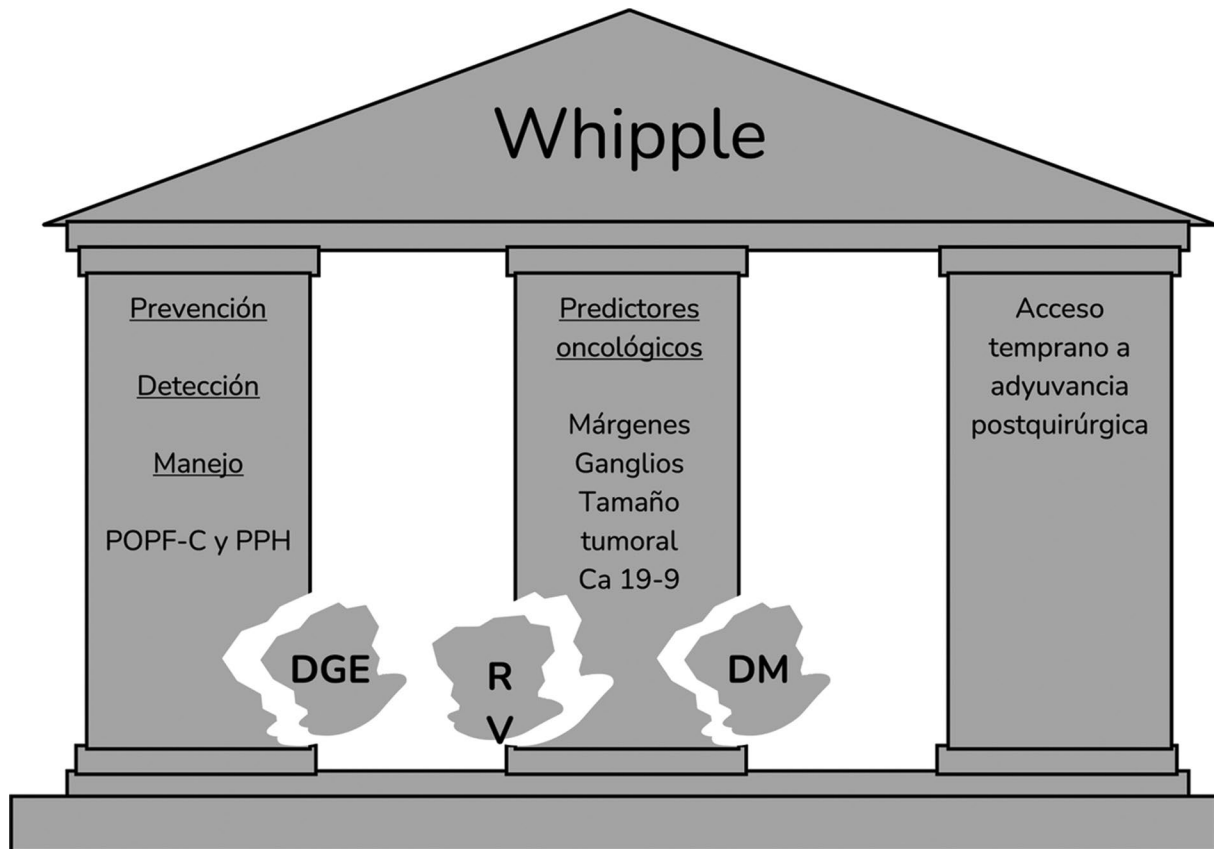
Las complicaciones mayores (Clavien-Dindo ≥ IIIa) redujeron de manera significativa la probabilidad de recibir quimioterapia adyuvante. La ausencia de adyuvancia se asoció con peor supervivencia global, indicando que el impacto clínico negativo proviene de la pérdida de la ventana oncológica más que de la complicación en sí.

Mensaje central: la complicación grave no afecta la supervivencia por sí misma; lo hace al impedir el acceso oportuno a la adyuvancia.

## **Discusión**

Los resultados publicados del estudio RAW aportan una visión contemporánea que respalda conceptos previamente establecidos, pero al mismo tiempo cuestiona y redefine otros aspectos de la PD.

En primer lugar, confirma lo descrito en revisiones previas que identificaban a la fístula pancreática



**Figura 1.** Modelo conceptual Partenón del Whipple derivado del proyecto RAW, que ilustra los pilares determinantes del éxito oncológico tras la pancreatoduodenectomía y los factores que han demostrado tener menor impacto pronóstico. DGE: retraso en el vaciamiento gástrico; DM: diabetes mellitus; POPF-C: fístula pancreática postoperatoria de grado C; PPH: hemorragia pospancreatectomía; RV: resección venosa.

postoperatoria de grado C y a la hemorragia pospancreatectomía como las complicaciones con mayor impacto en mortalidad, reintervención y deterioro clínico<sup>3,6</sup>. No obstante, contradice el peso atribuido históricamente al retraso en el vaciamiento gástrico; aunque la literatura lo señalaba como una complicación relevante por su frecuencia y asociación con estancias prolongadas<sup>3</sup>, se demostró que no incrementa la mortalidad<sup>6</sup>.

Además, en relación con los hallazgos sobre acceso a adyuvancia, el impacto fisiológico limitado del retraso en el vaciamiento gástrico implica que no compromete de manera significativa la ventana oncológica para iniciar la quimioterapia adyuvante, a diferencia de la fístula pancreática postoperatoria de grado C y la hemorragia pospancreatectomía, que sí condicionan retrasos sustanciales o incluso pérdida definitiva de la adyuvancia<sup>9</sup>. En este contexto, se sugiere que el verdadero impacto clínico de una complicación debe medirse no solo por su frecuencia o mortalidad inmediata, sino por su capacidad de impedir un tratamiento oncológico oportuno.

Por otro lado, aunque los estudios epidemiológicos habían planteado que la DM podría asociarse con peores desenlaces oncológicos por su relación con inflamación crónica y disfunción metabólica<sup>1</sup>, se ha observado que la DM no afecta la recurrencia, la supervivencia global, la supervivencia libre de enfermedad ni el beneficio de la terapia adyuvante<sup>7</sup>. Este hallazgo contradice interpretaciones previas y desplaza el foco hacia los verdaderos predictores pronósticos independientes: variables de biología tumoral, particularmente márgenes R1, ganglios positivos, tumores mayores de 3 cm y CA19-9 elevado<sup>1,3,7</sup>.

Finalmente, en cuanto a la técnica quirúrgica y el temor histórico de que la resección venosa incrementa la mortalidad o comprometa los resultados oncológicos, mediante análisis con *propensity score* se demostró que no aumenta la morbilidad ni la mortalidad y que ofrece resultados oncológicos equivalentes a los de la PD sin resección venosa, siempre que se realice en centros con experiencia<sup>8</sup>.

Los cuatro análisis del estudio RAW permiten reinterpretar de manera integrada los determinantes del éxito oncológico después de una PD. A partir de estos hallazgos, es posible conceptualizar un Partenón, en el que el vértice superior representa el resultado oncológico final (supervivencia y control de la enfermedad) y las columnas corresponden a los elementos que realmente lo sostienen: la reducción de las complicaciones críticas, el acceso oportuno a adyuvancia y las variables de biología tumoral (Fig. 1).

## Limitaciones

Aunque los cuatro análisis del estudio RAW aportan información valiosa, existen limitaciones inherentes. La naturaleza multicéntrica conlleva heterogeneidad en la técnica quirúrgica, la selección de los pacientes y los protocolos perioperatorios. Además, los estudios derivados de RAW, aunque robustos, no constituyen un metaanálisis ni permiten establecer causalidad definitiva.

## Direcciones futuras

- Determinar estrategias estandarizadas de «rescate después de una complicación» y su impacto en la ventana oncológica.
- Validar modelos predictivos combinando biología tumoral, complicaciones críticas y tiempos de adyuvancia.

Estas cuestiones podrían orientar las próximas fases del estudio RAW o investigaciones multicéntricas futuras.

## Conclusiones

Los análisis derivados del estudio RAW permiten reinterpretar de manera integrada los determinantes del éxito oncológico tras la PD, al demostrar que las complicaciones críticas, la fístula pancreática postoperatoria de grado C y la hemorragia pospancreatectomía, y el acceso oportuno a la terapia adyuvante, son los principales factores que condicionan la supervivencia y el control tumoral. Por otro lado, aspectos tradicionalmente sobrerrepresentados, como el retraso en el vaciamiento gástrico, la DM y la resección venosa, muestran un impacto pronóstico limitado. Los hallazgos refuerzan la necesidad de estrategias dirigidas a prevenir y tratar tempranamente las complicaciones mayores, preservar la ventana oncológica para la

adyuvancia y centrar la toma de decisiones en la biología tumoral. Se requieren estudios adicionales que estandaricen algoritmos de rescate y validen modelos pronósticos combinados que optimicen aún más los resultados de la PD en centros especializados.

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## Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

## Consideraciones 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, consentimiento informado y aprobación ética.** El estudio no involucra datos personales, historias clínicas ni muestras biológicas humanas, por lo que no requiere aprobación ética. No se aplican las guías SAGER.

**Declaración sobre el uso de inteligencia artificial.** Los autores declaran que no se utilizó ningún tipo de inteligencia artificial generativa para la redacción ni la creación de contenido de este manuscrito.

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## The letter to editor regarding “Association of NRF-2 changes in plasma and pericardial fluid with renal injury in patients undergoing cardiac surgery”

*Carta al editor sobre el artículo "Asociación entre las alteraciones de NRF-2 en plasma y líquido pericárdico y la lesión renal en pacientes sometidos a cirugía cardíaca"*

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Dear Editor,

I read with great interest, the study by Padak et al. investigating changes in nuclear factor erythroid 2-related factor 2 (NRF-2), kidney injury molecule-1 (KIM-1), and heme oxygenase-1 (HO-1) levels in plasma and pericardial fluid (PF) among patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).<sup>1</sup> The authors should be commended for addressing an important and underexplored aspect of cardiorenal interactions, particularly the novel evaluation of oxidative stress-related biomarkers within PF.

Acute kidney injury remains a frequent and clinically significant complication after cardiac surgery, and early detection continues to be challenging. While traditional markers, such as serum creatinine lack sensitivity in the early post-operative period, the exploration of molecular biomarkers reflecting oxidative stress and inflammation is of high clinical relevance. In this context, the simultaneous assessment of NRF-2, HO-1, and KIM-1, provides valuable mechanistic insight into renal stress responses during CPB.

A notable strength of this study lies in the comparison between systemic circulation and PF. The finding that NRF-2 and HO-1 levels were higher in PF than in plasma, while KIM-1 predominated in plasma, supports the concept that PF represents a biologically active compartment rather than a passive ultrafiltrate.

This observation reinforces the potential role of PF as both a diagnostic reservoir and a therapeutic target, particularly for localized interventions aimed at modulating oxidative stress.

The demonstrated correlations between NRF-2, oxidative stress indices, and renal function parameters further emphasize the central role of redox imbalance in CPB-associated renal injury. Importantly, the dynamic changes observed during different CPB phases suggest that NRF-2-related pathways may respond rapidly to ischemia-reperfusion injury, highlighting their potential utility for early risk stratification.

Despite limitations related to sample size and the absence of urinary biomarker analysis, this study provides meaningful translational insight. Future investigations incorporating longitudinal outcomes and interventional strategies targeting NRF-2 signaling may further clarify its clinical applicability. Overall, this work represents an important contribution to the evolving understanding of cardiorenal syndrome in cardiac surgery.

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## **Conflicts of interest**

The authors declare that they have no conflicts of interest.

## **Ethical considerations**

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

**Confidentiality, informed consent, and ethical approval.** This study does not involve personal patient

data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

### **Declaration on the use of artificial intelligence.**

The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

## **Reference**

1. Padak M, Dikme R, Temiz E, Göç Ö, Ersöz E, Hacıoğlu Y. Association of NRF-2 changes in plasma and pericardial fluid with renal injury in patients undergoing cardiac surgery. *Cir Cir.* 2025;93:599-607.