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# The Medical Bulletin of Haseki

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# The Medical Bulletin of Haseki

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The Medical Bulletin of Haseki is the official scientific journal of the University of Health Sciences Turkey, Istanbul Istanbul Haseki Training and Research Hospital. It covers subjects on general medicine, published both in Turkish and English, and is independent, peer-reviewed, international periodical and is published quarterly (January, March, June, September and November).

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# The Medical Bulletin of Haseki

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The manuscript should not exceed 5000 words in total. All pages of the manuscript should be numbered at the top right-hand corner, except for the title page. Papers should include the necessary number of tables and figures in order to provide better understanding.

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Patients have a right to privacy. When not essential, identifying information, patient names and photographs should not be published, unless the written informed consent of the patient (parent or guardian) has been given.

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Results should also be given in detail to allow the reproduction of the study.

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Conclusion section should provide highlighted and interpreted with the study's new and important findings.

Acknowledgements should be as brief as possible. Any support should be acknowledged in this section. (Acknowledgements should be only send with the "Cover Page".)

The excessive use of abbreviations is to be avoided. All abbreviations should be defined when first used by placing them in brackets after the full term. Abbreviations made in the abstract and in the text are taken into consideration separately. Abbreviations of the full terms stated in the abstract must be re-abbreviated after the same full term in the text.

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The reference list should be typed on a separate page at the end of the manuscript. If there are more than 6 authors, abbreviation of "et al." should be used for the authors out of the first three. Journal titles should be abbreviated according to the style used in the Index Medicus. All the references should be written according to the Vancouver system as follows:

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## Original Articles



## Case Reports

Original Article

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# A Detailed Scientometric Analysis of Global Publication Trends in COVID-19 Related Hematology and Oncology Research

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**Abstract**

**Aim:** A comprehensive scientometric analysis produced in hematology and oncology on coronavirus disease-2019 (COVID-19) research is lacking. This study presents a detailed analysis of COVID-19 related hematology and oncology literature.

**Methods:** The Web of Science (WoS) Core Collection was used for data collection. All published documents between 2020 and 2021 were included. The data exported from WoS enabled the extensive details of COVID-19 related literature in the hematology and oncology categories, including countries, institutions, authors, citations, and keywords. Scientometric interaction visualization of keywords and countries, and published journal co-authorships were created with free software. Worldwide participation of the countries in COVID-19 related hematology and oncology literature were shown by a graphic.

**Results:** The search question displayed 4761 documents. The leading type of document was original articles (34.4%). The United States of America was the number one country, publishing 32.6% of all documents on COVID-19 related hematology and oncology research, followed by Italy, the United Kingdom, China, and France. Huazhong University of Science and Technology was the most contributing institution in the literature (2.8%), followed by Harvard Medical School and Memorial Sloan Kettering Cancer Center. The journal Blood has published the most documents about this field. The average citations per item was 7.2. The most used keywords over this period were "COVID-19," "SARS-CoV-2," "coronavirus," and "cancer".

**Conclusion:** The results of the present study may assist health professionals interested in this field to better figure out the current trends in COVID-19 related hematology and oncology research worldwide, and it can provide them to reach a more accurate information in a shorter time.

**Keywords:** COVID-19, coronavirus, SARS-CoV-2, hematology, oncology

## Introduction

By late 2019, a novel virus, also named severe acute respiratory syndrome coronavirus-2, had been identified as an etiologic agent for pneumonia patients in central China (1). This novel, high-spread virus has turned into a pandemic and has forced a burden on healthcare facilities. Patients with malignancy are a susceptible group due to the immunocompromised situations caused by their malignancy treatments, the malignancy itself, and comorbidities (2). Patients with cancer are more likely to have worse outcomes (mortality ranging from 11.4% to 35.5%) when diagnosed with Coronavirus disease-2019 (COVID-19) compared to patients without cancer (3,4). Oncology practice patterns have changed their daily routines; e.g., delay of treatment or less effective, safer treatment regimens, more frequent use of white blood cell growth factors (5). Similarly, hematological associations have rapidly published fresh interim recommendations for physicians, in particular for hematopoietic stem cell transplantation practice patterns during this COVID-19 virus outbreak time (6).

Bibliometrics analyzes publications produced in a specific discipline of academic literature to identify patterns and trends (7). Scientometrics, also known as the "science of science," is a relatively new and popular statistical discipline that investigates all aspects of scientific literature (7-9). Parallel to the spread of pandemic effects

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all around the world, the scientific activity on COVID-19 has been rapidly elevated to a higher level with reduced peer-review processes and/or early access options in scientific journals. Thus, the rapid increase in COVID-19 literature in all fields of science was remarkable, especially after the second half of 2020. Though COVID-19 related publications about hematology and oncology are the trend topics of hematology and oncology practice during this pandemic, there has been no recent scientometric analysis of publications published on COVID-19 in the hematology and oncology literature.

This study presents a comprehensive analysis of academic literature about COVID-19 that has been published in hematology and oncology categories.

## Methods

### Study Design and Scientometric Analysis

This study was designed as a cross-sectional online literature analysis. The Web of Science (WoS) Core Collection (Thomson Reuters, New York, USA) was used for data collection. The data used in this study was obtained on April 29, 2021. A search question including keywords for "Covid" or "Covid-19" or "2019 novel coronavirus disease" or"coronavirus disease 2019" or "Covid-19 infection" or "SARS-CoV-2 disease". All documents from the WoS database produced between 2020 and 2021 were included in the analysis. The data acquired from the abovementioned search query has been refined to only include the "Hematology" and "Oncology" fields by selecting hematology and oncology from the "WoS Categories" option. Data was exported from WoS in two formats: "full record and cited references" and "Tab-delimited for Mac". A world map originated to show the global contribution of each country regarding publications in this category by the "Tableau Public" application, a free web source (7,10). Scientometric landscape visualization was performed by VOS viewer freeware (Leiden University, Leiden, Netherlands) (7,11). Citation counts represent all the data collected on April 29, 2021, when the WoS database search process was executed. Institutions were determined using the "Organizations-Enhanced" field. The records in England, Wales, Scotland, and Northern Ireland were merged into a single country, the United Kingdom (UK) (7).

### Statistical Analysis

Data retrieved from online literature sources has been recorded on the Excel worksheet (Office 365 for Mac). Only the descriptive statistical methods (frequencies and percentages) were used for data analysis. Due to a lack of conventional statistical comparison methods, no p-values were obtained in this study.

## Results

### Document Characteristics

The initial search query revealed 109,830 documents. After refinement for year periods and hematology/oncology categories, 4671 records were displayed during the period 2020-2021, 34.4% of which were original articles. A greater proportion of documents (2779, or 59.5%) were related to the oncology field. The documents published in 2020 were more numerous (3,624 vs. 999) than the documents published in 2021 as of the access date of this study. Oncology, hematology, cardiovascular system, radiology, and experimental research medicine were the trending research fields (64.9%, 40.3%, 10.4%, 4.8%, and 4%, respectively). The first document about this category was published in June 2020. The predominant language of the literature was English (98.7%), followed by French, German, Spanish, and Russian (0.5%, 0.5%, 0.1%, and 0.1%, respectively) (Table 1).

### The Most Influential Authors, Journals, Meetings, and Institutions

Thachik J has published the maximum number of records with 25 articles after anonymous authors in this area (Table 1). The blood was the leading journal with 191 articles, followed by Clinical Cancer Research, Annals of Oncology, British Journal of Hematology, Transfusion, Thrombosis Research, and Journal of Thrombosis and Thrombolysis (n=161, 141, 138, 135, 112, and 104 items, respectively; Table 1). The Annual Meeting of the European Society for Medical Oncology-ESMO has been found to be the leading meeting with the highest record among meetings in this field. The most prolific organizations worldwide were in China and the United States. Huazhong University of Science and Technology has published the most records among organizations, with 127 documents, followed by Harvard Medical School and Memorial Sloan Kettering Cancer Center (Table 2).

### Global Productivity

The United States of America (USA) was the leading country in COVID-19 literature in the Hematology and Oncology category and covered 32.6% of all productivity with 1523 items. Italy was the second leading country with 720 records, followed by the UK, China, and France (n=533, 513, and 298 items, respectively; Table 1). North America and Europe dominated the publication density around the world, but the least contribution to this field was observed in Africa (Figure 1).

### Citations, Keyword Analysis, and a Network of Co-authorship for Countries and Institutions

A total of 13764 (11102 without self-citations) citations have been displayed with a h-index of 78. The average

| Table 1. General characteristics of publications on COVID-19 research in hematology and oncology category | | | |
|---|---|---|---|
| **Document Types** | **Record count** | | **% of 4671** |
| Article | 1606 | | 34.4 |
| Letter | 1036 | | 22.2 |
| Meeting Abstract | 778 | | 16.7 |
| Editorial Material | 700 | | 15 |
| Review | 481 | | 10.3 |
| Early Access | 387 | | 8.3 |
| News Item | 39 | | 0.8 |
| Correction | 30 | | 0.6 |
| Retracted Publication | 1 | | 0.02 |
| Retraction | 1 | | 0.02 |
| **Total** | **4671** | | **100** |
| **Research Areas** | **Record count** | | **% of 4671** |
| Oncology | 3029 | | 64.9 |
| Hematology | 1883 | | 40.3 |
| Peripheral Vascular Disease | 484 | | 10.4 |
| Radiology Nuclear Medicine Medical Imaging | 224 | | 4.8 |
| Medicine Research Experimental | 185 | | 4 |
| Immunology | 138 | | 3 |
| Cardiac Cardiovascular Systems | 125 | | 2.7 |
| Surgery | 111 | | 2.4 |
| Pediatrics | 108 | | 2.4 |
| Nursing | 105 | | 2.3 |
| **The 20 most prolific authors** | **Record count** | | **% of 4671** |
| Anonymous | 31 | | 0.6 |
| Thachik J | 25 | | 0.5 |
| Wang J | 24 | | 0.5 |
| Wang Y | 23 | | 0.5 |
| Curıglıano G | 22 | | 0.5 |
| Lıu Y | 22 | | 0.5 |
| Gupta S | 21 | | 0.5 |
| Peters S | 21 | | 0.5 |
| Lippi G | 20 | | 0.4 |
| Van Hemelrıjck M | 20 | | 0.4 |
| **The 10 most productive source titles** | **Country** | **Records** | **% of 4671** |
| Blood | USA | 191 | 4 |
| Clinical Cancer Research | USA | 161 | 3.5 |
| Annals of Oncology | Netherlands | 141 | 3 |
| British Journal of Hematology | UK | 138 | 3 |
| Transfusion | USA | 135 | 2.9 |
| Thrombosis Research | UK | 112 | 2.4 |
| Journal of Thrombosis and Thrombolysis | Netherlands | 104 | 2.3 |
| Pediatric Blood Cancer | USA | 100 | 2.1 |
| Journal of Thrombosis and Haemostasias | USA | 94 | 2 |
| Annals of Translational Medicine | China | 92 | 2 |
| **The top 10 countries** | **Records** | | **% of 4671** |
| USA | 1523 | | 32.6 |
| Italy | 720 | | 15.4 |
| England | 533 | | 11.4 |
| Peoples R China | 513 | | 11 |
| France | 298 | | 6.4 |
| Canada | 263 | | 5.6 |
| Spain | 249 | | 5.3 |
| India | 234 | | 5 |
| Germany | 214 | | 4.6 |
| Netherlands | 170 | | 3.6 |
| COVID-19: Coronavirus disease-2019 | | | |

citations per item was 7.2. A full-length article by Klok, F. A. et al. titled "Incidence of thrombotic complications in critically ill ICU patients with COVID-19" and published in Thrombosis Research in 2020, has gained the maximum citations (Table 3). The most used keywords over this period were "COVID-19", "SARS-CoV-2", "coronavirus", and "cancer" (Table 2). The scientometric network of keywords showed a "dichotomous pattern" in which COVID-19 was centered in the intersection (Figure 2). The USA was the most collaborative country, with 1523 documents, followed by Italy (Figure 3). The Journal of Blood and The Journal of Clinical Cancer Research were the leading source titles (Figure 4).

## Discussion

Scientometric studies display the publication trends and creativity of the countries, authors, and organizations in a certain area (7,8). Scientometrics enables the qualitative and quantitative assessment of academic literature and provides details of the most popular, active, and trending fields (7,12). Contrary to scientometrics growing popularity, there have been few articles investigating COVID-19 in the hematology and oncology fields (7).

Masjedi et al. (13) reported an overview of the oncology research of Iranian scholars between 1974 and 2019. The authors discovered an upward trend in all cancer research conducted by Iranian institutions, both in terms of productivity and citations received. However, the authors reported that complementary and alternative

medicine treatment subfields have not been well-studied in the oncology literature produced by Iran. The authors included the research records indexed in either the Pubmed, Scopus, or WoS databases, which were different from this study (13).

A report by Acevedo et al. (14) focused on the distribution and trend of hematology and oncology research in Latin America. The authors reported that the most contributing country to the hematology and oncology fields in Latin America was Brazil (60% of all published documents) (14). In contrast to this study, only the abstracts presented at 4 major hematology and oncology annual scientific meetings were analyzed. Only approximately 18% of abstracts were published as full-text articles in a median of 1 year after presentation. In contrast to this study, the network analysis between authors, keywords, countries, and institutions of all documents was absent in that study.

An interesting paper has presented the details of the European cancer research perspective regarding cancer sites and the economic wealth status of countries (15). The authors found that cancer sites (e.g., central nervous system, blood cancers) seemed to be over-researched, whereas some gastrointestinal (e.g., pancreas, esophageal) cancers were under-researched (15). Furthermore, European countries were found to be insufficient contributors to cancer research compared to their economic wealth status (15). The main distinction between this study and the aforementioned studies was

**Table 2. The 10 most productive institutions and most cited keywords on COVID-19 research in hematology and oncology category**

| Organizations | Country | Records | % of 4671 |
|---|---|---|---|
| Huazhong Univ Sci Technol | China | 127 | 2.7 |
| Harvard Med Sch | USA | 119 | 2.5 |
| Mem Sloan Kettering Canc Ctr | USA | 107 | 2.3 |
| Univ Milan | Italy | 96 | 2 |
| Univ Texas Md Anderson Canc Ctr | USA | 94 | 2 |
| Univ Toronto | Canada | 74 | 1.6 |
| Dana Farber Canc Inst | USA | 69 | 1.5 |
| Univ Washington | USA | 68 | 1.5 |
| Massachusetts Gen Hosp | USA | 61 | 1.3 |
| Univ Calif San Francisco | USA | 61 | 1.3 |
| **Keywords** | | | **Records** |
| Covid-19 | | | 1389 |
| Sars-cov-2 | | | 414 |
| Coronavirus | | | 235 |
| Cancer | | | 244 |
| Pandemic | | | 177 |
| Thrombosis | | | 125 |
| Covid$#8208 | | | 105 |
| 19 | | | 99 |
| Mortality | | | 83 |
| Cov$#8208 | | | 47 |

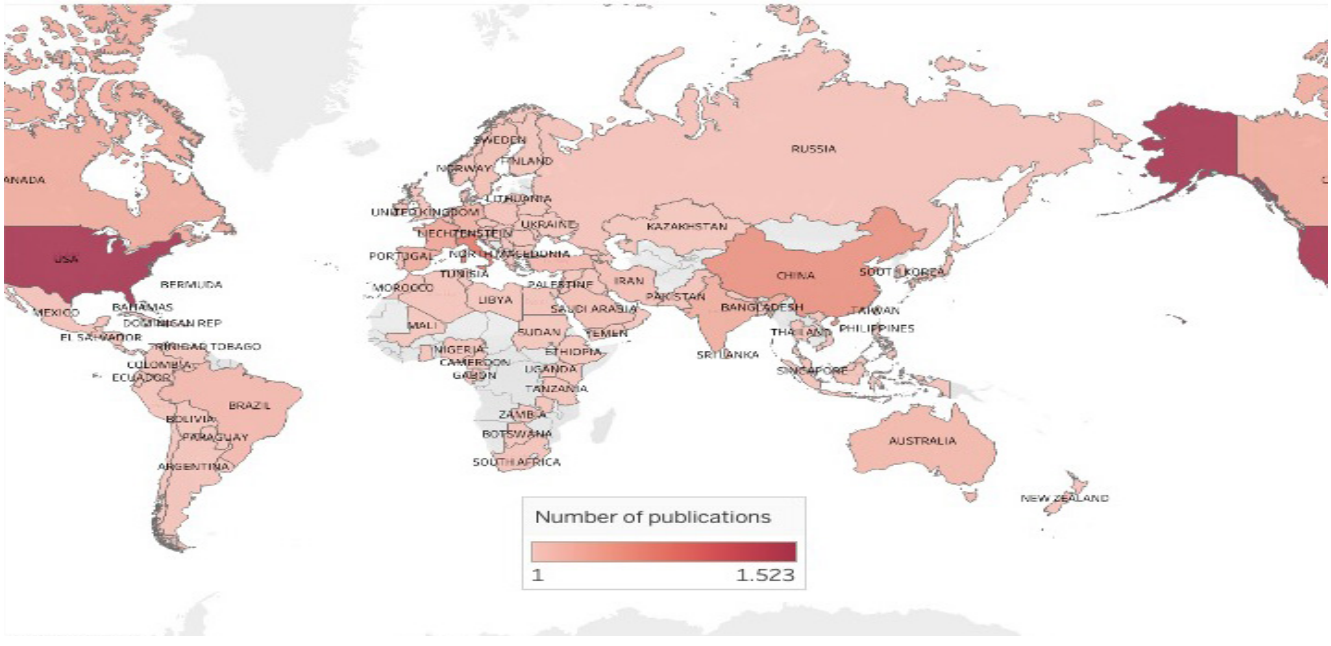


**Figure 1.** Publication density of world countries in COVID-19 related Hematology and Oncology research
COVID-19: Coronavirus disease-2019

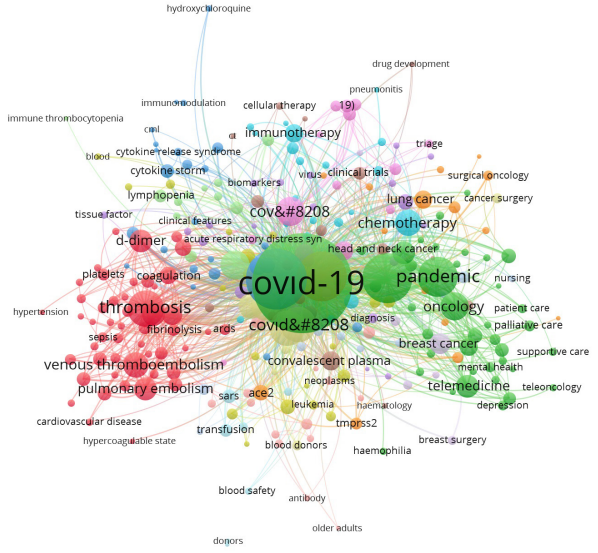


**Figure 2.** Scientometric interaction of the most used keywords in COVID-19 related Hematology and Oncology literature
COVID-19: Coronavirus disease-2019

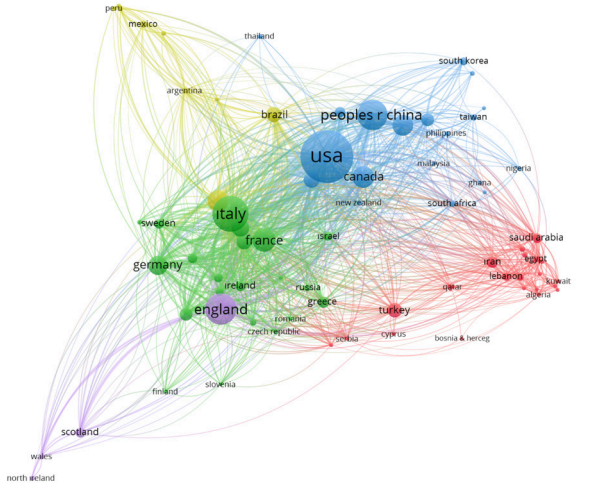


**Figure 3.** Scientometric interaction of the most cooperative countries in COVID-19 related Hematology and Oncology literature
COVID-19: Coronavirus disease-2019

**Table 3. Most cited articles on COVID-19 literature in haematology and oncology category**

| Article | Author(s) | Journal | Year | Total citations | Average citations per year |
|---|---|---|---|---|---|
| Incidence of thrombotic complications in critically ill ICU patients with COVID-19 | Klok, F. A., Kruip, M. J. H. A., Van der Meer, et al | *Thrombosis Research* | 2020 | 1336 | 668 |
| ISTH interim guidance on recognition and management of coagulopathy in COVID-19 | Thachil, J., Tang, N., Gando, S. et al. | *Thrombosis and Haemostasias* | 2020 | 586 | 293 |
| Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy | Lodigiani, C., Iapichino, G., Carenzo, L., et al | *Thrombosis Research* | 2020 | 584 | 292 |
| COVID-19 and its implications for thrombosis and anticoagulation | Connors, J. M., & Levy, J. H | *Blood* | 2020 | 583 | 291.5 |
| Pulmonary pathology of early-phase 2019 novel coronavirus disease-2019 (COVID-19) pneumonia in two patients with lung cancer. | Tian, S., Hu, W., Niu, L., Liu, H., Xu, H., et al | *Thoracic Oncology* | 2020 | 492 | 246 |
| Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China | Zhang, L., Zhu, F., Xie, L., et al | *Annals of Oncology* | 2020 | 437 | 218.5 |
| Hematological findings and complications of COVID-19 | Terpos, E., Ntanasis-Stathopoulos, I., Elalamy, et al | *American Journal of Hematology* | 2020 | 417 | 208.5 |
| Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2 | Gheblawi, M., Wang, K., Viveiros, A., et al. | *Circulation Research* | 2020 | 417 | 208.5 |
| Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19 | Zhang, P., Zhu, L., Cai, J., et al. | *Circulation Research* | 2020 | 390 | 195 |
| Incidence of thrombotic complications in critically ill ICU patients with COVID-19 | Klok, F. A., Kruip, M. J. H. A., et al. | *Thrombosis Research* | 2020 | 384 | 192 |

COVID-19: Coronavirus disease-2019, ICU: Intensive care unit, SARS-COV-2: Severe acute respiratory syndrome coronavirus-2, ACE-2: Angiotensin converting enzyme

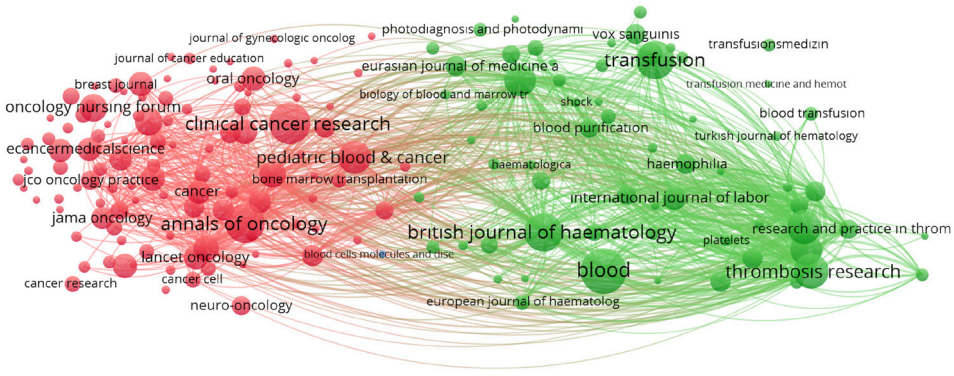


**Figure 4.** Scientometric interaction of the most cooperative source titles (journals) in COVID-19 related Hematology and Oncology literature

COVID-19: Coronavirus disease-2019

that a comparison of contributing countries according to their economic status was lacking (15).

Andersen et al. (16) analyzed the global myeloma research published between 2005 and 2013. The authors reported that an annual increase of up to 43% was observed in global publication density for myeloma research (16). European countries and the USA showed the highest intra-cluster collaboration between each other (16). Similar to this study, USA-originated myeloma research clusters dominated the total productivity and citations (16).

In a bibliometric analysis of acute myeloid leukemia (AML) research conducted between 1999 and 2018, the authors reported an increasing trend in AML studies after 2009 (17). The Blood journal has published the highest number of AML studies (17). The USA and Kantarjian H were found to be the most productive countries and authors of AML research, respectively (17). Similarly, in this report, the journals Blood and USA dominated the COVID-19 research in the hematology and oncology categories.

More than 50% of the global productivity on COVID-19 in hematology and oncology category documents was achieved by the USA and a few European countries (Italy, UK, and France). Except for China, all the first 5 leading contributing countries in COVID-19 in hematology and oncology categories were developed ones. The relatively higher productivity of China could be attributed to the fact that the COVID-19 outbreak was first spread from this country to the world.

Kappi et al. (18) have recently reported a bibliometric analysis of world COVID-19 research that was comparable to this study. As of September 10, 2020, 17,133 published documents were related to COVID-19 (18). A logarithmic increase in COVID-19 research was observed as of April 29, 2021 by the time this study was conducted compared with the Kappi et al.'s (18) report (109,830 vs 17,133). This logarithmic increase trend was also observed in the hematology and oncology categories. A total of 988 (564 in oncology and 424 in hematology) documents were related to COVID-19 as of 10 September, which has increased more than 5-folds (3029 in oncology and 1883 in hematology) in a 7-months-period (18). At two time points, the USA was the leading country regarding global productivity of COVID-19 research in this category. As the outbreak of COVID-19 has spread worldwide, China's contribution to global productivity in this category has decreased.

### Study Limitations

This study has several limitations. First, though WoS has been speculated as a more valid data source than other counterparts, the data obtained from only one data source might not represent all documents (7,19). A similar study on COVID-19 in the hematology and oncology categories was absent to achieve healthy comparisons with this report (7). However, this is the first report focusing on COVID-19 related hematology and oncology research by scientometric analysis.

### Conclusion

The results of this study may assist health professionals interested in this field to better figure out COVID-19 related hematology and oncology research worldwide. Beneficial information about dynamic and trending search topics in COVID-19 related hematology and oncology research fields may be obtained from this study. It can also contribute to researchers' access to information in a shorter time. Policymakers worldwide could better allocate their resources to improving and monitoring COVID-19-related hematology and oncology research.

### Ethics

**Ethics Committee Approval:** Ethical approval was not applicable and not obtained for this study due to not including human or animal research.

**Informed Consent:** Informed consent was not obtained.

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# Worldwide Evaluation of Public Interest in Gynecological Tumors during COVID-19 Pandemic

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## Abstract

**Aim:** During the coronavirus disease-2019 (COVID-19) pandemic, women seeking information about gynecological cancer frequently turn to the internet for help, as they frequently have difficulty accessing gynecological healthcare services. We aimed to determine the global public affinity for gynecologic tumors during the COVID-19 pandemic by using Google Trends (GT).

**Methods:** This GT analysis study was conducted from July 1st to July 5th, 2020. Authors determined twenty-two keywords related to gynecological cancers and all terms were searched on GT using filters of "Worldwide", "all categories", and "Web search". To evaluate public affinity for gynecologic cancer during the COVID-19 pandemic, three-four-week periods (2020) at the beginning of the COVID-19 pandemic were compared to the same periods (2016-2019) of the past four years.

**Results:** Comparison of the pandemic era and the past revealed that all terms except "gynecological oncology" were searched less frequently. During the pandemic era, the relative search volume for thirteen of the twenty-two terms decreased significantly. Twelve of twenty-two terms had a lower relative search volume, but three terms, including sarcoma, vulvar cancer, and gynecological cancer, had a significantly higher search volume between May 11th and June 9th, 2020.

**Conclusion:** There was a significant decrease in public interest in gynecological tumors at the beginning of the COVID-19 pandemic. In the eight weeks after the COVID-19 pandemic announcement, some terms, including gynecological oncology, sarcoma, and vulvar cancer, became significantly more popular than in the pre-pandemic era. During the COVID-19 outbreak, online interest in gynecologic cancers decreased.

**Keywords:** Coronavirus, COVID-19, Google, Google trends, gynecological tumor, gynecological oncology

## Introduction

The new coronavirus disease-2019 (COVID-19), originating from the China, has caused a global health crisis and continues to spread all around the world. According to the latest updates, 45 million COVID-19 cases have been confirmed, and COVID-19 is responsible for about 1.2 million deaths (1). On March 11, the World Health Organization (WHO) recognized a new coronavirus infection as a pandemic. Many governments have implemented social distancing, stay-at-home policies, and quarantine policies. Additionally, outpatient clinic appointments and elective surgical procedures were postponed. Due to difficulties in achieving a professional health system, patients started to use alternative methods to obtain information regarding their disease, including newspapers, television, and the internet (2).

Search engines are the most commonly used way to find any information on the Internet. Google Search (Google Inc., Mountain View, California, USA) is the world's most popular search engine, with nearly all internet users (90%) preferring it for their research (3). Google Trends (GT) is a tool to define search trends properties that show how frequently a given search term is entered into Google's search engine relative to the site's total search volume over a given period. Previously, Lampos et al. (4) used GT to investigate the public interest in influenza-like illnesses. In another study, Teng et al. (5) analyzed the forecasting of the Zika virus epidemic by using GT.

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While GT was used to describe public interest in different medical fields such as dermatology, otolaryngology, rheumatology, and urology during the COVID-19 outbreak, none of the studies investigated public interest in gynecological tumors during the COVID-19 pandemic. In this study, we determined the affinity of the public for gynecological tumors during the COVID-19 outbreak.

## Methods

### Study Design

Since the subject analyzed in the present study does not contain any confidential information, personal or patient data, ethics committee approval was not obtained. This retrospective study was conducted from July 1st to July 5, 2020. Authors determined twenty-two keywords related to gynecological cancers, including endometrial cancer, uterine cancer, cervical cancer, cervical dysplasia, ovarian cancer, sarcoma, vaginal cancer, vulvar cancer, postmenopausal bleeding, human papilloma virus (HPV), brachytherapy, granulosa cell tumor, choriocarcinoma, dysgerminoma, mole hydatiform, womb cancer, gynecological oncology, CA-125, hysterectomy, ovarian cyst, large loop excision of the transformation zone (LLETZ) and smear test. All terms were searched on GT using filters of "Worldwide", "all categories", and "Web search".

### Google Trends

GT provides information about any term among similar samples of all searches performed using the Google search engine at a specified time interval. The situation of Internet research could be achieved and downloaded from the website of GT (https://trends.google.com). The score of GT is introduced on a scale ranging from 0 to 100, and a higher score of GT is associated with a higher relative interest in the term (6).

To evaluate public interest in gynecologic cancer during the COVID-19 pandemic, three-four-week periods from the beginning of the COVID-19 pandemic (March 12th- April 10th, April 11th-May 10, and May 11th-June 9th) were compared to the same periods of the past four years (2016-2019). Dates after March 11th, 2020, were evaluated because WHO declared COVID-19 as a pandemic on that date.

### Statistical Analysis

Data was analyzed by using SPSS Statistics for Windows, Version 21.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Continuous variables were shown using an arithmetic mean and standard deviations. The normality assumption was checked using the Kolmogorov-Smirnov test. Paired samples, the t-test, and the Wilcoxon test were used to compare differences between groups. P-values less than 0.05 were considered statistically significant.

## Results

A comparison of March 12th-April 10th, 2020 and March 12th-April 10th, 2016–2019 revealed that all terms except gynecological oncology were searched less frequently. Additionally, questioning the terms endometrial cancer, uterine cancer, cervical cancer, cervical dysplasia, ovarian cancer, sarcoma, vaginal cancer, HPV, choriocarcinoma, womb cancer, gynecological oncology, CA-125, hysterectomy, ovarian cyst, LLETZ, and smear test statistically significantly decreased. Only the relative search volume of gynecological oncology terms did not decrease during the first period of the pandemic (+10.4, p=0.853) (Table 1).

In the April 11th-May 10th, 2020, period, the relative search volume for 13 of the 22 terms (endometrial cancer, uterine cancer, cervical cancer, cervical dysplasia, ovarian cancer, postmenopausal bleeding, HPV, brachytherapy, granulosa cell tumor, CA-125, hysterectomy, ovarian cyst, and smear test) statistically significantly decreased. Conversely, the relative research volume of nine terms was comparable with pre-pandemic era. None of the terms were searched significantly more frequently than in the previous four years (Table 1).

In the May 11th-June 9th, 2020, period, the relative search volume for 12 of 22 terms (uterine cancer, cervical cancer, cervical dysplasia, ovarian cancer, postmenopausal bleeding, HPV, choriocarcinoma, CA-125, hysterectomy, ovarian cyst, LLETZ, and smear test) had a lower relative search volume. However, the inquiry of seven terms (endometrial cancer, vaginal cancer, brachytherapy, dysgerminoma, granulosa cell tumor, mole hydatidiform, and womb cancer) was similar; however, the search terms (sarcoma, vulvar cancer, and gynecological cancer) had statistically significantly increased compared to the prior 4 years (p=0.045, p=0.015, and p=0.001, respectively). Overall, public interest in 22 terms decreased statistically significantly during the pandemic (-30.2, p=0.001 from March 12th to April 10th, 2020; -30.6, p=0.001 from April 11th to May 10, 2020; and -15.2, p=0.001 from May 11th to June 9th, 2020, respectively) (Table 1).

## Discussion

The sources of achieving knowledge have gained variety today, and many people prefer to use the Internet instead of written sources. According to Google data, 4 billion people preferred GT as a search engine, and 25% of that population used GT in the English language (7). During the COVID-19 pandemic, we have the chance to evaluate the public's interest in gynecological tumors by

**Table 1. Relative search volume of gynecologic oncology terms**

| | March 12 - April 10 | | | | April 11 - May 10 | | | | May 11 - June 9 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2020** | **2016-2019** | **% change** | **P-value** | **2020** | **2016-2019** | **% change** | **P-value** | **2020** | **2016-2019** | **% change** | **P-value** |
| Endometrial cancer | 24.3±11.3 | 35.3±12.7 | -31.2 | **0.001** | 42.5±12.5 | 51.5 ±15.4 | -17.5 | **0.003** | 54.6±18.4 | 56.7±19.5 | -3.7 | 0.583 |
| Uterine cancer | 30.2±11.3 | 49.9±15.8 | -39.5 | **0.001** | 35.7±5.2 | 55.5±15.4 | -35.1 | **0.001** | 42.6±10.7 | 49.0±12.3 | -13.1 | **0.014** |
| Cervical cancer | 28.9±7.3 | 50.5±12.3 | -42.8 | **0.001** | 42.8±6.1 | 65.9±11.5 | -35.1 | **0.001** | 44.6±5.7 | 58.5±9.1 | -23.8 | **0.001** |
| Cervical dysplasia | 23.1±14.7 | 35.5±21.8 | -34.9 | **0.007** | 22.6±11.6 | 31.1±12.9 | -27.3 | **0.005** | 26.7±14.8 | 37.2±15.5 | -28.2 | **0.001** |
| Ovarian cancer | 32.7±5.1 | 58.7±12.1 | -44.3 | **0.001** | 32.9±4.7 | 49.3±8.6 | -33.3 | **0.001** | 50.0±6.1 | 62.8±8.7 | -20.4 | **0.001** |
| Sarcoma | 49.8±12.1 | 62.9±13.8 | -20.8 | **0.001** | 55.2±8.4 | 58.3±9.3 | -5.3 | 0.128 | 17.9±3.1 | 16.2±3.7 | 10.5 | **0.045** |
| Vaginal cancer | 28.2±11.8 | 39.0±17.4 | -27.7 | **0.002** | 47.3±8.7 | 49.8±10.9 | -5.0 | 0.349 | 50.6±16.9 | 52.2±13.8 | -3.1 | 0.600 |
| Vulvar cancer | 31.9±11.4 | 33.6±15.8 | -5.1 | 0.170 | 14.7±8.4 | 16.4±6.7 | -10.4 | 0.252 | 52.7±11.9 | 44.7±16.4 | 17.9 | **0.015** |
| Postmenopausal bleeding | 22.7±11.5 | 27.6±12.2 | -17.8 | 0.619 | 21.0±8.8 | 36.1±9.7 | -41.8 | **0.001** | 22.3±8.9 | 28.8±16.9 | -22.6 | **0.044** |
| HPV | 33.2±6.6 | 55.5±12.1 | -40.2 | **0.001** | 48.7±5.3 | 73.3±13.3 | -33.6 | **0.001** | 28.2± 3.9 | 37.3±7.4 | -22.8 | **0.001** |
| Brachytherapy | 30.8±13.6 | 35.8±16.7 | -14.0 | **0.074** | 34.4±16.5 | 45.4±19.8 | -24.2 | **0.006** | 30.9±10.6 | 30.6±15.5 | 1.0 | 0.920 |
| Granulosa cell tumor | 17.5±8.8 | 21.3±9.6 | -17.8 | **0.386** | 18.2±7.6 | 19.1±8.2 | -4.7 | 0.761 | 21.2±8.2 | 22.1±7.6 | -4.1 | 0.867 |
| Choriocarcinoma | 19.2±13.2 | 34.5±9.9 | -44.3 | **0.004** | 24.5±12.5 | 29.8±16.7 | -17.8 | 0.107 | 28.8±13.7 | 40.2±19.9 | -28.4 | **0.004** |
| Dysgerminoma | 19.8±12.4 | 20.1±12.7 | -1.5 | 0.639 | 6.7±2.4 | 17.4±11.2 | -61.5 | **0.001** | 24.9±6.8 | 25.9±6.8 | -3.9 | 0.857 |
| Mole hydatiform | 30.1±15.6 | 35.6±20.1 | -15.4 | 0.967 | 36.7±6.7 | 39.8±8.2 | -7.8 | 0.765 | 42.2±7.8 | 46.1±5.9 | -8.5 | 0.645 |
| Womb cancer | 33.4±21.8 | 45.7±25.0 | -26.9 | **0.001** | 21.8±7.4 | 25.3±7.6 | -13.8 | 0.222 | 28.3±11.8 | 29.3±13.1 | -3.4 | 0.698 |
| Gynecological oncology | 37.1±14.3 | 33.6±21.2 | 10.4 | 0.853 | 36.2±5.6 | 32.2±6.5 | 12.4 | 0.451 | 42.6±4.1 | 33.2±5.8 | 28.3 | **0.001** |
| Ca-125 | 30.3±11.2 | 54.6±16.2 | -44.5 | **0.001** | 32.7±8.6 | 55.7±12.5 | -41.3 | **0.001** | 42.9±9.3 | 54.8±11.6 | -21.7 | **0.001** |
| Hysterectomy | 42.5±8.1 | 69.2±9.2 | -38.6 | **0.001** | 44.8±4.2 | 77.7±10.3 | -42.3 | **0.001** | 56.4±7.3 | 71.0±10.7 | -20.6 | **0.001** |
| Ovarian cyst | 53.4±10.8 | 79.1±11.6 | -32.5 | **0.001** | 58.2±6.5 | 78.1±10.1 | -25.5 | **0.001** | 63.2±6.5 | 73.7±10.3 | -14.2 | **0.001** |
| LLETZ | 33.2±18.1 | 43.2±20.1 | -23.1 | **0.009** | 27.1±8.1 | 30.9±9.8 | -12.3 | 0.176 | 23.7±9.3 | 31.3±12.9 | -24.3 | **0.010** |
| Smear test | 19.7±6.1 | 40.5±15.1 | -51.4 | **0.001** | 21.8±5.8 | 46.2±11.2 | -52.8 | **0.001** | 32.9±8.7 | 48.7±16.4 | -32.4 | **0.001** |
| TOTAL | 30.5±12.3 | 43.7±16.8 | -30.2 | **0.001** | 32.7±17.7 | 47.1±24.7 | -30.6 | **0.001** | 38.2±17.6 | 45.1±22.5 | -15.2 | **0.001** |

Data were presented as mean with standard deviation. Statistical analyses were performed using t-test and Wilcoxon tests.
HPV: Human papillomavirus, LLETZ: Large loop excision of the transformation zone, Ca: Cancer antigen

using GT due to restrictions on public transportation, quarantine rules, and difficulties in accessing a professional health system. The study revealed a significant decrease in public interest in gynecological tumors in the first 12 weeks of the COVID-19 pandemic. However, the search for gynecological oncology, sarcoma, and vulvar cancer in GT underwent a significant increase in the 3rd month of the COVID-19 pandemic.

Previous reports compared the public attention to different diseases in different medical disciplines between the pre-COVID-19 period and the COVID-19 period. Kardeş et al. (8) investigated public interest in 32 terms about rheumatic diseases in the United States of America, and the authors claimed that public interest significantly decreased in the first two months of the COVID-19 pandemic. In another study by Guzman and Barbieri (9), physicians stated a significant decrease in public interest in general dermatological conditions, malignant conditions, and cosmetic procedures in the first 15 days of the COVID-19 pandemic. However, interest in general dermatological terms returned to the pre-COVID-19 period one month after the first days of the COVID-19 pandemic. In the aforementioned studies, we found a significant decrease in public attention to gynecological tumors in the first 12 weeks of the pandemic compared to the prior 4 years of the pandemic era.

Every term that is searched on the Google search engine has a different relative search volume. In this study, we found a significantly higher search volume for "gynecological oncology" between 8 and 12 weeks after the beginning of the pandemic compared to the previous four years. We believe that two reasons may have a role in this result; the first is that the term "gynecological oncology" covers all kinds of cancer, and secondly, that term is known by the public better than specific cancer types. We obtained a similar result in terms of "vulvar cancer" and "sarcoma". Due to the aggressive nature of these two tumors and possible delays, the progression of the stage may increase the public interest in these tumors.

Delay in treating any disease due to factors related to COVID-19 and/or COVID-19 may increase disease cost, morbidity, or mortality in patients. Caplan (10) stated that a six-week delay in breast cancer was related to more advanced disease. In another study on endometrial cancer, Dolly et al. (11) found an increase in mortality in patients due to the prolongation of the time from diagnosis to treatment. Jella et al. (12) investigated the effects of the COVID-19 pandemic on hip and knee arthroplasties, and the authors claimed that the COVID-19 pandemic resulted in greater patient volume and economic burden after the crisis. However, there is no literature yet focusing on the impact of the COVID-19 outbreak on the diagnosis and treatment of gynecological tumors, which may be the subject of another study.

### Study Limitations

When evaluating the findings of this study, some limitations must be addressed. These findings apply solely to Google search queries. Although Google is the most popular search engine on the planet, more research is needed to determine whether the search behavior described here is similar or different for other search engines or platforms. Our study includes data generated throughout the world; this can be a disadvantage in terms of country-based interpretation. Despite the limitations of the study, it is the strength of the study that it contains a unique and detailed analysis on a curious subject.

## Conclusion

Public interest in gynecological tumors significantly decreased at the beginning of the COVID-19 pandemic compared to similar periods in the previous four years. Moreover, this study revealed that eight weeks after the COVID-19 pandemic announcement, some terms including gynecological oncology, sarcoma and vulvar cancer became significantly more popular than the pre-pandemic period compared to the similar periods in the previous four years.

### Acknowledgments

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### Ethics

**Ethics Committee Approval:** Since the subject analyzed in the present study does not contain any confidential information, personal or patient data, ethics committee approval was not obtained.

**Informed Consent:** Since the subject analyzed in the present study does not contain any confidential information, personal or patient data, informed consent was not obtained.

### Authorship Contributions

Concept: M.E., F.E., F.Y.G., Design: M.E., F.E., F.Y.G., Data Collection and/or Processing: M.E., F.E., F.Y.G., Analysis and/or Interpretation: M.E., F.E., F.Y.G., Literature Research: M.E., F.E., F.Y.G., Writing: M.E., F.E., F.Y.G.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Original Article

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# Evaluation of Oxygenation in Low- and High-Flow Anesthesia Applications by Oxygen Reserve Index: A Randomized Prospective Study

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**Abstract**

**Aim:** While arterial blood gas (ABG) analysis is invasive, intermittent, and costly, the oxygen reserve index (ORI) is a new method that can be non-invasive and continuous measurement aimed at providing information about the patient's $O_2$ status in the moderately hyperoxic range. In our study, the ORI to $PaO_2$ relationship in different fresh gas flows was evaluated.

**Methods:** This randomized prospective study was conducted between November 2018 and November 2019. All patients were ventilated for the first 10 min after intubation with 50% $O_2$/air and 6 L/min fresh gas flow. Then, the flow rate was randomly set to 4 L/min for high-flow anesthesia (group H) or 1 L/min for low-flow anesthesia (group L). ABG's were taken before preoxygenation, intraoperative 60$^{th}$ min, and at the end of surgery, and simultaneous ORI and $SpO_2$ were recorded.

**Results:** The study was completed with 70 patients. Mean $PaO_2$ values were higher in group H, apart from before preoxygenation ($p<0.05$). Mean ORI values differed between groups except before preoxygenation and the intraoperative 10$^{th}$ min ($p<0.05$). A statistically significant, positive and weak correlation was identified between ORI and $PaO_2$. According to the regression analysis, the ORI value was approximately 0.2 when the $PaO_2$ value was ≥100 mmHg at the intraoperative 60$^{th}$ min and at the end of the surgery, and 0.3 when the $PaO_2$ was ≥150 mmHg.

**Conclusion:** ORI may be an alternative to $PaO_2$ in monitoring the oxygen status of intraoperative patients.

**Keywords:** General anesthesia, hyperoxia, low flow anesthesia, oxygen reserve index

## Introduction

Low-flow anesthesia is based on the principle of returning at least 50% of the exhaled gases to the patient via a breathing system after the elimination of carbon dioxide in the anesthesia circuit (1). In low-flow anesthesia applications, the difference between the amount of oxygen ($O_2$) and the $O_2$ centration in the gas composition provided to the patient increases as the fresh gas flow decreases. Because the oxygen-depleted gas mixture takes up a large amount of space in the rebreathing volume, the $O_2$ concentration delivered to the patient may drop significantly, increasing the risk of hypoxia (1,2).

Peripheral $O_2$ saturation ($SpO_2$) and arterial partial oxygen pressure ($PaO_2$) are monitored to detect hypoxia during anesthesia applications. Oxygen reserve index (ORI) is a measurement technique derived from hemoglobin sensors, which shows the $O_2$ reserve in arterial blood and can instantly evaluate tissue oxygenation. It is an index with a unitless scale between 0 and 1, which is a relative indicator of changes in $PaO_2$, especially in the mild hyperoxic range ($PaO_2$ 100-200 mmHg) (3). The ORI reportedly gives an early warning during a possible oxygenation impairment-before any change in $SpO_2$ occurs-and shows the response to the oxygen administration (4,5). Recently, it has been reported that ORI can be used to prevent hyperoxia during general anesthesia and after surgery (6,7). This study evaluates the ORI-$PaO_2$ relationship in different fresh gas flows.

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## Methods

### Compliance with Ethical Standards and Study Design

The study was conducted at the Zonguldak Bulent Ecevit University between November 2018 and November 2019, with the approval of the Zonguldak Bulent Ecevit University Clinical Research Ethics Committee (date: 07.11.2018, protocol no: 2018-221-07/11) and the written consent of the patients. The trial was registered before subject enrollment at ClinicalTrials.gov (Ref: NCT04698863; principal investigator: G.K.; date of registration: January 6, 2021). The flow diagram of the study according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 is presented in Figure 1 (8).

### Patient Population

In this prospective study, randomization was performed using the sealed-envelope method. Patients between the ages of 18 and 65 who were in the ASA I-II risk group and who were scheduled for a tympanomastoidectomy under elective conditions, with a minimum operation time of 1.5 h, were included in the study. Patients with morbid obesity, a history of malignant hyperthermia, opioid sensitivity, alcohol or drug abuse problems, congestive heart failure, coronary artery disease, significant anemia, liver and kidney disease, pregnant or lactating women, and patients allergic to the drugs used in the study were excluded.

Before each patient, the seal of the anesthesia circuits was checked, the gas monitors were calibrated, and the lower limit of the inspired $O_2$ fraction ($FiO_2$) was set to 30%. The carbon dioxide ($CO_2$) absorbent was replaced after each patient.

### Oxygen Reserve Index and Arterial Blood Gas Measurements

Routine hemodynamic monitoring was performed on patients in the operating room. Additionally, the ORI sensor (ORi™, Masimo Corp., Irvine, CA, USA) was placed on the fourth finger of the arm without a blood pressure cuff. The sensor was covered to avoid light exposure, and it was connected to the oximeter device (Root® platform Pulse CO-Oximetre, Masimo Corp., Irvine, CA, USA) and monitored. The vascular access of all patients without premedication was opened with an 18 gauge (G) granule and the saline infusion was started at a 10 mL/kg/h rate. The Allen test was performed for arterial blood gas (ABG) analysis, and

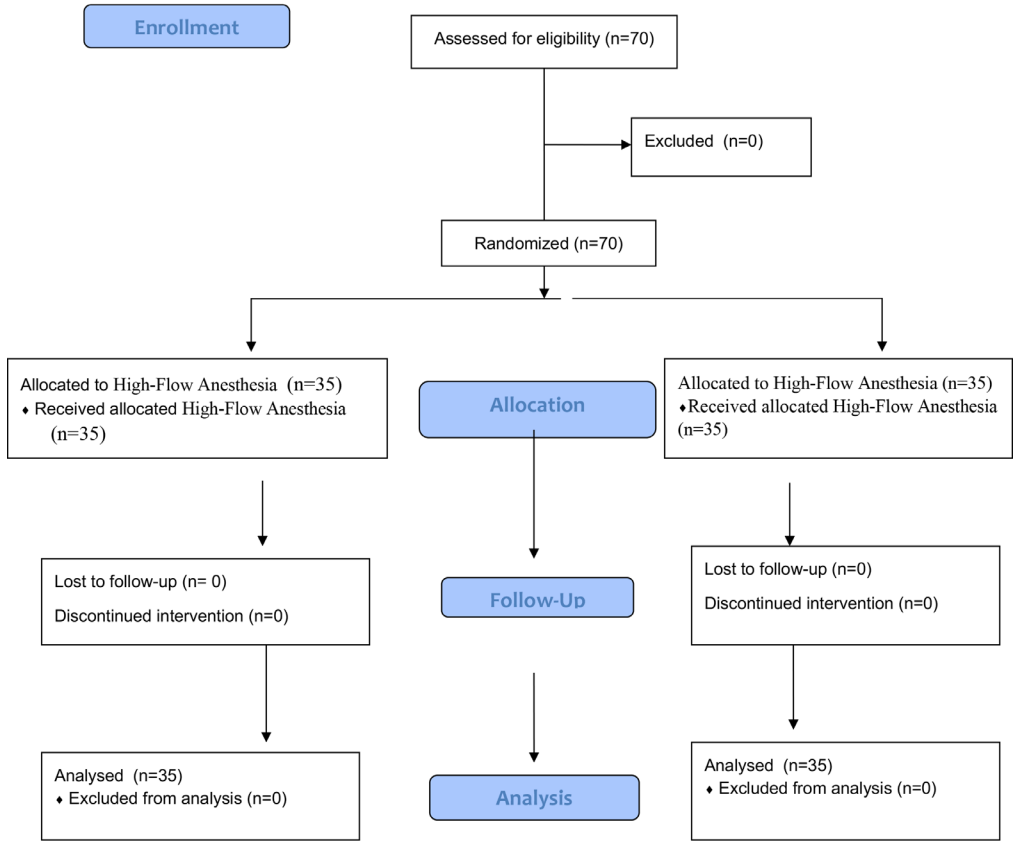


**Figure 1.** CONSORT flow diagram

20 G granules were placed in the radial artery in the non-dominant hand, if possible. Hemodynamic parameters before preoxygenation, ORI values, and ABG samples were taken, and the $PaO_2$ values in the blood gas device (I-STAT®1 Analyzer, Abbott, California, USA) were recorded.

**Anesthesia Management**

The patients were preoxygenated by administering 100% $O_2$ with a face mask for 5 min. Standard anesthesia induction was applied. Afterwards, a remifentanil infusion was started. All patients were ventilated with the same anesthesia device. The respiratory rate was adjusted so that the tidal volume was 8 mL/kg and the end-tidal carbon dioxide ($EtCO_2$) was between 35 and 45 mmHg.

In terms of the maintenance of anesthesia, the patients were divided into two groups: high-flow anesthesia (group H, n=35) and low-flow anesthesia (group L, n=35). For all patients, the fresh gas flow was provided with 50%/50% $O_2$/air (3/3L/min) and 6% desflurane for the first 10 minutes after intubation. After the first 10 min, the anesthesia was maintained with flow rates of 4 L/min in group H and 1 L/min in group L.

It was planned to increase the fresh gas flow to 4 L/min if the $FiO_2$ fell below 30%, the $EtCO_2$ above 45 mmHg, or the $SpO_2$ fell below 92%. It was planned to change the remifentanil dosage if the mean arterial pressure (MAP) increased more than 20% compared to the control value, administer 5 mg of ephedrine iv if it decreased more than 20%, and administer 0.5 mg of atropine iv if the heart rate (HR) value fell below 50 beats/min.

Ten minutes before the end of the operation, the fresh gas flow was increased to 6 L/min. Anesthetic agents were discontinued at the end of the surgery. Patients with routine wake-up protocols were extubated and taken to the recovery unit.

HR, MAP, $SpO_2$ and ORI values of all patients were recorded before preoxygenation and intraoperatively at 10., 15., 30., 45., 60 minute (min), and then at 30-min intervals until the end of surgery. Also, three ABG samples were taken from all patients before preoxygenation, intraoperative 60 min, and at the end of the surgery, just before starting ventilation with 6 L min, 100% $O_2$, and the $PaO_2$ values and simultaneous ORI and $SpO_2$ values were recorded. In the study, $PaO_2$ of more than 100 mmHg was determined as hyperoxia, and <60 mmHg as hypoxia.

All patients were administered 1 mg/kg tramadol iv and 10 mg/kg acetaminophen infusion intravenously for postoperative pain control 15 min before the end of the operation, and 10 mg/kg metoclopramide iv for nausea and vomiting prophylaxis.

**Statistical Analysis**

Data was analyzed using the Statistical Package for the Social Sciences version 23.0 (IBM SPSS Inc. Chicago, IL, USA) program. Considering the mean ORI values, it was determined that there should be a minimum of 35 patients in each group, with 95% confidence and 99.99% test power (9). The normality of data distribution was analyzed with the Kolmogorov-Smirnov test. An independent sample t-test was used for the normally distributed data. A paired samples t-test was used for normally distributed data to examine two time-dependent changes. Repeated measures variance analysis was used to examine three or more time-dependent changes. Pearson's correlation coefficient was used to measure the relationships between normally distributed quantitative variables. The effect of the $PaO_2$ parameter on ORI was analyzed by linear regression. For quantitative data, the results were presented as mean and standard deviation, and for categorical data, as frequency (percentage).The significance level was determined as $p<0.05$.

**Results**

The study was completed with 70 patients. The groups were similar in terms of demographic characteristics, ASA risk groups, and duration of surgery ($p>0.05$) (Table 1).

A comparison of $PaO_2$ values between and within groups is presented in Table 2. It was observed that $PaO_2$ values increased in both groups in the intraoperative period (Table 2).

A comparison of mean values of ORI between and within groups is presented in Table 3. Intraoperative ORI values increased during surgery in both groups (Table 3).

There was a statistically significant, positive weak correlation found with the correlation analysis performed between the mean ORI and $PaO_2$ values obtained at the intraoperative $60^{th}$ minute and at the end of the surgery, excluding the preoxygenation values between the groups (Table 4).

When the effect of the independent $PaO_2$ variable on the ORI value measured at the $60^{th}$ min intraoperative and at the end of surgery was examined by linear regression analysis, the regression models established by the time were found to be statistically significant (fintraoperative $60^{th}$ min=5,326, $p_{intraoperative\ 60^{th}\ min}$=0.024, $F_{End}$= 6,084, $p_{End}$=0.016). With the regression model established for the $60^{th}$ min after intubation, it was found that when $PaO_2$ increased by one unit, the ORI value increased by 0.002 units, and with the regression model established for the time measured at the end of the surgery, there was an increase of 0.002 units in the ORI value for one unit increase in $PaO_2$ value (Table 5).

If $PaO_2$ was 100 mmHg, the ORI value at the intraoperative 60th minute was 0.244 (~0.2), and the ORI at the end of the surgery was 0.205 (~0.2), according to the linear regression analysis in which $PaO_2$ was determined as the independent variable and ORI as the dependent variable. Accordingly, when $PaO_2$ was ≥100 mmHg, ORI >0.20 was found in 62.8% of patients at the intraoperative 60th min and in 72.8% at the end of surgery (Figures 2 and 3).

According to the regression analysis, when $PaO_2$ was 150 mmHg, ORI was 0.344 (~0.3) at the intraoperative 60th minute and was 0.305 (~0.3) at the end of surgeries. Similarly, when $PaO_2$ was ≥150 mmHg, ORI >0.30 was found in 63.3% of patients at the intraoperative 60th min and in 75.7% at the end of surgery (Figures 4 and 5).

## Discussion

In this study, in which the effectiveness of ORI in oxygenation monitoring in low- and high-flow anesthesia applications was evaluated, it was concluded that ORI could be used as a non-invasive method, especially in determining hyperoxia due to its positive correlation with $PaO_2$ and because hyperoxia, which is a feared situation in low-flow anesthesia applications, can also be seen in addition to hypoxia.

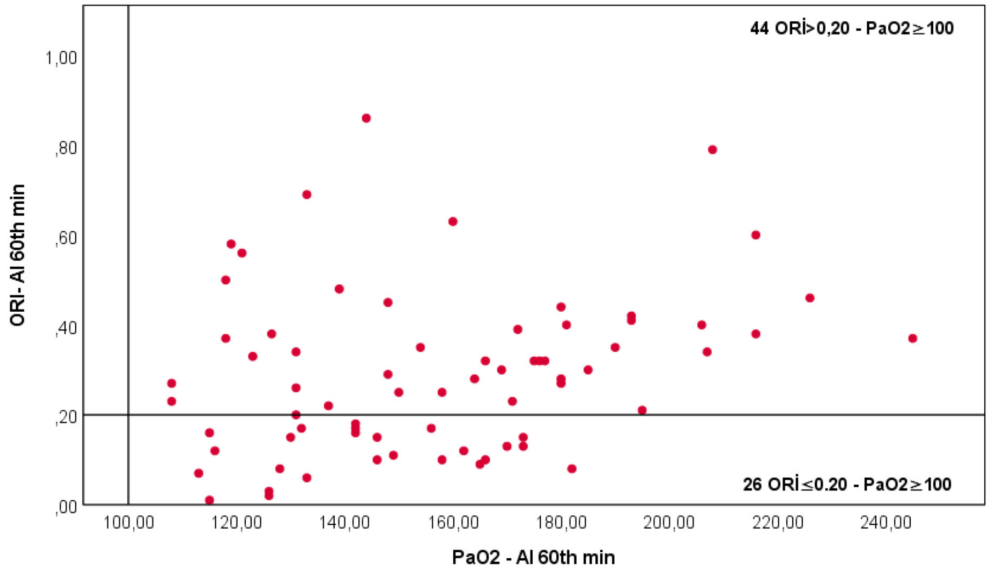


**Figure 2.** ORI values that in 100 mmHg of $PaO_2$ measured at AI 60th min
AI: After Intubation, ORI: Oxygen reserve index

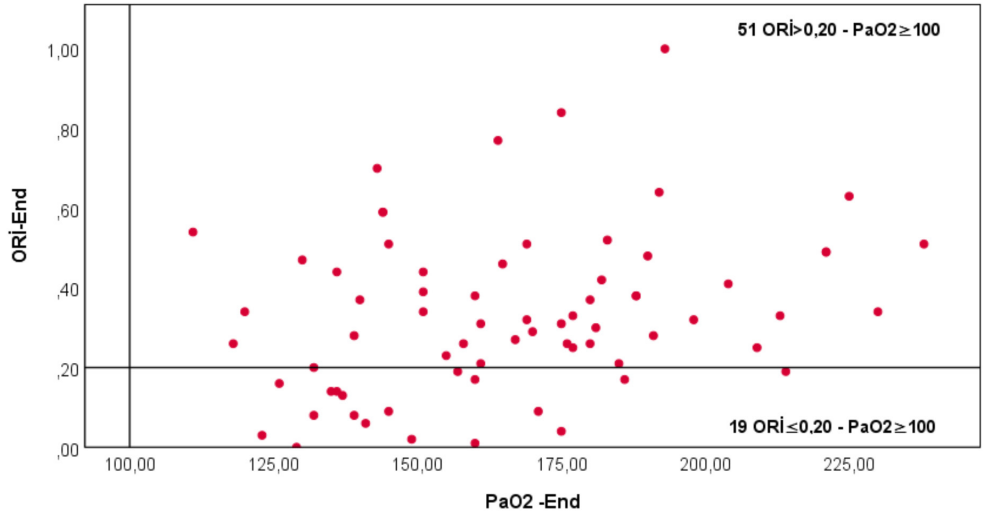


**Figure 3.** ORI values that in 100 mmHg of $PaO_2$ measured at the end of surgery
End: End of surgery, ORI: Oxygen reserve index

There are concerns, especially among anesthetists using low-flow techniques, that oxygen cannot reach the tissues in sufficient amounts (10,11). In the study of Çukdar et al. (12), in which low-flow [1 L/min ($O_2$/$N_2O$=0.5/0.5)] and high-flow [4.4 L/min ($O_2$/$N_2O$=1.4/3)] desflurane anesthesia with $FiO_2$ greater than 30% was compared, it was reported that in none of the cases, $FiO_2$ fell below 30% and $SpO_2$ below 97%. Similarly, the fact that the $SpO_2$ value did not fall below 97% in any of the patients in this study and that hypoxia findings were not found in the ABG analysis suggests that this study is compatible with the literature.

Although oxidative stress caused by hypoxia has been a well-known fact for many years, interest in the negative effects of hyperoxia has been increasing recently (13). There have been studies suggesting pathological changes in alveolar cells subjected to hyperoxia ($FiO_2$: 80-90%) for 48 h (14). In the animal study by Clerch and Massaro (15) it was reported that pleural effusion and pulmonary edema appeared in the 48$^{th}$-60$^{th}$ hours with exposure to intense oxygen ($FiO_2$: >95%). Animals started to die at the 60$^{th}$ hour, and most of them were dead at the 72$^{nd}$. It is common practice to use 100% $O_2$ in general anesthesia

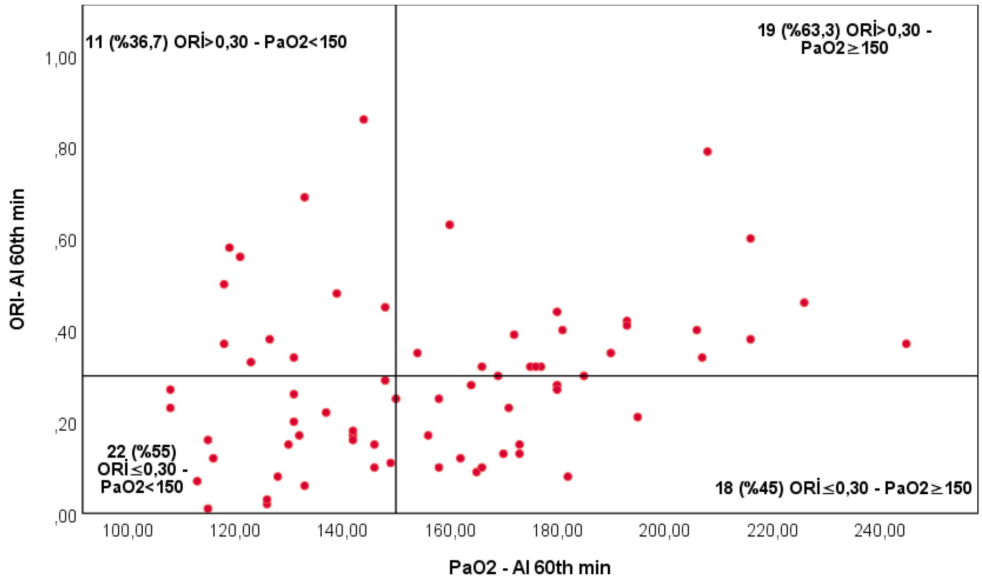


**Figure 4.** ORI values that in 150 mmHg of $PaO_2$ measured at AI 60$^{th}$ min
AI: After Intubation, ORI: Oxygen reserve index

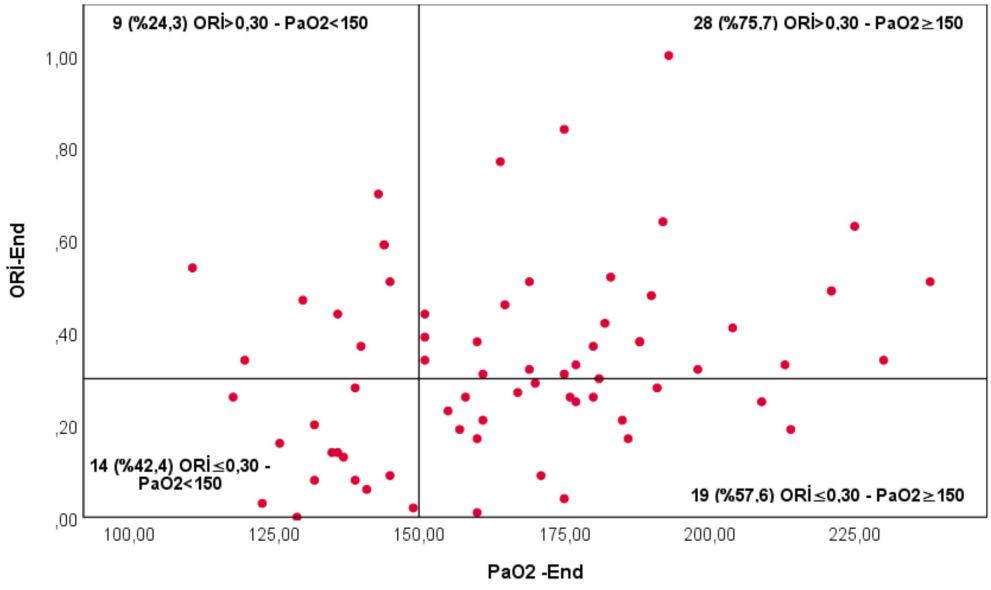


**Figure 5.** ORI values that in 150 mmHg of $PaO_2$ measured at the end of surgery
End: End of surgery, ORI: Oxygen reserve index

induction and before extubation. However, studies have shown that even a short time (~20-30 minutes) of high $O_2$ use causes atelectasis (16-18). Using computed tomography, Benoit et al. (16) reported that using 100% $O_2$ at the end of general anesthesia (<2.5 h) triggers the formation of atelectasis and low $FiO_2$ levels prevent it. Rothen et al. (19) reported that after the "recruitment" maneuver they applied during general anesthesia, it took 40 min for atelectasis to occur in the group ventilated with low $FiO_2$ (0,4), while atelectasis occurred in the 5th minute in the group getting high $FiO_2$ (1,0) (19). In a multicenter study with 14,441 intensive care patients, it was reported that severe hyperoxia ($PaO_2$>200 mmHg) was associated with higher mortality rates, and weaning

**Table 1. Comparison of demographic characteristics, ASA risk class and duration of surgery**

| | Group L (n: 35) | Group H (n: 35) | p-value |
|---|---|---|---|
| **Age (year)** | 37.1±11.4 | 40.2±11.7 | 0.259 |
| **Body weight (kg)** | 75.9 12 | 75.1±12.7 | 0.788 |
| **Height (cm)** | 164.6±5.3 | 165.1±5.1 | 0.445 |
| **Male/Female** | 18/17 | 22/13 | 0.334 |
| **ASA risk class (I/II)** | 14/21 | 15/20 | 1.000 |
| **Surgery time (min)** | 285.6±122.1 | 256.9±112.3 | 0.309 |

Group L: Low-flow anesthesia, Group H: High-flow anesthesia, Independent Sample t-test, chi-square test
ASA: The American Society of Anesthesiologists, min: Minute

**Table 2. Comparison of mean $PaO_2$ values within and between groups (mmHg)**

| Time | Group L (n: 35) | Group H (n: 35) | p* |
|---|---|---|---|
| **Before preoxygenation** | 84.35±7.96[a] | 81.73±8.08[a] | 0.178 |
| **Intraoperative 60th min** | 145.71±24.81[b] | 168.07±33.36[b] | **0.002** |
| **End of surgery** | 155.37±23.51[c] | 177.22±30.98[c] | **0.001** |
| **P**** | **<0.001** | **<0.001** | |

Group L: Low-flow anesthesia, Group H: High-flow anesthesia
*Independent Sample t-test, **Anova test,
*Comparing between groups,
**Compared within groups,
a-c: There is no difference between times with the same letter in a group

**Table 3. Comparison of mean ORI values within and between groups**

| Time | Group L (n: 35) | Group H (n: 35) | p* |
|---|---|---|---|
| **Before preoxygenation** | 0.018±0.05[a] | 0.030±0.10[c] | 0.402 |
| **Intraoperative 10th min** | 0.252±0.169[b] | 0.317±0.166[b] | 0.110 |
| **Intraoperative 15th min** | 0.224±0.110[b] | 0.370±0.144[ab] | **<0.001** |
| **Intraoperative 30th min** | 0.211±0.133[b] | 0.376±0.189[ab] | **<0.001** |
| **Intraoperative 45th min** | 0.230±0.178[b] | 0.355±0.188[ab] | **0.005** |
| **Intraoperative 60th min** | 0.185±0.125[b] | 0.392±0.168[ab] | **<0.001** |
| **Intraoperative 90th min** | 0.197±0.134[b] | 0.375±0.153[ab] | **<0.001** |
| **Intraoperative 120th min** | 0.219±0.117[b] | 0.465±0.378[ab] | **0.001** |
| **Intraoperative 180th min** | 0.250±0.146[b] | 0.420±0.214[ab] | **0.002** |
| **Intraoperative 210th min** | 0.240±0.147[b] | 0.427±0.185[a] | **0.001** |
| **Intraoperative 240th min** | 0.259±0.160[b] | 0.437±0.198[a] | **0.004** |
| **End of surgery** | 0.245±0.180[b] | 0.419±0.187[a] | **<0.001** |
| **P**** | **<0.001** | **<0.001** | |

Group L: Low-flow anesthesia, Group H: High-flow anesthesia
*Independent Sample t-test, **ANOVA test,
*Comparing between groups,
**Compared within groups,
a-c: There is no difference between times with the same letter in a group
ORI: Oxygen reserve index

| Table 4. Correlation analysis between ORI and PaO2 | | | |
|---|---|---|---|
| **Time** | | | **$PaO_2$** |
| **Before preoxygenation** | ORI | r | 0.024 |
| | | p | 0.843 |
| **Intraoperative 60th min** | ORI | r | **0.270** |
| | | p | **0.024** |
| **End of surgery** | ORI | r | **0.287** |
| | | p | **0.016** |
| r: Pearson's correlation coefficient, ORI: Oxygen reserve index | | | |

was more difficult than both mild hyperoxia ($PaO_2$: 120-200 mmHg) and normoxia ($PaO_2$<100) (20). The optimal $PaO_2$ level is not yet clearly defined (3,21-23). Elmer et al. (22) define hypoxia as a $PaO_2$ of 60 mmHg, normoxia as a $PaO_2$ of 60-100 mmHg, moderate hyperoxia as a $PaO_2$ of 101-299 mmHg, and severe hyperoxia as a $PaO_2$ of >300 mmHg (21). In this study, in which $PaO_2$<60 mmHg was determined as hypoxia and $PaO_2$>100 mmHg as hyperoxia, all the patients were at a normoxic level before preoxygenation, but it was found that $PaO_2$ values at the intraoperative 60th minute and at the end of surgery were $PaO_2$>100 mmHg for all patients. This suggests that hyperoxia rather than hypoxia should be considered in low-flow anesthesia.

Supplying high concentrations of oxygen (>50%) for more than 48 h is reported to possibly cause $O_2$ toxicity. Therefore, $O_2$ application of more than 50% should be limited to 48 h (24). In this study, $O_2$ was used at a concentration of 50% during an average of 5 hours of surgery in both groups.

The most common method for monitoring oxygenation under anesthesia is the pulse oximeter, which has become a universal standard of care and can be measured continuously (25). Reports of respiratory complications during anesthesia have decreased significantly since the use of the pulse oximeter (26). $SpO_2$ has a major limitation when it comes to evaluating hypoxia or hyperoxia in patients receiving oxygen therapy. That is, due to the sigmoid shape of the Oxyhemoglobin dissociation curve, a small change in $PaO_2$ in the vertical part of the curve causes a large difference in $SpO_2$. Consequently, when $SpO_2$ is ≥97%, the $PaO_2$ level can be anywhere between 90 and 600 mmHg. Therefore, monitoring $SpO_2$ alone cannot exclude unwanted hyperoxia in patients receiving $O_2$ treatment. In the impending hypoxia state, the $SpO_2$ decrease is slower than the $PaO_2$ decrease. $SpO_2$ may not decrease before $PaO_2$ is <70 mmHg and $SpO_2$ may be insufficient for the impending danger (27). In cases where $SpO_2$ is insufficient in oxygenation, $PaO_2$ gives precise information, but being costly and invasive, waiting for results, and causing blood loss are the weaknesses of this method (28). In this study, no clinical findings of hypoxia or any decrease in $SpO_2$ and $PaO_2$ values were detected in either group. However, when $SpO_2$ was more than 97%, $PaO_2$ was found to be in a wide range, such as 70-240 mmHg. According to the literature on the subject, the researchers of this study believe that $SpO_2$ cannot be used as a guide in intraoperative $O_2$ management and hyperoxia prevention. Because hyperoxia in ABG increased gradually in both fresh gas flows during the prolonged surgical period and $SpO_2$ remained limited in this regard, it is necessary to be more careful with $O_2$ applications, especially at high currents, and routine ASA monitoring may be insufficient for intraoperative hyperoxia detection.

Studies have reported that ORI can provide an early warning when arterial oxygenation is impaired without any change in peripheral $O_2$ saturation (9,29,30). In the study by Szmuk et al. (29) with 25 healthy children, it was found that during the induction of anesthesia, ORI detected the approaching desaturation (on mean) 31.5 seconds before any change in $SpO_2$ and that this represents a clinically important warning period. This can give clinicians enough time to intervene. Tsymbal et al. (31) also showed that the added warning time provided by the ORI was 46.5 s in obese and 87.0 s in normal BMI patients. Fleming et al. (32) found that the ORI allowed an added warning time of 48.4 s compared to the $SpO_2$ in cardiac surgical patients. In the study of Applegate et al. (9), where they examined the relationship between the intraoperatively measured 1594 ORI value in 106 patients and $PaO_2$ values in the ABG samples taken when clinically necessary, $PaO_2$

| Table 5. Linear regression analysis of the relationship between ORI and PaO2 | | | | | |
|---|---|---|---|---|---|
| | | **Beta coefficient *** | **95.0% confidence interval** | | **p** |
| **Time** | | | **Lower limit** | **Upper limit** | |
| **Intraoperative 60th min** | Constant | 0.044 | -0.171 | 0.260 | 0.682 |
| | $PaO_2$ | 0.002 | 0.000 | 0.003 | **0.024** |
| **End** | Constant | 0.005 | -0.265 | 0.274 | 0.973 |
| | $PaO_2$ | 0.002 | 0.000 | 0.004 | **0.016** |
| End: End of surgery,<br>*Not standardized, dependent variable: ORI, $R^2$intraoperatif 60th min=0.073,<br>$R^2$End=0.082, adjusted $R^2$ intraoperatif 60th min=0.059, adjusted $R^2$End=0.069<br>ORI: Oxygen reserve index | | | | | |

was found to be 100 mmHg in all measurements for ORI >0.24, while when ORI>0.55, $SpO_2$ was >96% and $PaO_2$ was ≥150 mmHg (3). In the same study, during the decrease of $PaO_2$ from 500 mmHg to 100 mmHg in 30 min, ORI also decreased, but the response of $SpO_2$ to such various $O_2$ changes was monitored only as from 99% to 96%. Saraçoğlu et al. (33) showed in their study investigating the effect of ORI-guided oxygen titration on morbidity in one lung ventilation with low fresh gas flow, that adjusting ORI with $SpO_2$ and blood gas analysis can prevent hyperoxemia in patients under low-flow or high-flow anesthesia. In this study, $SpO_2$ did not fall below 97% in any patient, and no decrease was observed in ORI values. As reported in the literature, the researchers of this study also believe that ORI can be used as a guide in determining the hyperoxia that may occur at different gas flows, in addition to its role of providing an early warning when arterial oxygenation is impaired without any change in $SpO_2$. According to the linear regression analysis, ORI was 0.244 (~0.2) at the intraoperative 60$^{th}$ min, when $PaO_2$ was 100 mmHg, and ORI was determined to be 0.344 (~0.3) when $PaO_2$ was 150 mmHg.

Accordingly, considering the values at the intraoperative 60$^{th}$ minute, it was observed that although $PaO_2$ was ≥100 in all patients, while the ORI values were >0.244 in 62.8% of them, this rate increased to 72.8% at the end of the surgery. Similar rates were found for the ORI values determined for ≥150 mmHg of $PaO_2$. This suggests that the relationship between ORI and $PaO_2$ gets stronger with the duration of surgery.

### Study Limitations

There are some limitations in our study. The limitations of this study can be listed as the inclusion of only the patients who were in the ASA I-II risk group without any problems with their lung mechanics and not being able to evaluate the effectiveness of ORI for situations that may be affected by peripheral perfusion, due to the absence of a condition (such as severe hypotension, etc.). Despite these limitations, our study is valuable as it is one of the few studies showing that ORI is effective in detecting hyperoxia in different fresh gas streams and contributes to the literature.

## Conclusion

It is the strong belief of the researchers of this study that ORI, which can be useful in every stage of monitoring oxygenation starting from preoxygenation, can be a guide in terms of titrating the $O_2$ levels in long operations with its relationship with $PaO_2$. Considering the defining power of the model designed in the study (R2=0.059, R2=0.069), it can be evaluated whether the identification power of the model increases by increasing the number of participants. By evaluating variables other than $PaO_2$ that affect the ORI value, regression models with higher definition powers can be developed with the inclusion of these variables. The usefulness of the ORI values determined for Pa100 mmHg and 150≥mmHg of $PaO_2$ should be tested with different clinical studies.

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### Ethics

**Ethics Committee Approval:** This study approved by the Zonguldak Bulent Ecevit University Clinical Research Ethics Committee (date: 07.11.2018, protocol no: 2018-221-07/11).

**Informed Consent:** Written informed consent was obtained from the patients.

### Authorship Contributions

Concept: H.O., G.K., B.G.A., R.D.O., O.P., H.A., Design: H.O., G.K., B.G.A., R.D.O., O.P., H.A., Data Collection and/or Processing: H.O., G.K., B.G.A., O.P., H.A., Analysis and/or Interpretation: H.O., G.K., B.G.A., O.P., H.A., Literature Research: H.O., G.K., H.A., Writing: H.O., G.K., B.G.A., H.A.

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Original Article

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# Accuracy of Transcutaneous Bilirubin Measurement from Unexposed Skin with a New Generation Device in Neonates Receiving Phototherapy

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## Abstract

**Aim:** Transcutaneous bilirubin (TCB) measurement methods cause false results during and after phototherapy (PT), so bilirubin levels are followed by total serum bilirubin (TSB) measurement, which causes taking blood samples and increases the risk of infection. We compared the TCB measurements made with Bilicare™ and TSB measurements by preventing PT exposure of a part of the skin in newborns receiving PT and evaluating the reliability of the measurements made with Bilicare™ after PT.

**Methods:** This study was conducted between 01 February-30 June 2020 as a single-center cross-sectional study. The study included newborns aged 35 weeks and up who were admitted to a neonatal intensive care unit for PT. TSB measurements were reviewed by the hospital automation system. Bilicare™ bilirubin meter was used for TCB measurements. Simultaneous TSB and TCB measurements were made before PT. The skin area to be measured was covered with a radio-opaque patch. After PT, simultaneous TSB, exposed skin area TCB, and patched skin area TCB were measured. Simultaneous TSB and TCB measurements were repeated 24 h after the end of PT. The relationship between these data was evaluated statistically.

**Results:** This study was conducted with 171 late preterm and term newborns with a gestational age of ≥35 weeks. 79 (46.1%) were female and 92 (53.9%) were male newborns. The mean gestational age was 38.3±1.15 weeks. When maternal and newborn blood groups were evaluated, 107 (62.5%) had no blood incompatibility, 53 (30.9%) had ABO incompatibility incompatibility, 9 (5.2%) had Rh incompatibility, 1 (0.6%) had subgroup incompatibility, and 1 (0.6%) had ABO incompatibility and Rh incompatibility. The correlation coefficient (r) of TSB and TCB measurements made before PT was 0.97 and a strong correlation was found. A correlation coefficient (r) of 0.98 and a strong correlation between closed skin area TCB measurement and TSB measurement immediately after PT were detected. The correlation coefficient (r) was 0.96 and a strong correlation was found between the TCB and TSB measurements performed 24 h after the PT was terminated.

**Conclusion:** This study shows that TCB measurements made from unexposed areas can be safely measured in patients with PT.

**Keywords:** Jaundice, phototherapy, transcutaneous bilirubin, total serum bilirubin

## Introduction

Jaundice is one of the most common clinical cases in the neonatal period requiring follow-up. Although hyperbilirubinemia is usually temporary, it can reach levels that require phototherapy or transfusion. Bilirubin levels in newborns can reach levels that necessitate phototherapy in 10% of term newborns and 25% of preterm newborns (1). Total serum bilirubin (TSB) measurement is the gold standard in neonatal jaundice. It is diagnosed with TSB measurement, and the TSB level should be examined periodically during phototherapy to prevent excessive or inadequate treatment (2). Blood samples should be taken from the newborn, and samples must be transported quickly without exposure to light and evaluated in the biochemistry laboratory for measuring TSB. Additionally, venous or capillary blood collection is an invasive procedure that causes disruption of skin integrity, an increased risk of sepsis, anemia, and pain in newborns (3).

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New generation transcutaneous bilirubin (TCB) meters show jaundice of subcutaneous tissue by measuring the optical density of light between 450 nm-550 nm wavelength regions (4). Bilicare™ is the only TCB meter that uses LED light resource. Unlike other new generation devices, the measurement is made from the scaphoid fossa of the auricle. It is fixed with the help of a clamp on the device. Pressure is applied automatically, not by the user. The transmitted light passes through the tissue. Some of it is absorbed by the bilirubin in the tissue, and some is reflected back to the outside. A receiver in the sensor collects and analyzes the reflected light. It is possible to get results quickly without invasive procedures with TCB measurement methods (5). With the widespread use of TCB measurement methods, the incidence of severe hyperbilirubinemia, re-hospitalization, and the number of babies receiving phototherapy has significantly decreased (6). Thanks to the advantages of TCB measurement, the use of TCB measuring devices has increased recently. In this study, we determined the correlation between TCB measurement and TSB measurements and the reliability of TCB measurement in newborns receiving phototherapy.

## Methods

### Study Design

After this study was planned, approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Haseki Training and Research Hospital with a decision dated April 29, 2020 and numbered 2020-38. Both verbal and written informed consent were obtained from the families of the babies. This study was conducted between 01 February-30 June 2020 as a single-center cross-sectional study.

This study was conducted on 171 infants with phototherapy indications hospitalized in the Neonatal Intensive Care Unit of University of Health Sciences Turkey, Haseki Research and Training Hospital, Pediatrics Clinic. Newborns with a gestational age of ≥35 weeks, scheduled for blood collection due to jaundice, and scheduled for phototherapy in the neonatal intensive care unit were included in the study. Gestational age was calculated according to the last menstrual period. Babies with a postnatal age greater than 28 days, skin diseases, ear structure anomalies, and previous blood transfusions were excluded from the study.

### Bilirubin Measurement Technique

After the venous blood sample was taken from the babies whose TSB level was to be determined, the sample was transferred to the biochemistry laboratory of our hospital with unadulterated gel BD (Beckton Dickinson, New Jersey, USA) vacutainer biochemistry tubes. Samples were centrifuged at 1500 g for 10 min and TSB was measured spectrophotometrically after diazo reaction in a biochemistry autoanalyzer (Beckman Coulter™ AU5800 model Kyoto/Japan). Two consecutive measurements were made from the auricle scaphoid fossa with the Bilicare™ TCB measuring device within one minute after blood samples were taken, and the device was set to display the average of these two measurements. The average value shown by the device was recorded. Just before the onset of PT, the scaphoid fossa of the right auricle was covered with a non-translucent (radio-opaque) patch that was easily removable and did not damage skin integrity (Figure 1). Before PT, all newborns were stripped except for the diapers. Phototherapy was started while the newborns wore eye patches. After 4 h of PT, venous blood samples were taken from the newborns and sent to the biochemistry laboratory of our hospital in unadulterated gel BD vacutainer biochemistry tubes. The patch was removed from the auricle. Two consecutive measurements were made with the TCB measuring device from the exposed and covered auricles during PT. Average values were recorded. Venous blood samples were taken from all newborns 24 h after PT. Samples were delivered to the biochemistry laboratory of our hospital with unadulterated gel vacutainer biochemistry tubes. TCB was measured using Bilicare™ from the right ear simultaneously with venous blood collection.

**Figure 1.** Measurement method with Bilicare™ transcutaneous bilirubinometer

### Statistical Analysis

The analyses were performed using SPSS 15.0 Statistics for Windows. Descriptive statistics: numbers and percentages for categorical variables, and mean and standard deviation for numerical variables were given. Comparisons of numerical variables in two independent groups were made using the Student's t-test in two groups when the normal distribution condition was met, the One-Way ANOVA test in more than two groups, the Mann-Whitney U test in two groups when the normal distribution condition was not met, and the Kruskal-Wallis test in more than two groups. In the non-parametric test, subgroups analyzed in more than two independent groups were made with the Mann-Whitney U test and interpreted with Bonferroni correction. Dependent group analyses were performed when the differences in numerical variables provided the normal distribution condition, paired t-test, and when the normal distribution condition was not met, with the test. The relationships between numerical tests were analyzed using Pearson correlation coefficient when the parametric test conditions were met if not Spearman correlation analysis was performed.

### Results

The study was conducted with 171 late preterm and term newborns with a gestational age of ≥35 weeks. All the patients were hospitalized in our clinic and received phototherapy. Seventy-nine (46.1%) were female and 92 (53.9%) were male newborns. The mean gestational age was 38.3±1.15 weeks, and the mean birth weight was 3135±412 grams (Table 1). The distribution of Bilicare™ and TSB values measured before PT, after PT from the exposed and covered skin, and 24 h after PT is shown in Table 2 and Figure 2.

Before PT, there was a strong (r=0.976) and statistically significant positive correlation between Bilicare™ and TSB measurements (p<0.01). There was a strong (r=0.984) and statistically significant positive correlation between Bilicare™ and TSB measurements from the unexposed skin area after phototherapy (p<0.01). Additionally, there was a strong (r=0.965) and statistically significant correlation between Bilicare™ and TSB measurements at 24 h after PT (p<0.01) (Table 3).

TSB values were divided into two groups as ≤12 mg/dL and >12 mg/dL, and the measurements were evaluated between these two groups by Sperman Correlation Analysis. In the group with a TSB value of ≤12 mg/dL, there was a strong (r=0.953) and statistically significant positive correlation between Bilicare™ and TSB measurements before PT. There was a strong (r=0.920) and statistically significant positive correlation between Bilicare™ and TSB measurements from the unexposed skin area. Additionally, there was a strong (r=0.947) and statistically significant positive correlation between Bilicare™ measurements at 24 h after PT and the TSB measurements (p<0.01) (Table 3).

In the group with a TSB value >12 mg/dL, a strong (r=0.925) and statistically significant positive correlation

**Table 1. Epidemiological features of cases**

| | **Mean ± SD** | |
|---|---|---|
| Birth week | 38.3±1.5 | |
| Age (days) | 3.5±3.6 | |
| Birth scale | 3135±412 | |
| Gender | n | % |
| Girl | 79 | 46.1 |
| Male | 92 | 53.9 |
| Delivery type | | |
| NSVD | 100 | 58.4 |
| C/S | 71 | 41.6 |
| Birth week | | |
| Late preterm | 19 | 11.1 |
| Early term | 76 | 44.5 |
| Full term | 70 | 40.9 |
| Late term | 6 | 3.5 |
| Jaundice in siblings | | |
| None | 158 | 92.5 |
| Not received treatment | 10 | 5.8 |
| Received treatment | 3 | 1.7 |
| Blood type incompatibility | | |
| None | 107 | 62.5 |
| ABO incompatibility | 53 | 30.9 |
| Rh incompatibility | 9 | 0.6 |
| Subgroup incompatibility | 1 | 0.6 |
| ABO+Rh incompatibility | 1 | 9.1 |
| Coombs test | | |
| Positive | 11 | 6.5 |
| Negative | 160 | 93.5 |
| Consanguineous marriage | | |
| Yes | 45 | 26.3 |
| No | 126 | 73.7 |
| Postnatal age (hours) | | |
| 0-24. hour | 35 | 20.4 |
| 25-48. hour | 34 | 19.8 |
| 49-72. hour | 10 | 5.8 |
| 73-96. hour | 16 | 9.3 |
| 97-119. hour | 11 | 6.4 |
| 120. hour and above | 65 | 38 |

SD: Standard deviation, NSVD: Normal spontaneous vaginal delivery, C/S: Cesarean section

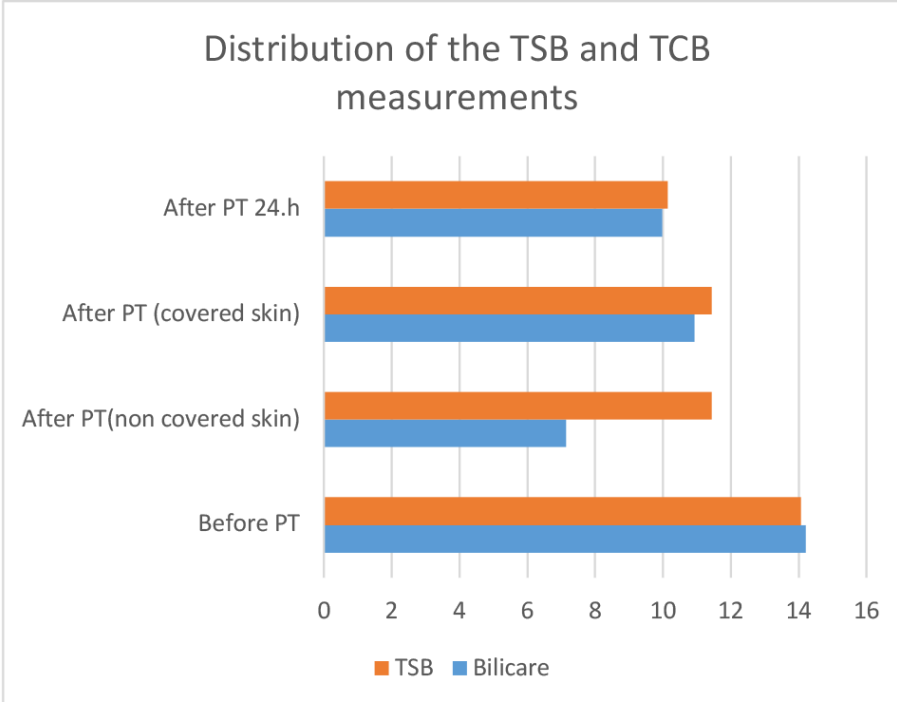


**Figure 2.** Mean values of TSB and TCB measurements in different time periods
TCB: Transcutaneous bilirubin, TSB: Total serum bilirubin, PT: Phototherapy

was found between the measurements made with Bilicare™ before phototherapy and TSB measurements, a strong (r=0.972) and statistically significant positive correlation was found between the measurements made with Bilicare™ from the unexposed skin area after phototherapy and TSB measurements; and a strong (r=0.955) and statistically significant positive correlation was found between Bilicare™ measurements at 24 h after PT and the TSB measurements (p<0.001) (Table 3).

| **Table 2. Distribution of the TSB and TCB measurements** | |
|---|---|
| **Before PT** | **Mean. ± SD** |
| Bilicare™ | 14.21±4.71 |
| TSB | 14.08±4.63 |
| After PT (exposed skin) | |
| Bilicare™ | 7.15±3.60 |
| TSB | 11.44±4.06 |
| After PT (unexposed skin) | |
| Bilicare™ | 10.94±3.94 |
| TSB | 11.44±4.06 |
| After PT 24. hour | |
| Bilicare™ | 9.98±2.54 |
| TSB | 10.15±2.61 |
| SD: Standard deviation, TCB: Transcutaneous bilirubin, TSB: Total serum bilirubin, PT: Phototherapy | |

## Discussion

Today, TCB measuring devices are routinely used in the follow-up of neonatal jaundice. TCB measuring devices have provided us with the advantage of determining and monitoring the bilirubin level of newborns in their mother's arms without invasive intervention. However, current guidelines emphasize that TCB measurement is not sufficient when deciding on the need for treatment and that the result should be confirmed with TSB measurement. Additionally, it is recommended that patients who have received PT should be followed up with a TSB measurement. In the Guidelines for Approach, follow-up, and Treatment of Neonatal Jaundice published by the Turkish Neonatal Society in 2014, it is recommended that newborns who receive PT should be followed up with TSB measurement (7). Studies have shown that TCB measurements performed during and after PT in newborns may give inaccurate results (8). For this reason, frequent TSB measurement is performed in the follow-up of patients receiving PT, especially those with high bilirubin levels. In this study, we tested the reliability of the TCB measuring device in infants receiving PT to increase patient comfort and decrease the frequency of invasive procedures. The presence of hyperpigmentation, hair growth, and birthmarks in the skin area where TCB measurement is performed may affect the results. It has also been shown that there may be differences in TCB

measurement results according to different skin colors between races (9). The patients included in our study did not have any skin anomalies in the scaphoid fossa of the auricle.

In this study, we investigated whether the measurement results made with the new generation TCB measurement device Bilicare™ were correlated with TSB measurements in newborns with a gestational age of ≥35 weeks, TSB levels of 3.5-24.00 mg/dL, and newborns receiving phototherapy. During PT, we prevented the contact of one auricle with photons using a radio-opaque patch, and we measured TCB from this ear with Bilicare™ and simultaneously measured TSB from the other ear after PT. We found a strong correlation between the two measurements as well as between the Bilicare™ and TSB measurements performed 24 h after PT. Additionally, TCB measurement is considered unreliable in patients with a TCB level of 12 mg/dL or above, and TSB measurement is recommended in these patients. In newborns with a TCB level of 12 mg/dL and above, we found a significant positive correlation between TSB and TCB measurements performed before PT, from the unexposed skin area immediately after PT, and 24 h after PT (r: 0.925, r: 0.972, r: 0.955, p<0.001).

**Table 3. Correlation of TSB and TCB measurements**

| **All cases** | | |
|---|---|---|
| | Before PT TSB (mg/dL) | |
| | r | p |
| Bilicare™ (Before PT) | 0.976* | <0.001 |
| | After PT TSB (mg/dL) | |
| | r | p |
| Bilicare™ (Unexposed skin) | 0.984* | <0.001 |
| | After PT 24. hour TSB (mg/dL) | |
| | r | p |
| Bilicare™ (24. hour) | 0.965* | <0.001 |
| Cases with TSB measurements 12 mg/dL and under | | |
| | Before PT TSB (mg/dL) | |
| | r | p |
| Bilicare™ (Before PT) | 0.953* | <0.001 |
| | After PT TSB (mg/dL) | |
| | r | p |
| Bilicare™ (Unexposed skin) | 0.920* | <0.001 |
| | After PT 24. hour TSB (mg/dL) | |
| | r | p |
| Bilicare™ (24. hour) | 0.947* | <0.001 |
| Cases with TSB measurements above 12 mg/dL | | |
| | Before PT TSB (mg/dL) | |
| | r | p |
| Bilicare™ (Before PT) | 0.925* | <0.001 |
| | After PT TSB (mg/dL) | |
| | r | p |
| Bilicare™ (Unexposed skin) | 0.972* | <0.001 |
| | After PT 24. hour TSB (mg/dL) | |
| | r | p |
| Bilicare™ (24. hour) | 0.955* | <0.001 |

*Bilicare™ measurements and TSB measurements were evaluated with Spearman Correlation Analysis. There is a strong correlation between TSB and Bilicare™ measurements made before phototherapy,the unexposed skin at the end of phototherapy and 24 h after phototherapy. A strong correlation was found between TSB and Bilicare™ measurements at high bilirubin levels (>12 mg/dL).
TCB: Transcutaneous bilirubin, TSB: Total serum bilirubin, PT: Phototherapy

There are limited studies in the literature conducted with Bilicare™, which is a new TCB measurement system. Several studies have reported correlations between TSB and TCB measurements (10-12). In the 2017 study by Yamana et al. in Japan (n=82), the correlation coefficient (r) was 0.91. In the study by Kitsommart et al. (10) (n=93) in Thailand, the correlation coefficient (r) was found to be 0.76. In the 2016 study of Pratesi et al. (11) in Italy (n=458), the correlation coefficient (r) was 0.56, while the correlation coefficient (r) was reported to be 0.86 in the study of Chokemungmeepisarn et al. (12) (n=214). We think that racial differences and the use of different TSB measurement methods may have caused the difference between the correlation coefficients.

The preferred method of measurement in follow-up and treatment of babies receiving PT is TSB measurement. This is because PT rays can affect the results of skin measurements. However, when skin areas are covered and not affected by PT, similar to the method in our study, it is still unclear whether measurements made from these skin areas are reliable. In the study by Costa-Posada et al. (13), a radio-opaque patch was placed on the sternum of 217 newborns before PT, and consecutive measurements were made with the Drager JM-105 TCB meter from the area closed with the patch after PT. These measurements were compared with TSB measurements made at 48, and 72 h. At the 24$^{th}$ hour, a difference of 0.74±1.35 mg/dL was found between bilirubin levels in the patch-covered area, and a strong correlation was found between all measurements and TSB measurements from the patch-covered area. In this study, we found a difference of 0.20±0.61 and a strong correlation in the measurements we made at the 24$^{th}$ hour. The difference between the results may be due to the different TCB measurement devices used and the different TSB measurement methods.

In the study conducted by Casnocha Lucanova et al. (14) in Slovakia, 150 term newborns were examined, and measurements were made from the forehead, sternum, and lower abdomen covered by the diaper with a Billcheck TCB meter 2 h after the end of phototherapy. A difference of 2.9±0.2 mg/dL was found between the measurements

made from the area covered by the diaper and the TSB measurements. In this study, we found a difference of 0.5±0.66 mg/dL between Bilicare™ measurement from the area covered with the radio-opaque patch and TSB levels. We think that the difference between the results may be because the light transmittance of the diaper is higher compared to the radio-opaque patch. Furthermore, different TCB measurement methods were used, and the measurements in this study were made immediately after PT.

In a study by Radfar et al. (15) in Iran, a radiopaque patch was placed in the lower abdomen area covered by the diaper of 134 term and 36 preterm newborns, and Billcheck TCB measurements were compared with TSB measurements. In the Unlthissent study, measurements were made at least 6 h after PT and TSB measurement was performed on blood samples taken from the heel and evaluated with a non-chemical spectrophotometric device. A strong correlation was found between the measurements.

In the study by Alsaedi (16) in Saudi Arabia, 151 term newborns were included in the study. Consecutive measurements were made with the Billchek TCB meter using a radio-opaque patch, and TCB measurements from this area after PT were compared with TSB measurements (16). The correlation coefficient (r) was reported as 0.85 in the comparison before PT, and the correlation coefficient (r) of the measurements after PT was reported as 0.80. It was found that the measurements made on the covered area unexposed to photons strongly correlated with TSB measurements. Similar to this study, the results show that there is a strong correlation between measurements.

We found a strong correlation between TCB measurements made from the covered skin area and TSB measurements in babies who received PT. Additionally, we found that TCB measurements were correlated with TSB measurements in babies for whom treatment was planned before PT. We found a strong correlation between TSB and TCB measurements 24 h after phototherapy. This study shows that TCB measurements made from skin areas covered against exposure during PT are safe and reliable. However, further studies and meta-analyses with larger patient series are needed before TCB measurements from unexposed skin areas become part of routine newborn practice.

### Study Limitations

The main limitation of our study was that only one device was used on a small group of patients. It was a single-center study. A multicenter study with a larger number of patients would reveal more valuable results. Despite these limitations, the comparison of measurements at high bilirubin levels is valuable in terms of demonstrating the safety of the measurement technique. Measurements made 24 h after the end of the phototherapy are important in terms of providing data that the applied method can be reliable in terms of bilirubin-level monitoring.

## Conclusion

We found a strong correlation between TCB measurements made from the unexposed skin area and TSB measurements in babies who received PT. Additionally, we found that TCB measurements were correlated with TSB measurements in babies for whom treatment was planned before PT. We found a strong correlation between TSB and TCB measurements 24 h after phototherapy. This study shows that TCB measurements made from skin areas covered against exposure during PT are safe and reliable. However, further studies and meta-analyses with larger patient series are needed before TCB measurements from unexposed skin areas become part of routine newborn practice.

### Ethics

**Ethics Committee Approval:** Study approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Haseki Training and Research Hospital with a decision dated April 29, 2020 and numbered 2020-38.

**Informed Consent:** Both verbal and written informed consent were obtained from the families of the babies.

### Authorship Contributions

Concept: I.Y., D.O., M.E., Design: I.Y., D.O., M.E., E.A., Data Collection and/or Processing: I.Y., E.A., Analysis and/or Interpretation: I.Y., D.O., Literature Research: I.Y., D.O., M.E., E.A., Writing: I.Y., D.O., M.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# Analysis of the Knowledge and Attitude of Turkish Urology Residents on the Use of Fluoroscopy Working in University Hospitals and Training and Research Hospitals: A National Survey-Based Comperative Study

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## Abstract

**Aim:** Tendency, knowledge, awareness, and behavior patterns of urology residents in Turkey regarding the use of fluoroscopy may vary depending on the institutions. The study analyses and compares the awareness and tendencies of urology residents in university hospitals and training and research hospitals.

**Methods:** In this qualitative research, a 13-question survey prepared using "Google Forms" as of 01.03.2021 was shared for four weeks in the "WhatsApp" application group, which includes 279 urology residents studying at university hospitals and training and research hospitals in Turkey. One hundred and thirteen participants, who completed the questionnaire were included in the study. The data was analyzed by comparing two groups: university hospitals (group 1) and training and research hospitals (group 2).

**Results:** Of the 113 urology residents included in the study, 56 (49.6%) were in group 1 and 57 (50.4%) were in group 2. Sixty-seven point three percent (67.3%) of the residents stated that they never hesitated to participate in the operations in which fluoroscopy was used. Additionally, the residents stated that 43.4% of the auxiliary healthcare staff frequently refrain from being involved in these cases ($p<0.001$). While 21 (37.5%) of the residents in group 1 reported that they hesitated in these cases, this rate was found to be 16 (28.2%) in group 2 and a significant difference was observed between the two groups ($p<0.016$).

**Conclusion:** Although the residents who work in training in university hospitals are more scared of radiation exposure from fluoroscopy than their colleagues working in training and research hospitals, the lack of education is present and the use of dosimeters is very low in both groups.

**Keywords:** Fluoroscopy, radiation, survey

## Introduction

With the advances in technology, open surgical interventions have decreased in modern urology practice and the use of endourological procedures has increased (1). Frequently used endourological procedures such as percutaneous nephrolithotomy (PNL), endoscopic ureter stone treatments, and retrograde intrarenal operations are mostly performed under fluoroscopy guidance. During these fluoroscopic-guided procedures, surgeons, patients, and operating room staff are exposed to a significant amount of ionizing radiation (2).

Stochastic (mutation and cancer) and deterministic effects may occur because of radiation exposure (RE). This effect is related to the duration, dose, and protection

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used (1). For this reason, the International Radiation Commission recommends that the radiation dose exposed should not exceed an average of 20 mSv (millisieverts)/year for five years (3).

To avoid these negative effects of radiation, personal protective equipment such as a lead apron, thyroid shield, radiation protection gloves, and goggles should be used, and basic principles should be observed (1). Additionally, it is necessary to use a dosimeter to determine the cumulative radiation dose exposed. However, studies on this subject have revealed that protective equipment and dosimeters are not used enough among urologists, and there is a lack of knowledge and awareness about this subject (2,4,5).

The urology residency is an important occupational group with a high risk of RE (6). In Turkey, urology residency training is applied in university hospitals or training and research hospitals. There are studies evaluating the awareness of RE among urology residents. However, according to our literature research, there is no study comparing the tendency to use fluoroscopy in different institutions. In this study, we evaluated the tendencies, knowledge, awareness, and behavior patterns of urology residents in Turkey regarding the use of fluoroscopy in different institutions.

## Methods

### Ethical Standards

This study protocol was reviewed and approved by the Ankara City Hospital Local Ethics Committee on May 18, 2021 (approval number: E2-21-502). Participants were informed that the data will be used for scientific purposes only.

### Study Design

Physicians working as urology residents in university hospitals (group 1) and training and research hospitals (group 2) in Turkey were included in the study. The 13-question survey was prepared via "Google Forms" (Table 1). The questionnaire form was shared once every two days for four weeks as of January 3, 2021, via the "WhatsApp" application, which includes 279 urology residents and 113 urology residents completed the questionnaire. The answers given by the participants were kept confidential.

The survey included questions about the range of participants' ages, the year of urology residency, the institution (university hospital or training and research hospital), and the surgical techniques using fluoroscopy during their training. Additionally, the participants were also questioned about their own and the auxiliary healthcare staff's tendency to refrain from surgeries using fluoroscopy and to replace a surgery requiring fluoroscopy with a non-fluoroscopy method. It was evaluated whether they and their auxiliary healthcare staff received training on dosimeter usage, the radiation dose of fluoroscopy, and protection methods. Their opinions on the protective equipment and its adequacy and regular controls, and their knowledge of ionizing radiation protection methods were questioned too.

### Statistical Analysis

Statistical data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, Ill., United States). Numerical data was expressed as the number of participants and the percentage [n (%)]. The chi-square and Fisher's exact tests were used to compare categorical data and a p-value of less than 0.05 was considered statistically significant.

## Results

One hundred and thirteen participant urology residents completed the questionnaire. Of the residents, 56 (49.6%) were training in university hospitals (group 1) and 57 (50.4%) were in training and research hospitals (group 2). Eighty-one (71.7%) of the residents were between the ages of 25-30 and 60 (53.1%) were in 1-3 years of their education. One hundred and twelve (99.1%) of the participants reported that they preferred to use fluoroscopy in PNL, 75 (66.4%) of them preferred retrograde intrarenal surgery (RIRS), and 71 (62.8%) preferred nephrostomy/double J (DJ) insertion operations.

The hesitation rate to participate in a surgery requiring fluoroscopy was 67.3% and 43.4% for the residents and healthcare staff, respectively. This difference between the two healthcare worker groups was statistically significant ($p<0.001$). Furthermore, in groups 1 and 2, residents were hesitant to participate in a fluoroscopy-required surgery at a rate of 37.5% and 28.2%, respectively. This difference was also found to be statistically significant ($p=0.016$).

In group 1, 39 (69.6%) residents stated that they preferred methods (even if they required more sessions of operations) in which they would not use fluoroscopy at different frequencies, while in group 2 this number was 33 (57.9%), and the difference was found to be statistically significant ($p=0.042$).

In our study, 68.1% of the residents and auxiliary healthcare staff did not use dosimeters in any operation performed with fluoroscopy. Only six of the residents (5.3%) received training on the harmful radiation effects of fluoroscopy, radiation protection methods, etc. 107 of the participants (94.7%) reported that they used lead aprons in cases where fluoroscopy was used. One hundred-eleven (98.2%) of them used thyroid shields, while only two (1.8%) of them used radioprotective

| Table 1. The distribution of the responses of urology residents training in Turkey to the questionnaire questions evaluating their tendencies and awareness regarding the use of fluoroscopy in operations, according to institution types | | | | |
|---|---|---|---|---|
| | **Total (n=113)** | **Group 1 (n=56, 49.6%)** | **Group 2 (n=57, 50.4%)** | **p** |
| **Q1. Age (years), n (%)** | | | | |
| **<25** | 2 (1.8%) | 0 (0) | 2 (3.5) | |
| **25-30** | 81 (71.7%) | 35 (62.5) | 46 (80.7) | **0.009*** |
| **>30** | 30 (26.5) | 21 (37.5) | 9 (15.8) | |
| **Q2. Residency years, n (%)** | | | | |
| **≤3** | 60 (53.1) | 23 (41.1) | 37 (64.9) | **0.011**** |
| **>3** | 53 (46.9) | 33 (58.9) | 20 (35.1) | |
| **Q3. In which operations do you use fluoroscopy in your urology practice? n (%)** | | | | |
| **PNL** | 112 (99.1) | 56 (100) | 56 (98.1) | >0.99* |
| **RIRS** | 75 (66.4) | 34 (60.7) | 41 (71.9) | 0.207** |
| **Nephrostomy/DJ catheter insertion** | 71 (62.8) | 34 (60.7) | 37 (64.9) | 0.064** |
| **Q4. Do you hesitate to participate in operations that require fluoroscopy? n (%)** | | | | |
| **Never** | 76 (67.3) | 35 (62.5) | 41 (71.8) | |
| **Rarely** | 25 (22.1) | 11 (19.6) | 14 (24.6) | |
| **Sometimes** | 11 (9.7) | 10 (17.9) | 1 (1.8) | **0.016*** |
| **Often** | 1 (0.9) | 0 (0) | 1 (1.8) | |
| **Always** | 0 (0) | 0 (0) | 0 (0) | |
| **Q5. Do auxiliary healthcare staff hesitate to participate in operations that require fluoroscopy? n (%)** | | | | |
| **Never** | 7 (6.2) | 5 (8.9) | 2 (3.5) | |
| **Rarely** | 13 (11.5) | 5 (8.9) | 8 (14) | |
| **Sometimes** | 28 (24.8) | 9 (16.1) | 19 (33.3) | 0.147** |
| **Often** | 49 (43.4) | 28 (50) | 21 (36.8) | |
| **Always** | 16 (14.1) | 9 (16.1) | 7 (12.4) | |
| **Q6. Would you prefer to operate a case without using fluoroscopy in more sessions with different technique rather than in one session with using fluoroscopy? n (%)** | | | | |
| **Never** | 41 (36.3) | 17 (30.4) | 24 (42.1) | |
| **Rarely** | 41 (36.3) | 18 (32.1) | 23 (40.4) | |
| **Sometimes** | 23 (20.4) | 15 (26.8) | 8 (14) | **0.042*** |
| **Often** | 5 (4.4) | 5 (8.9) | 0 (0) | |
| **Always** | 3 (2.6) | 1 (1.8) | 2 (3.5) | |
| **Q7. Do you and your auxiliary staff use a dosimeter in cases where fluoroscopy is used? n (%)** | | | | |
| **Never** | 77 (68.1) | 43 (76.8) | 34 (59.6) | |
| **Rarely** | 15 (13.3) | 5 (8.9) | 10 (17.6) | |
| **Sometimes** | 13 (11.5) | 5 (8.9) | 8 (14) | 0.378* |
| **Often** | 6 (5.3) | 2 (3.6) | 4 (7) | |
| **Always** | 2 (1.8) | 1 (1.8) | 1 (1.8) | |
| **Q8. Have you been trained in the subjects on radiation effect caused by fluoroscopy, radiation protection method and etc.? n (%)** | | | | |
| **Yes** | 6 (5.3%) | 3 (5.4) | 3 (5.3) | >0.99* |
| **No** | 107 (94.7%) | 53 (94.6) | 54 (94.7) | |

| Table 1. Continued | | | | |
|---|---|---|---|---|
| | **Total (n=113)** | **Group 1 (n=56, 49.6%)** | **Group 2 (n=57, 50.4%)** | **p** |
| **Q9. Is there adequate ventilation in the operating room where fluoroscopy is used to reduce the effects of ionizing radiation? n (%)** | | | | |
| **Yes** | 41 (36.3) | 21 (37.5) | 20 (35.1) | 0.79** |
| **No** | 72 (63.7) | 35 (62.5) | 37 (64.9) | |
| **Q10. Do you believe that lead aprons worn during fluoroscopy surgeries are sufficiently protective? n (%)** | | | | |
| **Yes** | 8 (7.1%) | 2 (3.6) | 6 (10.5) | |
| **Partially** | 68 (60.2%) | 39 (69.6) | 29 (50.9) | 0.118* |
| **No** | 37 (32.7) | 15 (26.8) | 22 (38.6) | |
| **Q11. Which of the following protective equipment do you use regularly in operations where fluoroscopy is used? n (%)** | | | | |
| **Lead apron** | 107 (94.7%) | 51 (91.1) | 56 (98.2) | 0.113* |
| **Thyroid shield** | 111 (98.2%) | 54 (96.4) | 57 (100) | 0.243* |
| **Radiation protective glasses** | 2 (1.8) | 1 (1.8) | 1 (1.8) | >0.99* |
| **Radiation protective gloves** | 0 (0) | 0 (0) | 0 (0) | |
| **Q12. Do you think that protective equipment is regularly checked for effectiveness? n (%)** | | | | |
| **Yes** | 7 (6.2) | 1 (1.8) | 6 (10.5) | 0.113* |
| **No** | 106 (93.8) | 55 (98.2) | 51 (89.5) | |
| **Q13. Do you know/do you perform, what should be done to reduce the harmful radiation effect after fluoroscopy?"** | | | | |
| **I do not know/I do not do** | 109 (96.5) | 52 (92.9) | 57 (100) | |
| **I know/I do not do** | 3 (2.7) | 3 (5.4) | 0 (0) | 0.057* |
| **I know/I do** | 1 (0.8) | 1 (1.8) | 0 (0) | |

Q: Question, PNL: Percutaneous nephrolithotomy, RIRS: Retrograde intrarenal surgery, DJ: Double J, *: Fisher's exact test, **: Chi-square test

glasses. It was learned that none of the residents were using the radioprotective gloves.

Finally, 106 of the residents (98.2%) answered "no" to the question "Do you think that protective equipment is regularly checked for effectiveness?" and 109 (96.5%) residents answered "I don't know/I don't do" the question "Do you know/do you perform, what should be done to reduce the harmful radiation effect after fluoroscopy?". The data about the answers given by the residents to the survey are shown in Table 1. The answers of all urology residents regarding the main questions are shown in Figure 1 and 2.

## Discussion

In our study, even though all urology residents are at similar education levels on RE, the residents training in university hospitals had more anxiety about using fluoroscopy than their colleagues in training and research hospitals. Similarly, unlike their colleagues in training and research hospitals, the residents in university hospitals prefer to operate a case with a different method without using fluoroscopy in more sessions than in a single session using fluoroscopy. It may be because the residents working in the training and research hospitals care less about their safety due to the high workload. Additionally, auxiliary healthcare staff much more often avoid cases in which fluoroscopy is used than urology residents. This can be explained by the fact that residents with the concern of training in their occupation ignore ionizing RE. There are many studies in the literature about the awareness of RE of urology residents (1,4-7). However, this is the first study to evaluate the attitude and knowledge of urology residents concerning ionizing radiation according to their educational institutions.

Ionizing radiation is a serious health problem faced by practitioners when they apply it during medical diagnosis and treatment. While applying these procedures, the harmful effects of radiation must be taken into account. Especially recently, the increase in endourological interventions and the parallel increase in RE impose an important responsibility on urologists to protect themselves, auxiliary healthcare staff, and their patients

(8). For this purpose, the use of a lead apron, thyroid shield, radiation protective glasses, and gloves is recommended in cases where fluoroscopy is used, and it is known that this protective equipment prevents the harmful effects of ionizing radiation (1). However, many studies have shown that most urologists do not have sufficient knowledge about the harmful effects of radiation and do not take adequate precautions against radiation (1,9,10). In a recent study involving 309 urology residents from the United Kingdom, it was determined that 44.1% of the participants had not received any training on radiation protection methods (11). In a study that Harris et al. (4) evaluated 136 urology residents in the United States, it was shown that almost half of the residents did not receive formal radiation safety training. In the same study, it was reported that 99% of the residents used a thyroid shield, 97% of them regularly wore lead aprons, but only 9% of the residents used radiation protective glasses. Besides, it has been shown that none of the assistants wore radiation protective gloves. In another survey study conducted on urology residents in Canada, it was stated that although the rate of thyroid shield use was 96%, 24% of them used it irregularly. While the rate of use of radiation protective lead aprons is 13%, it has been

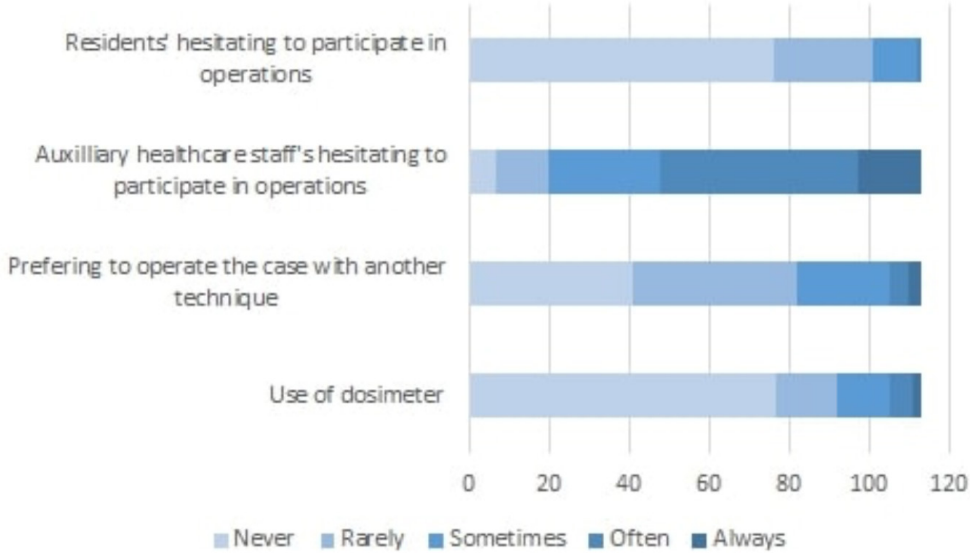


**Figure 1.** Distribution of urology residents' responses to Question 4, Question 5, Question 6 and Question 7

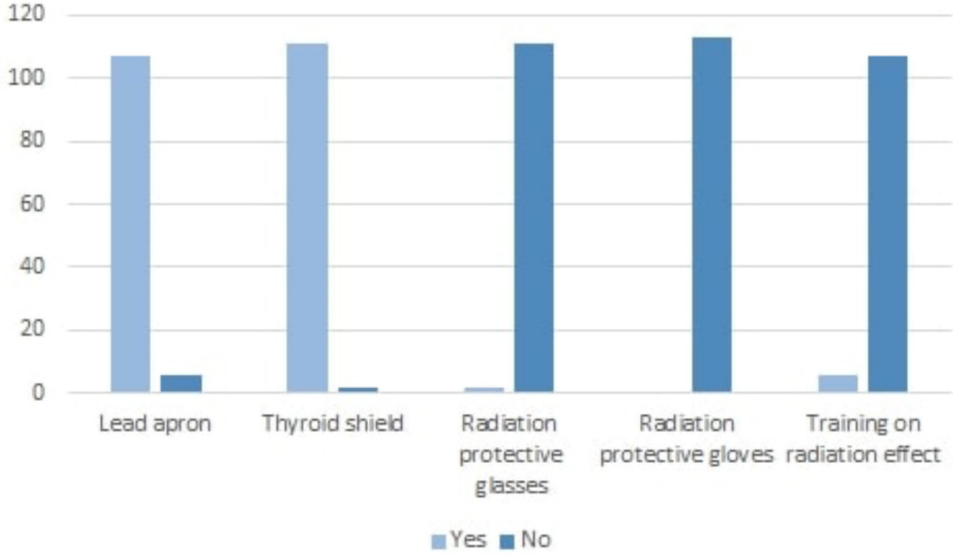


**Figure 2.** The urology residents' rate of use of the protective equipment and training on radiation effects

shown that almost no residents use radiation protective gloves. In this study, it was also emphasized that 70% of the residents did not use dosimetry (7). Similar results are also observed in studies conducted in Europe (5). In our study, it is seen that while the use of lead aprons and thyroid shields is quite high among urology residents in Turkey, almost none of the residents use radiation protective glasses and gloves. Additionally, 68.1% of the residents never used dosimetry and only 5.3% stated that they received training on radiation safety. Another striking result is that the vast majority of urology residents do not believe that protective equipment is regularly checked for effectiveness.

Fluoroscopy is used in many operations in urology. In the study by Altintas et al. (6), 53.9% of the participants answered the question "In which case do you need a fluoroscopy device the most" as PNL. In a recent study, it was reported that the duration of fluoroscopy used in ureteroscopy decreased with the experience of urology residents (12). In another study, it was shown that RE was not affected by the surgeon's experience (13). In our study, fluoroscopy was almost always used in PNL cases. In operations of RIRS and nephrostomy/DJ insertion, fluoroscopy was preferred in one of three patients. We think that this difference may have arisen due to studies showing the effectiveness and reliability of the non-fluoroscopic RIRS technique (14).

### Study Limitations

There are some limitations of our study. First, this study is a survey-based study, and only those who preferred to participate in the survey via "WhatsApp®" were included in the study. Apart from this, the small number of participants is another handicap. Additionally, the status of the auxiliary healthcare staff to avoid cases using fluoroscopy was evaluated according to their responses to urology residents. Despite these limitations, the study's strength is that it is the first study to be conducted due to the tendencies of urology residents training in different institutions in Turkey about the use of fluoroscopy.

## Conclusion

Although the use of a lead apron and thyroid shield is excellent in both groups, the rate of use of radiation protective glasses and gloves is almost zero. The residents who train in university hospitals are more scared of RE from fluoroscopy than their colleagues working in training and research hospitals. However, the lack of education is present and the use of dosimeters is very low in both groups. The tendency, awareness, and knowledge of urology residents about the effects of RE and methods of protection should be increased.

### Ethics

**Ethics Committee Approval:** This study protocol was reviewed and approved by the Ankara City Hospital Local Ethics Committee on May 18, 2021 (approval number: E2-21-502).

**Informed Consent:** Participants were informed that the data will be used for scientific purposes only.

**Peer-review:**

**Authorship Contributions**

Concept: E.G., H.C.D., Design: F.S., S.Z.S., Data Collection or Processing: E.G., A.Y.O., Analysis or Interpretation: H.C.D., Literature Search: E.G., S.S., Writing: S.S.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Original Article

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# Comparison of Perioperative Outcomes and Urethral Complications Between Using 24-French and 26-French Resectoscope Sheaths in Holmium Laser Enucleation of the Prostate

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## Abstract

**Aim:** Although the 26F resectoscope is frequently used in transurethral prostatectomy, there are some concerns with high-caliber shafts. We compared 24F and 26F resectoscope used for Holmium Laser Enucleation of the Prostate (HoLEP) in terms of effects on postoperative urethral complications and perioperative outcomes.

**Methods:** Data from patients undergoing HoLEP from 2017 to 2021 was retrospectively analyzed. All surgeries were completed by a single surgeon. The patients were divided into one of two groups according to the resectoscope diameter (24F or 26F). All patients were followed up for urethral complications for 12 months. Perioperative outcomes and urethral complications were compared between the groups.

**Results:** The study included 301 patients. The mean age of patients was 68.5±8.3 and 69.1±8.6 for the 26F group (n=180) and the 24F group (n=121), respectively (p=0.608). A total of seven in the 26F group (3.8%) and 3 patients in the 24F group (2.4%) had postoperative urethral stricture (US) (p=0.503). Besides, 2 patients (26F) and 1 patient (24F) had postoperative bladder neck contracture (BNC) (p=0.807). The operation efficiency was 1.25 g/min in the 26F group and 1.17 g/min in the 24F group (p=0.005).

**Conclusion:** The use of 24F or 26F RS was not shown to cause statistically significant differences in the incidence of US and BNC during the 12-month follow-up. The use of the 24F RS significantly reduces surgical and morcellation efficiency.

**Keywords:** Urethral structure Holmium laser enucleation of the prostate (HoLEP), prostatic hyperplasia, complications

## Introduction

Benign prostatic hyperplasia (BPH) is the main cause of lower urinary tract symptoms and is frequently seen in elderly men (1). Traditionally, the standard surgical treatment for BPH is transurethral prostatectomy (TUR-P). However, holmium laser enucleation of the prostate (HoLEP) is a strong alternative treatment method to TUR-P, providing advantages like short hospitalization duration, low complications, and low recurrence rates (2-4). Though HoLEP may be safely applied to all prostate sizes, complications like hemorrhage in the intraoperative or postoperative period, capsule perforation, bladder mucosa, and ureter orifice injury, urethral stricture (US), and bladder neck contracture (BNC) may be observed (5).

Excessive resection, urinary extravasation, use of thick urethral catheters, extended catheter use, and the presence of infection are situations that increase the incidence of urethral complications during transurethral surgeries (6,7). Additionally, previous studies showed that the use of a large-diameter resectoscope for TUR-P increases the risk of developing postoperative BNC and US (6,8). In our study, we aimed to compare the use of

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24-French (F) and 26F resectoscopes for HoLEP in terms of their effects on postoperative urethral complications and perioperative outcomes.

## Methods

### Study Design

After receiving ethical committee approval (Istanbul Okan University, date: 20.10.2021, approval number: 143) prospectively recorded data from patients undergoing HoLEP from 2017 to 2021 were retrospectively analyzed. All surgeries were completed by a single surgeon (MA) with appreciable HoLEP experience (200 cases). Patients with a history of prostate or urethra surgery, with US or BNC, and with neurogenic bladder diagnosed urodynamically were excluded from the study. The patients were divided into one of two groups according to the resectoscope diameter used for HoLEP (24F vs 26F).

Preoperative assessment included physical examination, digital rectal examination, transrectal ultrasound and biopsy when indicated, $Q_{max}$ measurement, post-voiding residual volume, prostate volume with transabdominal ultrasound, serum prostate-specific antigen (PSA), International Prostate Symptom Score (I-PSS), International Index of Erectile Function-5 (IIEF-5) and urinalysis. Preoperatively, patients were assessed with the Charlson Comorbidity Index for comorbidities (9,10).

### Technique and Equipment for the Procedure

All patients had HoLEP performed under general or spinal anesthesia using a 140 W Multipulse HoPLUS laser platform (Jena Surgical/Asclepion Laser, Jena, Germany) and a 600 nm laser fiber (Jena Surgical) with the 3-lobe technique. In the first section of the data collection stage, a 24F continuous-flow resectoscope (Wolf®) was used for patients. Due to a change in devices used in the surgery, later cases had a 26F continuous-flow resectoscope (Karl Storz) used. Energy setting was entered into the system with 140 W for the left pedal (4 J energy, 35 Hz frequency) and 60 W for the right pedal (2 J energy, 30 Hz frequency). In the morcellation stage, an integrated Multicut morcellator system (Jena Surgical) was used. For all procedures, normal saline was used as an irrigation fluid. At the end of the surgery, every patient had a 22 F 3-way Foley catheter inserted. All patients were administered perioperative antibiotic therapy.

### Perioperative Evaluation and Follow-up

Morcellation efficiency, enucleation efficiency, and operation efficiency were calculated by dividing the resected weight by the morcellation duration, enucleation duration, and operation duration, respectively. All patients were reevaluated at 1, 3, 6, and 12-month follow-up by I-PSS, IIEF-5, $Q_{max}$, PSA level, and the existence of complications. US/BNC was diagnosed by performing uroflowmetry and cystoscopy in patients with signs of lower urinary tract obstruction. Perioperative and postoperative complications were recorded according to the Clavien-Dindo system (11,12).

### Statistical Analysis

SPSS software (Statistical Package for the Social Sciences, Version 21.0, SSPS Inc., Chicago, IL, USA) was used for data analysis. Continuous variables are expressed as mean ± standard deviation, while categoric variables are expressed as a percentage (%). Normality analysis was performed using the Kolmogorov-Smirnov test. Differences between measurements at separate times were analyzed with ANOVA for repeated measures. Statistically, $p \leq 0.05$ were accepted as significant.

## Results

A total of 301 patients were included in the study. The mean age of 180 patients operated with a 26F resectoscope was 68.5±8.3 years, while the mean age of 121 patients operated with a 24F resectoscope was 69.1±8.6 years (p=0.608). A comparison of the preoperative demographic and clinical features of the patients according to the group is summarized in Table 1. The most frequent indication for HoLEP surgery was the failure of medical treatment (182/301, 60.5%), followed by refractive urinary retention (90/301, 29.9%), recurrent urinary tract infections (25/301, 8.3%), and recurrent hematuria (4/301, 1.3%).

The mean prostate volume was 112.8±43.7 mL in Group 1 and 108.6±39.2 mL in Group 2 (p=0.39). The surgical durations in Groups 1 and 2 were 71.1±19 and 72.2±20.2 min, respectively (p=0.63). The operation efficiency was calculated as 1.25 g/min in the 26F group and 1.17 g/min in the 24F group. This difference was statistically significant in favor of the 26F group (p=0.005). During the procedure, 77 patients in the 26F group (42.7%) and 7 patients in the 24F group (5.7%) had bougie dilators used (p=<0.001). While 12 patients in the 26F group had intraoperative Otis urethrotomy performed, only 1 patient in the 24F group had this performed (p=0.017). Intraoperative and perioperative outcomes are summarized in Table 2. The improvement in $Q_{max}$ levels and IPSS scores in the first, third, and twelfth follow-up months was similar in both groups (Figure 1).

The most common complications observed within the first 30 days postoperative were dysuria in 35/180 (19.4%) in the 26F group and 26/121 (21.4%) in the 24F group (p=0.884). During the 12-month follow-up, 7 patients in the 26F group (3.8%) and 3 patients in the 24F group (2.4%) had postoperative US (p=0.503). A total of 2 (26F) and 1 patient (24F) had postoperative BNC

| Table 1. Patients preoperative demographics and clinical characteristics according to groups | | | |
|---|---|---|---|
| | **26 fr group** | **24 fr group** | **p-value*** |
| Number of patients | 180 | 121 | |
| Age (years) | 68.5 (±8.3) | 69.1 (±8.6) | 0.608 |
| BMI | 23.8 (±2.1) | 23.6 (±2.2) | 0.427 |
| CCI | 3 (0-7) | 3 (0-7) | 0.707 |
| IPSS | 27.3 (±4.2) | 26.5 (±4.1) | 0.102 |
| $Q_{max}$ (mL/sec) | 11.6 (±6.1) | 10.9 (±5.7) | 0.317 |
| PVR (mL) | 150.9 (±79.2) | 151.1 (±83.6) | 0.983 |
| PSA (ng/mL) | 3.3 (±3.1) | 3.4 (±3.3) | 0.789 |
| Prostate volume (mL) | 112.8 (±43.7) | 108.6 (±39.2) | 0.395 |
| IIEF score | 18 (5-29) | 18 (5-26) | 0.182 |
| Coagulopathy | 26/154 | 14/107 | 0.471 |

*p-values were calculated using Student's t or Mann-Whitney U test for continuous and chi-squared test for categorical variables
BMI: Body mass index, CCI: Charlson comorbidity index, IPSS: International Prostate Symptom Score, $Q_{max}$: Maximum flow rate, PVR: Post-void residual volume, PSA: Prostate-specific antigen, IIEF: International Index of Erectile Function

(p=0.807). Additionally, postoperative US was observed in 3 (3.2%) and 2 (1.7%) patients who did not undergo bougie dilatation or Otis urethrotomy in the 26F and 24F groups, respectively (p=0.491). Complications in the postoperative early period (within 30 days) and long-term (12-month) are summarized in Table 3 according to the Clavien-Dindo rating system.

## Discussion

HoLEP is a reliable and effective surgical method for the surgical treatment of BPH (13). HoLEP improves the I-PSS and urine flow rate (13). However, HoLEP has some disadvantages, like lowering the postoperative quality of life (incontinence, retrograde ejaculation, dysuria, hematuria, etc.), and the development of US and BNC (5). These complications are also observed after the traditional gold standard surgical treatment method for BPH, TUR-P (14). Important risk factors for the increase in postoperative US and BNC rates are the type of catheter inserted after the operation, catheterization duration, the diameter of the resectoscope, resection duration, and patient-related factors (7,15,16). As far as we know, there is no current study in the literature comparing the perioperative outcomes and postoperative urethral complications during the 12-month follow-up for HoLEP performed with 24F and 26F resectoscopes.

In randomized controlled studies, the incidence of US after TUR-P varies from 0 to 14.7% (14). These results may vary, linked to the diameter of the resectoscope and patient-related factors. Günes et al. (8) showed that the use of a large resectoscope significantly increased the incidence of US in a study comparing the outcomes of 71 patients with TUR-P performed with a 24F and a 26F resectoscope. In studies comparing urethral complications in patients with HoLEP performed using 26F and 28F resectoscope, no

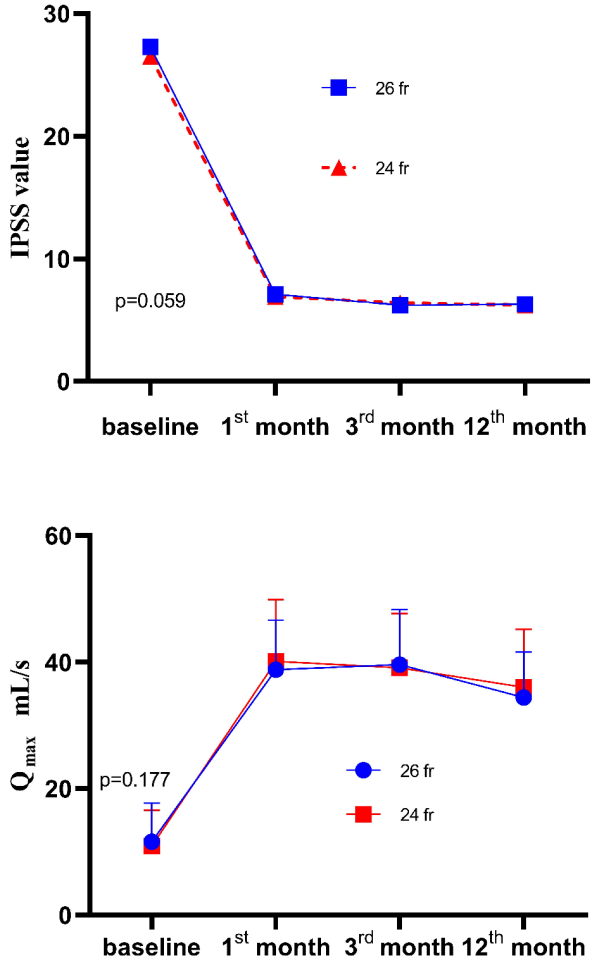


**Figure 1.** Changes in $Q_{max}$ levels and IPSS scores in the groups during the first, third and twelfth month of follow-up

| Table 2. Comparison of the intraoperative and perioperative parameters | | | |
|---|---|---|---|
| | **26 Fr (n=180)** | **24 Fr (n=121)** | **p-value[T]** |
| Urethral bougie dilation, n (%) | 77 (42.7%) | 7 (5.7%) | **<0.001** |
| Urethrotomy interna, n (%) | 12 (6.6%) | 1 (0.8%) | **0.017** |
| Pathologic specimen volume (g) | 89.3 (±26.3) | 84.7 (±29.1) | 0.155 |
| Operative time (mins) | 71.1 (±19.2) | 72.2 (±20.2) | 0.633 |
| Operation efficiency (g/mins) | 1.25 (±0.2) | 1.17 (±0.3) | **0.005** |
| Enucleation time (mins) | 57.5 (±14.3) | 56.9 (±14.1) | 0.152 |
| Enucleation efficiency (g/min) | 1.55 (±0.41) | 1.48 (±0.44) | 0.159 |
| Morcellation time (mins) | 13.6 (±5.9) | 15.3 (±6.1) | **0.016** |
| Morcellation efficiency (g/min) | 6.56 (±3.1) | 5.53 (±2.8) | **0.003** |
| Hematocrit decrease | 2.6 (±1.8) | 2.2 (±1.7) | 0.054 |
| Hospital stay (days) | 1.07 (±0.2) | 1.04 (±0.1) | 0.128 |
| Catheter removal time (days) | 2.3 (±1.1) | 2.2 (±1.2) | 0.456 |
| [T]Student's t-test. Data are presented as mean | | | |

significant difference was identified for the incidence of US and BNC (17). A retrospective study by Günes et al. (8) showed that the use of a large resectoscope (24F or 26F) significantly increased the development of stricture in the bulbar urethra after TUR-P. In our study, the development rates for the US after HoLEP were 3.8% and 2.4% in the 26F and 24F groups, respectively. Though the incidence of US development was lower in the 24F group, this was statistically insignificant. Additionally, 2 patients in the 26F group and 1 patient in the 24F group developed BNC. As the diameter of the resectoscope used increases, more urethral ischemia forms secondary to compression (6). We believe that this situation may be a cause of the different US incidences.

Urethral bougie dilation was performed intraoperatively in 77 patients in the 26F group (42.7%) and 7 patients in the 24F group (5.7%). Additionally, 12 patients in the 26F group (6.6%) had intraoperative Otis urethrotomy performed, whereas only 1 patient in the other groups required Otis urethrotomy (0.8%). All patients developing the US in the 26F group had intraoperative Otis urethrotomy performed. The use of a wide resectoscope increases the need for intraoperative dilatation or urethrotomy, which may cause urethral mucosal damage and an increase in postoperative US incidence.

Small-diameter resectoscopes cause slower continuous flow and this may worsen intraoperative vision. Worsening image quality may lower surgical efficiency by lengthening operation durations. In our clinic, we experienced a clear fall in image quality when using the 24F resectoscope. However, our study shows the operation and morcellation efficiency were lower in the 24F group, while the morcellation duration was higher. Additionally, the enucleation efficiency was higher in the 26F groups however, this difference was statistically insignificant.

To observe the effect of the resectoscope sizes on perioperative parameters, we compared the hospitalization duration, catheter removal duration, and decrease in the hematocrit for patients in both groups.

Statistically significant differences were not identified between hospitalization duration, catheter removal time, and hematocrit decreases between the groups.

| Table 3. Frequency of complications and assumed Clavien-Dindo grading of reported complications | | | | |
|---|---|---|---|---|
| | | **Groups, n (%)** | | |
| **Complication within 30-day period** | **Clavien grade** | **26 Fr group** | **24 Fr group** | **p-value** |
| Dysuria | 1 | 35 (19.4%) | 26 (21.4%) | 0.884 |
| Transient incontinence | 1 | 10 (5.5%) | 8 (6.6%) | 0.805 |
| Mild to moderate dysuria | 2 | 5 (2.7%) | 2 (1.6%) | 0.705 |
| Hematuria/blood transfusion | 2 | 1 (0.5%) | 0 | 1.000 |
| Urinary tract infection | 2 | 0 | 1 (0.8%) | 1.000 |
| Severe hematuria/clot retention | 3b | 1 (0.5%) | 1 (0.8%) | 1.000 |
| **12-month follow-up complication** | | | | |
| Bladder neck stenosis | 3b | 2 (1.1%) | 1 (0.8%) | 0.807 |
| Urethral stenosis | 3b | 7 (3.8%) | 3 (2.4%) | 0.503 |

Additionally, during the postoperative 12-month follow-up, when complications apart from stricture were assessed in our patients (dysuria, incontinence, hematuria, infection), we did not observe a significant difference between the two groups. Our perioperative findings and postoperative complication rates were similar to the results of a Holep review by Das et al. (18) in 2019.

### Study Limitations

There are some limitations to our study. The first one is the retrospective design of the study. Though our design was retrospective, data for each patient was entered into the system prospectively. Another limitation is that the difference in experience of the surgeon (though the same surgeon has performed all the operations.) in the period when surgery was performed in both groups was not considered. Despite these limitations, the study will guide our colleagues in clinical practice due to the limited number of similar studies in the literature and the fact that high-caliber shafts are a concern in the minds of all urologists.

## Conclusion

In our study, the use of a 24F or 26F resectoscope was not shown to cause statistically significant differences in the incidence of US and BNC during the 12-month follow-up. However, the use of a large-diameter resectoscope increases the need for perioperative urethral dilatation and urethrotomy, and this may cause more urethral ischemia and mucosal damage. The use of the 24F resectoscope significantly reduces surgical and morcellation efficiency. To identify the optimum resectoscope diameter for HoLEP, prospective randomized controlled studies on many participants on this topic will contribute to our preliminary outcomes.

### Ethics

**Ethics Committee Approval:** Ethical committee approval was obtained from Istanbul Okan University (date: 20.10.2021, approval number: 143).

**Informed Consent:** Retrospective study.

### Authorship Contributions

Concept: A.Y., S.A., M.A., Design: A.Y., S.A., M.A., Data Collection and/or Processing: A.Y., S.A., A.G., Analysis and/or Interpretation: A.Y., H.A., A.G., M.A., Literature Research: A.Y., H.A., A.G., Writing: A.Y., H.A., A.G.

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Original Article

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# Comparison of Treatment Modalities in Adult Idiopathic Sudden Hearing Loss: A 5-year Outcome from a Tertiary Referral Center

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## Abstract

**Aim:** Although there are many treatment options for the treatment sudden idiopathic sensorineural hearing loss (SSHL), the most effective treatment method is still unclear. The purpose of this study was to determine the optimal treatment option for SSHL by examining the 5-years patient data of our clinic.

**Methods:** The patients who were diagnosed as SSHL in our clinic between January 1, 2016 and July 31, 2021 were included in the present study. The treatment in groups were only oral steroid (OS) (group 1, n=30), OS and hyperbaric oxygen therapy (HBOT) (group 2, n=30), OS and intratympanic steroid therapy (ITS) (group 3, n=30) and OS+ITS+HBOT (group 4, n=30). The baseline pure tone audiometry (PTA), 3rd month PTA averages, audiological hearing gains and treatment success (a gain more than 15 Db in PTA) were determined and compared statistically.

**Results:** The initial PTA averages (dB) in groups were 46.07±14.20, 45±12.49, 45.83±10.92, and 45.93±10.29, respectively. There were significant differences between the groups according to the PTA after treatment ($p<0.05$). In the after-treatment PTA threshold evaluation, the mean of group 4 was statistically significantly lowest ($p<0.05$). There were significant differences between the groups according to the PTA gain ($p<0.05$). In the paired comparisons of the groups according to PTA gain, the value of group 4 was significantly highest in all groups ($p<0.05$). No significant difference was found between the groups according to the other parameters ($p>0.05$).

**Conclusion:** In this study, the combined (oral+IT+HBOT) therapy was superior to other treatment modalities.

**Keywords:** Audiometry, pure tone, hearing loss, sudden/therapy, prognosis, hyperbaric oxygenation, steroids

## Introduction

Sudden sensorineural hearing loss (SSHL) is described as a sensorineural hearing loss of at least thirty dB and above in at least 3 consecutive frequencies in pure tone audiometry (PTA) (1,2). It is one of the most common otorhinolaryngology emergencies with an incidence of 5-30 per 100000 people. It can affect all age groups. Together, it peaks in the 5-6th decade and the male-female ratio is equal (3). In almost all cases; it is unilateral and less than 2% has been reported as bilateral (4).

An underlying cause can be identified in 7-45% of patients presenting with SSHL (3,4). It is accepted as idiopathic SSHL if the etiology is not detectable after investigating autoimmune, infectious, functional, metabolic, neoplastic, neurological, otologic, toxic, traumatic and vascular causes. Many pathophysiological mechanism hypotheses have been proposed to explain SSHL. Among the most common hypotheses; viral infections, rupture of cochlear membranes and vascular events are blamed (5-10).

Different methods are used in the treatment of this situation, which is thought to have a spontaneous recovery rate of 32% to 65% (11-13). There are many agents and methods in the management of SSHL; hyperbaric oxygen (HBO) and bed rest, antimicrobials and anti-inflammatory drugs, vasodilators, calcium antagonists, vitamins,

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essential minerals, volume expanders, defibrinogens, diuretics are the main agents used in treatment (14). These options can be used alone or in combination. Oral steroid (OS) therapy is the first recommended treatment in the guidelines and its side effects are mostly tolerable (12,15-18). Intratympanic steroid (ITS) injection can be used as a stand-alone therapy, combined with OS therapy, or administered as a rescue therapy (17,19,20).

Although there is different information in the literature regarding the definition of success in the treatment of SSHL, Siegel (21) developed a classification according to the acquired hearing gain and divided the recovery into four categories; class I: patients with complete recovery class II: patients with a gain of more than 15 dB but who do not reach normal hearing, and average of better than 45 dB with a PTA, class III: Patients with a gain of more than 15 dB but worse than 45 dB in PTA, class IV: Patients with less than 15 dB gain or no gain at all. For the response to the treatment, starting the treatment late, hearing loss with descending audiogram curve, accompanied by vestibular symptoms and facial paralysis, bilateral hearing loss, total or near-total hearing loss, multiple vascular risk factors, and elderly patients were described as poor prognostic factor.

There are different studies in the literature regarding the superiority of treatment options for sudden hearing loss, which is still a matter of debate whether it requires treatment or not. In the present study, we purposed to determine the optimal treatment option by examining the 5-year patient data of our clinic, which is one of the largest centers in Turkey in terms of the number of patients admitted and followed.

## Methods

This cross-sectional study was performed in Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Otorhinolaryngology, after receiving the approval of the Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (decision date: 03.08.2021 and approval number: 604.01.01-152390) with the patients diagnosed as SSHL in our clinic between January 1, 2016 and July 31, 2021. This study was conducted retrospectively on the files of 120 patients who were diagnosed as sudden idiopathic sensorineural hearing loss and whose etiologies were not found.

All patients included in the study had at least 30 dB unilateral sensorineural hearing loss in at least three frequencies that started within 72 hours. The patients included in this study were between the ages of 18-60 and admitted to the hospital on the day of the onset of symptoms. Patients with acute or chronic infection in the affected ear, a history of surgery, and a known chronic disease were excluded from the study.

Among the patients whose diagnosis, treatment and follow-up were made in our clinic, 30 patients who received only OS (1 mg/kg prednisolone) treatment (group 1), 30 patients who received OS and HBO therapy (HBOT) (20 sessions in total for 2 hours at 2.5 atm pressure) (group 2) 30 patients (group 3) who received OS and ITS therapy (a single dose of 4 mg on the 1$^{st}$, 3$^{rd}$, 5$^{th}$, 7$^{th}$, 14$^{th}$ days) and 30 patients (group 4) who received all of these treatments in combination were included in the study.

OS treatments were administered as a single dose per day. HBO treatments were applied in the same center. Intratympanic injections were made using a microscope. After the patient's head was rotated 45 degrees to the opposite direction of the affected ear, local anesthesia was achieved by keeping a piece of cotton impregnated with 10% lidocaine for 10 minutes on the tympanic membrane. After anesthesia, puncture was performed with a 22 gauge needle from the anterior superior quadrant, followed by 1 cc dexamethasone (8 mg/2 mL) with a 27 gauge needle from the posterior inferior quadrant. After the procedure, the patient was kept in the same position for 30 minutes without swallowing or speaking.

PTA averages were evaluated at 0.5-1.0 and 2.0 kHz frequencies at the beginning of the treatment and at the 3$^{rd}$ month of admission. A gain of more than 15 dB in PTA test was determined as a treatment success criterion. In study groups; baseline, 3$^{rd}$ month PTA averages, audiological hearing gains and treatment success were determined. The obtained data were analyzed statistically. Informed consent forms were obtained from patients.

### Statistical Analysis

Statistical Package for the Social Sciences (SPSS) 22 (SPSS Inc., USA) was used for statistical analysis. The normal distribution and homogeneity of data were evaluated with the Kolmogorov-Smirnov test and Levene's test. Kruskal-Wallis test, Mann-Whitney U test and Pearson chi-square test were used to compare the groups. Statistically significant level was accepted as $p<0.05$.

## Results

A total of 120 patients, 69 (57.5%) men and 51 (42.5%) women, were included in this study. The mean age of the patients was calculated as 40.84±7.29 (21-57) years. The groups were statistically similar according to the age characteristics of the patients ($p>0.05$) (Table 1).

When the initial PTA (dB) averages were evaluated, it was determined as 46.07±14.20 for group 1, 45±12.49 for group 2, 45.83±10.92 for group 3, and 45.93±10.29 for group 4. There was no significant difference between the groups according to initial PTA values ($p=0.958$, $p>0.05$) (Table 1).

When the PTA means (dB) were evaluated after the treatment, it was determined as 32.6±15.71 for group 1, 30.63±15.04 for group 2, 29.9±15.66 for group 3, and 22.73±11.51 for group 4. There was a significant difference between the groups according to the PTA values after treatment (p=0.04, p<0.05) (Table 1). In the pairwise comparisons made according to the PTA averages of the groups after the treatment, the value of group 4 was statistically significantly lower than all groups (respectively; p=0.07, p=0.029, p=0.04, p<0.05). No significant difference was obtained in the paired comparisons of the other groups (p>0.05) (Table 2).

When the groups were evaluated in terms of the mean PTA gains (dB) which were obtained with the treatment, it was determined as 13.47±7.78 for group 1, 14.37±9.47 for group 2, 15.93±10.84 for group 3, and 23.2±15.24 for group 4. There was a significant difference between the groups according to PTA values after treatment (p=0.022, p<0.05) (Table 1). In the pairwise comparisons made according to the PTA gain values of the groups obtained with the treatment, the value of group 4 was statistically significantly higher than all groups (respectively; p=0.07, p=0.012, p=0.029, p<0.05). No significant difference was found in the paired comparisons of the other groups (p>0.05) (Table 2).

When the groups were compared according to the determined audiological success criteria, no significant difference was obtained between the groups (p=0.309, p>0.05) (Table 3).

## Discussion

Sudden idiopathic sensorineural hearing loss is one of the most controversial issues of otorhinolaryngology in terms of its etiology, prognosis, treatment modalities and the results of the modalities. In this study, we tried to reveal the optimal treatment method by retrospectively examining the data of our clinic, which is one of the largest otorhinolaryngology centers in Turkey. As a result of our study, we showed that the combination of OS+ITS+HBO is the treatment method that both provides the highest gain in post-treatment audiological thresholds and brings these thresholds closer to normal values. We did not detect a significant difference between the results of other treatment modalities.

Nowadays, various treatment protocols are applied for the treatment of SSHL. This diversity is due to the very different possible etiology and uncertainties in diagnosis. In its treatment, agents that provide hemodilution, antivirals, vasodilators, HBO and ozone therapy, and corticosteroids with different application routes are applied. Although many agents and combinations of agents are used in the treatment, oral corticosteroids are still preferred as the first treatment option in the treatment of SSHL (22).

In the present study, we purposed to determine the most effective treatment protocols using the data of our patients who met the inclusion criteria. Although we give different treatment combinations to patients with SSHL in our clinic, the steroids included in these treatments as a single dose in the morning to reduce the side effects (23). We applied ITS treatment every other day in order to increase patient compliance. We used the Siegel Criteria, one of the most frequently used criteria in the literature, to evaluate the success we achieved in the treatment of the patients in our study (21).

The American Academy of Otolaryngology-Head and Neck Surgery guidelines recommend an early treatment with steroids within 2 weeks (24). When we look from the perspective of ITS, although there are many protocols defined in the literature, there is no treatment protocol that has been shown to be superior (25). A published meta-analysis showed that ITS therapy alone was not superior to oral or IV steroid therapy (26). In terms of the combination of treatments, combined ITS and OS therapy have been shown to be superior to OS and ITS alone (27). In another study, combined intratympanicdexamethasone and OS therapy was not superior to OS alone (28). HBOT

**Table 1. Statistical analysis of study parameters according to groups**

| Parameters | | Treatment groups | | | | p |
|---|---|---|---|---|---|---|
| | | Group 1 (oral steroid) | Group 2 (oral steroid+hyperbaric oxygen) | Group 3 (oral+intratympanic steroid) | Group 4 (combination therapy) | |
| Age (years) | (min-max)<br>(median) | 21-57<br>38 | 28-55<br>44 | 25-55<br>41 | 25-50<br>42 | 0.529 |
| Pre-treatment PTA (dB) | (min-max)<br>(median) | 30-90<br>41.5 | 30-80<br>45 | 30-70<br>45 | 32-80<br>42 | 0.958 |
| Post-Treatment PTA (dB) | (min-max)<br>(median) | 2-70<br>30 | 5-60<br>33 | 3-60<br>33 | 7-63<br>21 | **0.04*** |
| Auditory gain (dB) | (min-max)<br>(median) | 5-32<br>11 | 2-40<br>10 | 2-42<br>11 | 5-70<br>20 | **0.022*** |

*Kruskal-Wallis test p<0.05.
PTA: Pure tone average, min-max: Minimum-maximum

**Table 2. Comparison of post-treatment values according to groups**

| | Groups | Post-treatment PTA | Auditory gain |
|---|---|---|---|
| p | 1-2 | 0.801 | 0.830 |
| | 1-3 | 0.767 | 0.562 |
| | 1-4 | **0.07*** | **0.07*** |
| | 2-3 | 0.912 | 0.624 |
| | 2-4 | **0.029*** | **0.012*** |
| | 3-4 | **0.04*** | **0.029*** |

*Mann-Whitney U test p<0.05.
PTA: Pure tone average

**Table 3. Evaluation of the treatment successes according to the treatment groups**

| Groups | Treatment results | | p* |
|---|---|---|---|
| | Successful | Failing | |
| Group 1 **n (%)** | 11 (36.7%) | 19 (63.3%) | 0.309 |
| Group 2 **n (%)** | 13 (43.3%) | 17 (56.7%) | |
| Group 3 **n (%)** | 13 (43.3%) | 17 (56.7%) | |
| Group 4 **n (%)** | 18 (60%) | 12 (40%) | |

*Pearson chi-square test p<0.05.

is a treatment method recommended not as a stand-alone option, but in combination with salvage therapy for severe hearing loss greater than 70 dB (29).

In the results of our study; although we determined that combined (oral+IT+HBOT) therapy was superior to other treatment modalities in terms of audiological gain, we could not detect a significant difference between the groups in terms of gaining more than 15 dB in the PTA test, which we determined as the treatment success criterion. Although there is a significant difference between the groups in terms of audiological values, the lack of difference between the groups in terms of patients considered successful can be explained by the small subject size of the present study.

### Study Limitations

There are some limitations of this study, which we conducted to determine the most effective treatment method for SSHL. The major limitation is that our study includes a retrospective file review. The second limitation is that we could not detect all of the prognostic factors of the patients included in the study due to the fact that we performed the study on patient files. Although we did not include patients with known chronic diseases in the study and there was no statistical difference between the patient groups in terms of age criteria, we cannot say that the study groups were similar in terms of prognostic factors. Another limitation is that we only used audiologically hearing thresholds in the study. A study in which the speech discrimination values were also examined would have been more valuable.

## Conclusion

SSHL is one of the emergencies in otorhinolaryngology which is the subject of discussion in every field from its etiology to its treatment. It can be said that the most effective treatment method for the treatment of the disease, which should be treated as soon as possible after the diagnosis is made, is the combination therapy.

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### Ethics

**Ethics Committee Approval:** The study were approved by the Istanbul University-Cerrahpasa, Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (decision date: 03.08.2021 and approval number: 604.01.01-152390).

**Informed Consent:** Retrospective study.

### Authorship Contributions

Concept: Y.Z.Y., S.U., Design: Y.Z.Y., S.U., Data Collection or Processing: Y.Z.Y., S.U., Analysis or Interpretation: Y.Z.Y., S.U., Literature Search: Y.Z.Y., S.U., Writing: Y.Z.Y., S.U.

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Original Article

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# Optic Nerve Head and Macular Vascular Density Changes in Different Stage Glaucoma

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## Abstract

**Aim:** The vascular theory is thought to have an important place in the pathophysiology of glaucoma. In the present study, we aimed to analyze the structural and vascular changes in both eyes of patients with glaucoma at different stages and to investigate the relationship between structural and vascular structures.

**Methods:** In this prospective cross-sectional study conducted between 2018 and 2019, 54 eyes of 27 patients with bilateral asymmetric glaucoma were included. Eyes with glaucoma were evaluated into 2 groups: an earlier stage and an advanced stage. All data is provided from the optical coherence tomography angiography (OCTA) device. The retinal nerve fiber layer (RNFL), ganglion cell inner plexiform layer (GCIPL) thickness, and rim area (RA) were measured using optical coherence tomography (OCT). The optic nerve head total (tVD), peripapillary (ppVD), intradisc (idVD), macular superficial (msVD), parafoveal (pasVD), perifoveal (pesVD), and deep macular vascular density values were compared with using OCTA. The correlation was investigated between thinning in the structural parameters and a decrease in the vascular density parameters.

**Results:** There was a significant difference in both optic nerve head vascular density parameters (tVD, ppVD) and superficial macular vascular density parameters between the eyes with asymmetric glaucoma ($p<0.001$). The thinning of macular GCIPL, which was very strongly correlated with the change in optic nerve perfusion (tVD, ppVD) ($r=0.899$ and 0.892, $p<0.001$), was well correlated with the change in msVD and pesVD ($r=0.642$ and 0.574). The correlation of RNFL with tVD and ppVD was high ($r=0.741$ and 0.813), and the correlation with msVD and pesVD was moderate ($r=0.480$ and 0.494). Macular pasVD, deep vascular density, and idVD showed no correlation with changes in structural parameters.

**Conclusion:** As the stage progresses, both the optic nerve head and macular perfusion are impaired in glaucoma. Macular superficial vascular density is affected more than deep vascular density. Thinning in the structural parameters correlates mostly with optic nerve head tVD and ppVD parameters.

**Keywords:** Optical coherence tomography angiography, glaucoma, microvascular density, angiography

## Introduction

Glaucoma, which is a progressive group of optic neuropathies, is characterized by progressive degeneration of retinal ganglion cells (RGC) and axons, accompanied by optic disc changes and vision loss (1-3). The etiology of primary open-angle glaucoma (POAG) is multifactorial, and no single mechanism adequately describes the susceptibility to glaucomatous damage and variations in damage patterns (4). The vascular theory is based on the notion that abnormal perfusion of the optic nerve head (ONH) and this ischemia play an important role in glaucomatous damage (5). In previous studies, using methods such as fluorescein angiography, color Doppler imaging, confocal laser ophthalmoscopic angiography, and laser Doppler flowmetry, evidence has been shown of decreased peripapillary optic nerve perfusion in glaucoma patients (6-9). However, it has not been proven due to difficulties in accurately measuring ocular blood flow and ONH perfusion.

Optical coherence tomography angiography (OCTA), which has been developed recently, is a noninvasive

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imaging method that can visualize and quantitatively evaluate vascularity in the retina, ONH, and peripapillary region with motion contrast created by erythrocytes and does not require a contrast agent injection (10). OCTA can evaluate the vascular density and blood flow of the ONH, the peripapillary retina, and macula (11). It has been shown that OCTA parameters such as blood flow index and capillary density of the ONH, the peripapillary retina, and macula are decreased in patients with glaucoma (12,14). Whether the reduction in vascular density is the effect or the cause of glaucoma is not fully known (15). Previous studies have focused more on papillary and peripapillary perfusion, and macular perfusion has received less attention in these studies. Additionally, these studies were conducted on the eyes of different patients at different stages and are subject to individual differences and the effects of the drugs used on vascular density.

This study aimed to evaluate the correlation between structural parameters [retinal nerve fiber layer (RNFL), ganglion cell complex, and rim area] and vascular parameters and to compare the ONH and macular perfusion between the two eyes of individuals with glaucoma at different stages to avoid systemic effects.

## Methods

### Compliance with Ethical Standards

This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Ethics Committee (number: 1648) and conducted between November 2018 and June 2019 in the glaucoma unit of the ophthalmology clinic and was performed in line with the principles of the Declaration of Helsinki. Informed consent for participation in the study was obtained from the patients.

### Study Participants

This was a cross-sectional, prospective observational study that included 54 eyes of 27 POAG patients with glaucoma at different stages in both eyes according to at least two reliable visual field (VF) tests performed in the last month were included in the study. Eyes with glaucoma were evaluated into 2 groups: the early stage and the advanced stage. Patients with glaucomatous optic nerve change, structural damage on optical coherence tomography (OCT), IOP >21 mmHg, and without VF defects were defined as having preperimetric glaucoma. Glaucoma staging was applied according to the Hodapp-Anderson-Parrish classification (16). Patients were excluded from the study if they had any retinal or optic nerve disease other than glaucoma, were taking drugs that affect the macula or optic nerve, had hypertensive retinopathy, diabetes, visual acuity of 0.6, refractive error of >3.0 spherical, >2.5 astigmatism, ocular media opacity, or had undergone any intraocular surgery other than uncomplicated phacoemulsification surgery.

All patients included in the study had visual acuity, refraction, biomicroscopy, fundus examination, gonioscopy, Goldman applanation tonometry, ultrasonic pachymetry, standard automatic perimetry, OCT, and OCTA scans performed on them. VF assessment was performed using the SITA-standard 24-2 VF test (Humphrey Instruments, Model 740, San Leandro, CA). VF tests with a loss of fixation, false positive, and negative response of 20% were considered reliable.

### Optical Coherence Tomography Imaging

For OCT measurements, Cirrus HD-OCT 5000 (Carl Zeiss Meditec, Dublin, CA, USA) was used for OCT imaging. Only shots with a signal strength of 6 or above were evaluated. Macular ganglion cell inner plexiform layer (GCIPL) (Macular 512x128 Cube protocol), RNFL, and ONH analysis (Optic Disc 200x200 Cube protocol) were performed. Mean RNFL, GCIPL thickness, and rim area were evaluated.

### Optical Coherence Tomography Angiography Imaging

OCTA measurements; OCTA was examined with an AngioVue (RTVue-XR, Optovue, Inc.; Fremont; California, USA; software version 2016.2.035) device. Shots with a signal strength of ≥ 6 were evaluated. Optic nerve vascular density measurements were made in the 4.5x4.5 mm area where the ONH was centered, and macular vascularity measurements were made in the fovea-centered area of 6x6 mm. Peripapillary vascular density was measured between the inner surface of the inner limiting membrane (ILM) and the outer surface of the RNFL. Macular superficial vascular density (msVD) was evaluated between the inner surfaces of the ILM and the outer surface of the inner plexiform layer (IPL). The macular deep vascular density (mdVD) was automatically measured between the outer surface of the IPL and the outer surface of the outer plexiform layer. Parafoveal vascular density was calculated through a 1-mm-wide circular ring with an inner diameter of 1 mm and an outer diameter of 3 mm in the fovea-centered area, and perifoveal vascular density was calculated through a 1.5-mm-wide circular ring with an inner diameter of 3 mm and an outer diameter of 6 mm.

The OCTA parameters of the optic nerve and macula in eyes at different stages of glaucoma were compared and correlations with OCT parameters (mean RNFL, mean GCIPL, rim area) were investigated. Optic nerve parameters, which were total vascular density (tVD), peripapillary vascular density (ppVD), intradisc vascular density (idVD), and macular parameters, which were

msVD, parafoveal superficial vascular density (pasVD), perifoveal superficial vascular density (pesVD), mdVD, parafoveal deep vascular density (padVD), and perifoveal deep vascular density (pedVD), were evaluated.

### Statistical Analysis

The data analysis was performed using SPSS statistical software (version 15.0; SPSS Inc., Chicago, Illinois). For categorical variables, descriptive statistics were expressed as a number and a percentage, while numerical variables were expressed as a mean, standard deviation, minimum, and maximum value. Dependent group analyses were performed with the Paired t-test when the differences in numerical variables met the normal distribution condition. Relationships between numerical variables were analyzed using Pearson Correlation analysis when the parametric test condition was met, and with Spearman Correlation analysis when the parametric test condition was not met. The statistical significance level of alpha was set at $p<0.05$.

## Results

The study consisted of 27 patients, 12 females, and 15 males. The age range of the patients is between 42 and 81. There were 18 POAG (33.3%) and 9 pseudoexfoliative (PEX) (66.7%) glaucoma patients. The glaucoma stages were determined as in nine patients, one eye was preperimetric and the fellow eye was at the early-moderate stage, ten patients had one eye at the early stage and the fellow eye at a moderate-advanced stage, and eight patients had one eye at a moderate stage and the fellow eye at an advanced stage. While seventeen of the patients were using beta-blocker and dorzolamide combinations and brinzolamide, ten of them were using prostaglandin analog and beta-blocker combinations. There was no significant difference between the two eyes of the patients in terms of drug use.

The mean deviation (MD) values in earlier and advanced stage eyes with asymmetric stage glaucoma were -4.4±3.6 and -13.2±9.0, respectively, while pattern standard deviation (PSD) values were -3.7±2.9 and 6.9±2.9, respectively (Table 1). We observed that the measurements were significantly lower in the eyes of patients with more advanced stage glaucoma (Table 2).

When the optic nerve perfusion was evaluated between eyes with asymmetric glaucoma, it was observed that the total and peripapillary vascular density were statistically significantly decreased in the more advanced eyes ($p<0.001$) (Table 3).

When msVD was examined; msVD, pasVD, and pesVD were significantly lower in the more advanced stages ($p<0.001$). When mdVD was examined, there was a statistically significant difference between mdVD, padVD, and pedVD in eyes at different stages ($p<0.05$) (Table 3).

The relationship was examined between thinning in structural parameters and changes in vascular parameters among eyes with asymmetric glaucoma. We observed that the structural parameter of GCIPL had the strongest correlation with tVD, ppVD, and pesVD ($r=0.899$, 0.892, and 0.674, respectively, $p<0.001$). RNFL and rim area, which correlated highly with tVD and ppVD, correlated moderately with msVD and pesVD (Table 4).

## Discussion

Recent studies have shown that peripapillary vascular densities measured by OCTA are as sensitive as RNFL in the diagnosis of glaucoma (17-19). Moreover, the relationship between peripapillary tVD, ppVD, and functional loss has been reported to be stronger than the relationship between structural loss and functional loss, and vascular density better reflects ganglion cell function than structural loss (20,21). There are also studies reporting that OCTA detects pre-perimetric glaucoma better than OCT (21-23). It has also been suggested that as the stage of glaucoma progresses, while the benefit of OCT parameters decreases due to the basal effect, the decrease in vascular density can be followed with OCTA. The new and noninvasive technology seems to be promising and useful for the early diagnosis, staging, and follow-up of glaucoma patients (23-26).

In this study, similar to the literature, it was found that as the stage of glaucoma progressed, ONH perfusion decreased. In the same patient's eye with more advanced glaucoma, a significant reduction was observed in both tVD and ppVD values compared to the earlier stage eye. Like these findings, Lommatzsch et al. (27) found significantly lower tVD values in patients with glaucoma compared to the control group. In the same study, ppVD was examined on average and in 6 sectors (superior-nasal, superior-temporal, nasal, inferior-nasal, inferior-temporal, and temporal), and a significant decrease was determined in both the average value and in all sectors.

Yarmohammadi et al. (23) investigated the diagnostic capacities of vascular density (VD) parameters in studies of healthy eyes with suspected glaucoma and glaucoma and stated that tVD has a better diagnostic value compared to ppVD. This was attributed to the fact that the device used a larger measurement area during tVD measurement and was better able to detect changes in axons located eccentrically along the temporal vessels. Chen et al. (28) found a significantly lower rate of idVD in glaucomatous eyes compared to healthy eyes. The same finding was reported in the study by Lommatzsch et al. (27). Hou et al. (29) reported that they found a decrease in peripapillary vessel density in the POAG group, but they did not observe a statistical difference in the inner disc. Although there was a significant difference in idVD values between eyes with

| Table 1. Ocular and systemic findings of the cases | | | |
|---|---|---|---|
| | **Earlier stage** | **Advanced stage** | **P-value** |
| Age, mean ± SD | 64.1±11.1 | 64.1±11.1 | - |
| Gender (male/female) | 15/12 | 15/12 | - |
| Spherical equivalent (D), mean ± SD | -1.25 (-0.5 to -2.25) | -1.5 (-0.75 to -2.25) | 0.391 |
| SAP MD (dB), mean ± SD | -4.4±3.6 | -13.2±9.0 | **<0.001** |
| SAP PSD (dB), mean ± SD | -3.7±2.9 | 6.9±2.9 | **<0.001** |
| Systolic BP (mmHg) | 130 (120 to 140) | 130 (120 to 140) | 1.000 |
| Diastolic BP (mmHg) | 75 (60 to 95) | 75 (60 to 95) | 1.000 |
| Use of topical glaucoma medication, n (%) | 100 | 100 | - |
| IOP (mmHg) | 16 (13 to 18) | 15 (13 to 18) | 0.867 |
| CCT (µm) | 530 (524 to 552) | 534 (520 to 557) | 0.741 |

SAP: Standard automated perimetry, MD: Mean deviation, PSD: Pattern standart deviation, BP: Blood pressure, IOP: Intraocular pressure, CCT: Central corneal thickness, SD: Standart deviation

asymmetric glaucoma in the current study, this difference was not as statistically significant as tVD and ppVD.

In this study, superficial and deep macular perfusion parameters were also evaluated together with optic nerve perfusion. In the comparisons of eyes with asymmetric glaucoma, the msVD, pasVD, and pesVD values were significantly lower in eyes with more advanced glaucoma. Other studies in the literature have reported different results regarding the change in macular vascular density in glaucoma patients. Penteado et al. (30) reported that the VD of the perifoveal area of the macula scan performed better than the parafoveal area of either scan size when differentiating between healthy and mild glaucoma. Khayrallah et al. (31) found that the pasVD and msVD were decreased in glaucoma proportionally to its severity. Unlike this study, Triolo et al. (13) found that there was no statistically significant difference between the groups in the mean or sectorial values of msVD in healthy, suspected glaucoma, and POAG patients and reported that msVD was not useful in the diagnosis of glaucoma (16). In the same study, although there was a statistically significant difference in the superior, inferior, and temporal sector ppVD values between the groups, there was no difference in the mean ppVD. This situation could be explained in two ways. The first is that structural damage occurs first and vascular damage later, and the second theory is that OCTA is not as sensitive as OCT in detecting early changes. Yarmohammadi et al. (25) also reported that msVD did not differ in glaucoma patients with unilateral VF defects, although there was a difference in VF, structural parameters, and ppVD between the two eyes. This was partly attributed to the smaller difference in mean vessel density measurements in the macular region compared to the peripapillary region. In contrast to those studies, Chen et al. (18) reported that the diagnostic performance of msVD was as good as ppVD (17).

| Table 2. Optical coherence tomography parameters in eyes with asymmetric glaucoma | | | |
|---|---|---|---|
| **OCT parameters** | **Earlier stage** | **Advanced stage** | **P-value*** |
| RNFL (µm) | 88.8±14.1 | 68.3±15.0 | **<0.001** |
| GCIPL (µm) | 81.2±9.5 | 66.3±12.3 | <0.001 |
| Rim Area ($mm^2$) | 1.36±0.31 | 0.91±0.33 | **<0.001** |

RNFL: Retinal nerve fiber layer, GCIPL: Ganglion cell inner plexiform layer
*Comparison was performed by using Paired t-test

Of the deep macular vascular density parameters examined in the current study, the mdVD, padVD, and pedVD values were also decreased in more advanced eyes compared to earlier stage eyes. Although this difference was statistically significant, it was not as significant as the superficial vascular density. Similarly, Takusagawa et al. (32) examined the superficial and deep capillary plexus vascularity in the macular area and stated that glaucoma affects the superficial plexuses rather than the deep plexuses. Some studies showed that the glaucoma diagnostic capabilities of superficial parafoveal and perifoveal vascular density were significantly better than those of deep perifoveal and parafoveal vascular density, regardless of the glaucoma stage (33,34).

When the correlations were examined between the thinning in structural parameters and the decrease in ONH and macular vascular density parameters due to glaucoma, there was a strong positive correlation between the decrease in RNFL, rim area, GCIPL thickness, and the decrease in tVD and mean ppVD values. While the correlation between GCIPL and tVD and ppVD was compelling, the correlation of RNFL and rim area with tVD and ppVD was also high. There was no correlation between structural parameters and changes in idVD. A statistically significant correlation was determined between the msVD parameters, such as msVD and pesVD, and the RNFL, GCIPL, and rim area. There was a high correlation of GCIPL with msVD and pesVD, while the

**Table 3. Optic nerve and macular perfusion in eyes with asymmetric glaucoma**

| Optic nerve head and retinal vascular density (%) | Earlier stage | Advanced stage | P-value* |
|---|---|---|---|
| tVD | 46.9±5.1 | 37.8±7.4 | **<0.001** |
| ppVD | 49.2±6.2 | 38.4±9.5 | **<0.001** |
| idVD | 48.7±4.3 | 44.5±7.3 | **0.003** |
| msVD | 47.7±5.2 | 40.4±6.0 | **<0.001** |
| pasVD | 49.7±6.0 | 44.7±6.2 | **<0.001** |
| pesVD | 48.5±5.2 | 40.9±6.3 | **<0.001** |
| mdVD | 50.3±5.3 | 46.8±5.9 | **0.008** |
| padVD | 54.6±3.7 | 52.5±4.8 | **0.021** |
| pedVD | 51.6±6.3 | 48.2±6.2 | **0.009** |

tVD: Total vascular density, ppVD: Peripapillary vascular density, idVD: Intradisc vascular density, msVD: Macular superficial vascular density, pasVD: Parafoveal superficial vascular density, pesVD: Perifoveal superficial vascular density, mdVD: Macular deep vascular density, padVD: Parafoveal deep vascular density, pedVD: Perifoveal deep vascular density
*Comparison was performed by using Paired t-est

**Table 4. The correlation between thinning in structural parameters and decreasing vascular parameters in eyes with asymmetric glaucoma**

| Optic nerve head and retinal vascular density (%) | RNFL | | Rim Area | | GCIPL | |
|---|---|---|---|---|---|---|
| | r | p* | r | p* | r | p* |
| tVD | 0.749 | **<0.001** | 0.773 | **<0.001** | 0.899 | **<0.001** |
| ppVD | 0.741 | **<0.001** | 0.813 | **<0.001** | 0.892 | **<0.001** |
| idVD | -0.255 | 0.199 | -0.202 | 0.313 | -0.165 | 0.420 |
| msVD | 0.480 | **0.011#** | 0.494 | **0.009#** | 0.642 | **<0.001#** |
| pasVD | -0.058 | 0.775 | 0.005 | 0.981 | 0.159 | 0.438 |
| pesVD | 0.487 | **0.010#** | 0.499 | **0.008#** | 0.674 | **<0.001#** |
| mdVD | -0.020 | 0.923 | 0.119 | 0.553 | -0.114 | 0.580 |
| padVD | -0.071 | 0.726 | 0.073 | 0.718 | -0.207 | 0.311 |
| pedVD | 0.066 | 0.742 | 0.092 | 0.650 | -0.101 | 0.624 |

RNFL: Retinal nerve fiber layer, GCIPL: Ganglion cell inner plexiform layer, tVD: Total vascular density, ppVD: Peripapillary vascular density, idVD: İntradisc vascular density, msVD: Macular superficial vascular density, pasVD: Parafoveal superficial vascular density, pesVD: Perifoveal superficial vascular density, mdVD: Macular deep vascular density, padVD: Parafoveal deep vascular density, pedVD: Perifoveal deep vascular density
*Comparison was performed by using Pearson correlation analysis
#Comparison was performed by using Spearman correlation analysis

correlation of RNFL and rim area with msVD and pesVD was moderate. It is not surprising that there is a statistically significant positive relationship between GCIPL and msVD and pesVD, due to the feeding of the macular GCIPL from the superior capillary plexus (12) and the concentration of RGC in the perifoveal region. Interestingly, the correlation of GCIPL with tVD and ppVD was seen to be stronger than its correlation with msVD and pesVD. There are conflicting findings in the literature about the relationship between OCTA and structural parameters. Most studies have shown a high correlation between tVD and ppVD with structural parameters (26-28,35-37). Mansoori et al. (38) reported that sector-based ppVD reduction correlated with RNFL thinning in the same sector, but mean ppVD did not correlate with mean RNFL and rim area. However, that study included patients with early glaucoma, and compared with the control group, ppVD differed only in the superotemporal and inferotemporal sectors. While Triolo et al. (13) found a strong correlation between mean RNFL and ppVD values in glaucoma patients, no correlation was determined for either GCIPL or RNFL with msVD (16). Richter et al. (39) also reported that peripapillary vascular density has slightly better diagnostic performance than macular superficial density and that msVD correlates with functional parameters rather than structural parameters.

These results, both in the current study and in similar studies in the literature, point to a significant relationship between vascular and structural parameters and support the vascular theory of the pathogenesis of glaucoma. GCIPL thickness has a more significant relationship with peripapillary perfusion than macular perfusion, suggesting

that the ONH circulation is responsible for apoptosis and subsequent axonal degeneration in ganglion cells rather than macular perfusion. Further research is needed on this subject.

### Study Limitations

This study had some limitations, primarily the small sample size, and although the patients had glaucoma with asymmetric involvement, the glaucoma stages were different in each patient. Using average values instead of sectoral values in the vascular density measurements could be interpreted as another deficiency of the study. Another limitation was that the axial lengths of the patients were not taken as a study parameter. Although the axial length differences may affect the structural and vascular parameters (40), it was attempted to minimize this situation with the refraction range values found in the inclusion criteria. Despite these limitations, the strongest aspect of the study was that the systemic factors were eliminated due to the fact that both eyes of the same patients were included in the study.

### Conclusion

Our study showed that both ONH and macular perfusion decrease as glaucoma progresses, independent of systemic factors. In the relationship between structural and vascular parameters, local perfusion reduction in the optic nerve head is significantly correlated with thinning of the RNFL thickness, while the high correlation between ganglion cell thickness and ONH perfusion suggests that axonal degeneration has an important place in ganglion cell deaths in addition to local perfusion. Both the ONH and the macular superficial VD decrease in glaucoma. However, ischemia in the peripapillary region shows a stronger correlation with structural parameters.

### Ethics

**Ethics Committee Approval:** This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Ethics Committee (number: 1648).

**Informed Consent:** Informed consent for participation in the study was obtained from the patients.

### Authorship Contributions

Concept: T.O., Design: N.S., Data Collection and/or Processing: F.O., Analysis and/or Interpretation: B.K., Literature Research: T.O., Writing: T.O.

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Original Article

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# Evaluation of the ATRIA and CHA2DS2-VASc Scores and Their Performance on Predicting Mortality in Patients with Acute Pulmonary Embolism

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## Abstract

**Aim:** Pulmonary embolism (PE) is a condition caused by thrombosis and is a common cause of death. Although there are studies of PE with CHA2DS2-VASc (C: congestive heart failure or left ventricular systolic dysfunction, H: hypertension, A: age of ≥75 years, D: diabetes mellitus, S: previous stroke, V: vascular disease, A: age between 65 and 74 years, Sc: female gender) and PE severity index (PESI) scores, there is no data on Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score in PE or comparison of CHA2DS2-VASc and ATRIA scores in PE. We investigated whether ATRIA and CHA2DS2-VASc scores can predict PE and mortality in cases of PE.

**Methods:** One hundred ninety-eight patients with PE and two hundred eighty controls between July 2017 and July 2021 were included in this retrospective study. Patients' data was provided from the hospital's digital system. Patients' PESI, ATRIA, and CHA2DS2-VASc scores were calculated, and in-hospital mortality was determined as the primary end-point.

**Results:** The mean age of the patients was 63.9±13.1 years. The frequency of male patients in the PE group was higher (p=0.04), but this difference was invalid in patients with PE who developed primary end-point (p=0.177). ATRIA and CHA2DS2-VASc scores were higher in the PE group (p<0.01 and p=0.02, respectively) and in patients who reached end-point (p=0.001 and p=0.004, respectively). A moderate-high correlation was found between the PESI score and the ATRIA and CHA2DS2-VASc scores (r=0.664, p<0.001, and r=0.484, p<0.001) in the PE group. Pairwise comparison of ROC curve analysis revealed that PESI, ATRIA, and CHA2DS2-VASc scores were not superior to each other in predicting mortality.

**Conclusion:** Both ATRIA and CHA2DS2-VASc scores are simple, easily calculated risk scores as an alternative to the PESI score in predicting mortality in PE.

**Keywords:** Hospital mortality, pulmonary embolism, risk factors

## Introduction

Pulmonary embolism (PE) is an emergency clinical status with a mortality rate of 25-30% if untreated (1). Even in those who are treated, 8-10% death and 5-20% recurrence are observed (2). Although sudden onset of dyspnea is the most common symptom, patients may also present with atypical chest pain or presyncope/syncope (3,4). Massive emboli, which may be accompanied by findings such as hypotension, shock, cardiac arrest, or right ventricular failure, constitute less than 5% of all PE (5). Many scoring systems have been developed that can predict the presence of PE, prognosis, and mortality, if any (6-8). Wells clinical scoring and Modified Geneve scoring are generally used to evaluate the probability of PE, while the PE severity index (PESI) score, which consists of 11 clinical criteria, is designed to be used to estimate the 30-day end-points (9-12).

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The most important factor in the pathogenesis of PE is thrombosis, which occurs in the deep veins at a rate of 90%, that is, the mechanism is the increase in thrombogenicity (13). Considering this information, it can be thought that the CHA2DS2-VASc (C: congestive heart failure or left ventricular systolic dysfunction, H: hypertension, A: age of ≥75 years, D: diabetes mellitus, S: previous stroke, V: vascular disease, A: age between 65 and 74 years, Sc: female gender) and anticoagulation and risk factors in atrial fibrillation (ATRIA) risk scores, which were mainly developed to predict the risk of stroke in atrial fibrillation patients, are associated with the presence and prognosis of PE. Although there are studies of PE with CHA2DS2-VASc and PESI scores, there is no data on ATRIA score in PE or comparison of CHA2DS2-VASc and ATRIA scores in PE.

This study aimed to investigate the relationship between CHA2DS2-VASc and ATRIA scores and PE risk and end-point in patients with PE and compare these two scores and PESI score in mortality.

## Methods

### Ethical Standards and Study Design

The study protocol was approved by the Adana City Training and Research Hospital Clinical Research Ethics Committee with the date 14.7.2021 and number 1492 and complies with the research ethics in the Helsinki statement. Participants were included in the study after their consent was obtained.

One hundred and ninety-eight patients with PE diagnosed with computed tomography (CT) angiography were analyzed retrospectively in this study as the study group, and 280 patients who had definitively excluded PE by CT angiography as the control group. Patients' medical history, laboratory data, and the baseline characteristic properties were recorded from the hospital digital system and national health information portfolio. Systolic heart failure (HF) was defined as a left ventricular ejection fraction <40%. Hypertension (HT) was deemed 140/90 mmHg or higher (or 150/90 mmHg or higher if you're over the age of 80). A fasting blood glucose value above 126 mg/dL on at least 2 tests was defined as diabetes mellitus (DM). A stroke is defined as a neurological deficit caused by an acute focal injury to the central nervous system caused by a vascular cause. Patients with a diagnosis of coronavirus 19, a history of PE or deep vein thrombosis, hematological disease, chronic liver disease, autoimmune and/or rheumatological disease, and missing laboratory results in their files were excluded from the study. In-hospital mortality was determined as the primary end-point.

### Laboratory Analysis

From venous blood samples, D-dimer and C-reactive protein (CRP) levels of all patients, troponin values, and complete blood counts were analyzed.

### Calculation of PESI, ATRIA, and CHA2DS2-VASc Scores

The PESI score has been validated to assess the probability of 30 and 90 day mortality post PE and is calculated by using mdcalc.com/pesi-pulmonary-embolism-severity-index (14).

The ATRIA risk score was calculated by adding 1 point for each of the following factors: female sex, DM, congestive HF, HT, proteinuria, and renal dysfunction (i.e., estimated glomerular filtration rate<45 mL/min/1.73 $m^2$ or end-stage renal disease) and by adding 0-9 points depending on the specific score weighting of patients' age according to the presence or absence of prior ischemic stroke (15). The CHA2DS2-VASc score was calculated by adding 1 point each for congestive HF, HT, DM, vascular disease, age 65 to 75 years, or female sex, and 2 points each for age ≥75 years or past stroke/transient ischemic attack (16).

### Statistical Analysis

All statistical analyses were performed using SPSS 17 (SPSS, Inc., Chicago, Illinois, USA). The Kolmogorow-Smirnov test was used to determine whether continuous variables have a normal distribution or not. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as numbers and percentages. The Student's t-test and Mann-Whitney U test were used to analyze the continuous variables between groups, and categorical variables were compared using the $\chi^2$ test or Fisher's Exact test. Correlations between variables were analyzed using the Pearson correlation test and Spearmen test, if appropriate. Pairwise comparison of receiver operating characteristics (ROC) curve analysis was used to determine the sensitivity and specificity of the ATRIA and CHA2DS2-VASc scores in showing PE and mortality. The results were stated as relative risk and a 95% confidence interval. A $p<0.05$ was considered significant.

## Results

This study consisted of 478 consecutive patients with a mean age of 63.9±13.1 years, 57.5% of whom were males. One hundred and ninety-eight of them had PE (8 patients had massive PE, 26 patients submassive PE, and 164 patients non-massive PE) detected in CT angiography and included in the PE group, and the remaining 280 patients were included in the non-PE group. The baseline characteristics and laboratory results of the groups are summarized in Table 1. The number of males in the PE group was higher than the ones in non-PE, and it was

statistically significant (p=0.04). The PE and non-PE groups were similar in terms of DM, HT, HF, and coronary artery disease (p>0.05, all). D-dimer, CRP, brain natriuretic peptide (BNP), WBC, neutrophil, lymphocyte, and troponin levels were higher in the PE group. Twenty-one patients (10.6%) reached the primary end-point in the PE group. Although the frequency of HF was higher in the mortality subgroup, it did not reach the level of significance (14.2% and 3.3%, p=0.057). Other demographic properties were similar between the mortality and non-mortality subgroups. The demographic characteristics and laboratory results of the mortality and non-mortality subgroups are summarized in Table 2.

Mean PESI, ATRIA and CHA2DS2-VASc scores were all different between PE and non-PE group (p<0.001 for PESI and ATRIA scores and p=0.02 for CHA2DS2-VASc score). In the PE group, the mortality-subgroup had the highest values of PESI, ATRIA and CHA2DS2-VASc scores with means of 129.5±40.2, 5.2±2.1 and 3.0±1.2, respectively.

In correlation analysis, a moderate-high correlation was found between the PESI score and the ATRIA and CHA2DS2-VASc scores (r=0.664, p<0.001, and r=0.484, p<0.001) in the PE group (Figure 1).

ROC curve analysis showed that ATRIA score with a cut-off value >3 had sensitivity of 48.99%, specificity of 70.40% and AUC=0.596, p<0.001 and CHA2DS2-VASc score with a cut off value >1 had sensitivity of 70.71%, specificity of 41.60% and AUC=0.568, p=0.01 predicted the PE and furthermore, pairwise comparison of ROC curve analysis revealed that ATRIA score was non-inferior to CHA2DS2-VASc score with a difference between AUC 0.0285, z statistics 1.757 and p=0.078 in predicting PE (Figure 2).

ATRIA score with a cut-off value greater than 4 had a sensitivity of 66.67%, specificity of 66.67% and AUC=0.716, p<0.001 and CHA2DS2-VASc score with a cut off value >2, sensitivity of 71.43%, specificity of 61.02% and AUC=0.685, p<0.001 and PESI score with a cut off value >108, sensitivity of 76.2%, specificity 59.7% and AUC=0.706, p=0.002 predicted mortality in the PE group. We found that ATRIA, CHA2DS2-VASc and PESI scores were all similar in predicting mortality in the PE group in pairwise comparison of ROC curve analysis (Table 3, Figure 3).

## Discussion

We evaluated the association of the ATRIA and CHA2DS2-VASc scores with PE and mortality in PE. The most important results of this study were: 1) ATRIA and CHA2DS2-VASc scores were higher in the PE group compared to the non-PE group, 2) there was a moderate-high correlation between ATRIA and CHA2DS2-VASc scores and the PESI score in the PE group; 3) the highest values of ATRIA and CHA2DS2-VASc scores were in the mortality sub-group in the PE group; and 4) ATRIA, CHA2DS2-VASc and PESI scores were non-inferior to each other in predicting mortality in the PE. These results were the first in the literature to present an association of ATRIA and CHA2DS2-VASc scores with PE and PESI scores.

PE is a common condition with a high mortality rate. The mortality rate is up to 60% in massive PE accompanied

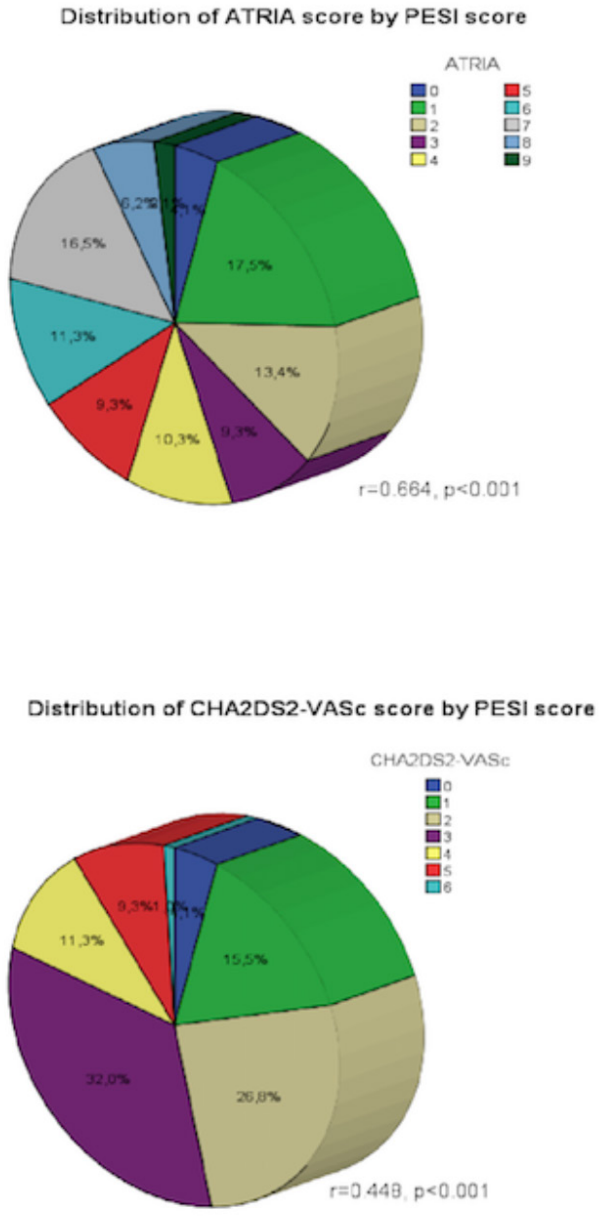


**Figure 1.** Distribution of ATRIA and CHA2DS2-VASc scores by PESI score

PESI: Pulmonary embolism severity index, ATRIA: Anticoagulation and risk factors in atrial fibrillation

by hemodynamic impairment (17-19). Even in non-massive PE without right ventricular dysfunction and hypotension, 10% of patients may die (20). In this study, death was observed in 5 (62.5%) of 8 patients with massive PE and 10 (6%) of those with non-massive PE. To date, many clinical entities, laboratory parameters, and scoring systems that determine the presence and prognosis of PE have been introduced or developed. The presence of hypotension and shock, the detection of right ventricular dysfunction in echocardiography, and elevated levels of biomarkers such as troponin, pro-BNP, and D-dimer all indicate poor prognosis (21-25). Many studies have shown that inflammation is the main mechanism in the pathogenesis of PE, and inflammatory markers such as higher neutrophil and platelet counts, higher NLR and PLR ratios, and lower levels of lymphocytes have diagnostic importance in PE (26,27). We also obtained results that support these data in our study.

The most commonly used scoring systems for the diagnosis and prognosis of PE are the Wells, revised Geneva, and PESI scores. Angriman et al. (28) reported that a high Wells score determines death and prognosis in PE. Choi et al. (29) revealed that the PESI score predicts mortality, and Guo et al. (30) determined that the Wells score is more diagnostic than the revised Geneva score in elderly patients, and the combination of these scores with D-dimer is safe to exclude PE (29). In contrast to these studies, Li et al. (31) found that cancer-specific PE/VTE scores outperformed the traditional PESI score in identifying low-risk patients with cancer. Furthermore, it was shown in the study by Girardi et al. (32) that Wells and Geneva scores could not predict PE in critically ill patients. These studies reveal the necessity of developing new scoring systems or adapting existing ones in addition to classical scores.

Risk factors for venous thromboembolism, the most common cause of PE, are also components of the CHA2DS2-VASc score. In a study on this subject, Gök et al. (33) revealed that the CHA2DS2-VASc score can predict right ventricular dysfunction in patients with PE. Onuk et al. (34) also stated that the mortality rate increased 16.8 times in patients with PE who had a CHA2DS2-VASc score above 4. The CHA2DS2-VAS score with cut-off value 2, with 71% sensitivity and 61% specificity, predicted mortality in this study. Like the CHA2DS2-VASc score, the ATRIA score is another scoring system that can be used to determine risk and prognosis for all diseases with thrombosis in their pathogenesis, especially cardiovascular diseases. Although the ATRIA score was

**Table 1. Clinical and laboratory data of the study population**

| | PE group (n=198) | Non-PE group (n=280) | p-value |
|---|---|---|---|
| Age, years | 64.4±16.8 | 63.6±9.7 | 0.142 |
| Male, n (%) | 103 (52) | 172 (61.4) | 0.040* |
| Hypertension, n (%) | 85 (42.9) | 87 (31) | 0.079 |
| Diabetes mellitus, n (%) | 38 (19.1) | 64 (22.8) | 0.108 |
| Coronary artery disease, n (%) | 47 (23.7) | 83 (29.6) | 0.116 |
| Heart failure, n (%) | 9 (4.5) | 20 (7.1) | 0.234 |
| Stroke, n (%) | 2 (1) | 8 (2.8) | 0.146 |
| Malignancy, n (%) | 20 (10.1) | 8 (2.8) | 0.001* |
| History of operation, n (%) | 22 (11.1) | 10 (3.59) | 0.001* |
| Deep vein thrombosis, n (%) | 84 (42.4) | 33 (11.7) | <0.001* |
| HG, g/dL | 13.1±2.0 | 13.6±2.1 | 0.245 |
| WBC, $10^3$/µL | 10.9±4.8 | 5.2±3.2 | <0.001* |
| PLT, $10^3$/µL | 235.3±107.7 | 248.0±74.7 | 0.007* |
| Neutrophil, $10^3$/µL | 8.4±4.3 | 5.9±2.4 | <0.001* |
| Lymphocyte, $10^3$/µL | 1.7±1.2 | 2.2±1.4 | 0.006* |
| D-dimer, µg/L | 12187.0±1947.5 | 469.9±239.4 | <0.001* |
| CRP, mg/L | 80.3±7.1 | 5.9±2.4 | <0.001* |
| Troponin, ng/L | 326.6±113.2 | 24.8±15.1 | 0.001* |
| BNP, µg/L | 948.6±120.1 | 85.3±28.5 | <0.001* |
| ATRIA score | 3.5±2.5 | 2.7±2.3 | <0.001* |
| CHA2DS-VASc score | 2.2±1.3 | 1.9±1.4 | 0.020* |

PE: Pulmonary embolism, ATRIA: Anticoagulation and risk factors in atrial fibrillation, BNP: Brain natriuretic peptide, CHA2DS2-VASc: C: Congestive heart failure or left ventricular systolic dysfunction, H: Hypertension, A: Age of ≥75 years, D: Diabetes mellitus, S: Previous stroke, V: Vascular disease, A: Age between 65 and 74 years, Sc: Female gender, HG: Hemoglobin, PLT: Platelets, WBC: White blood cell count

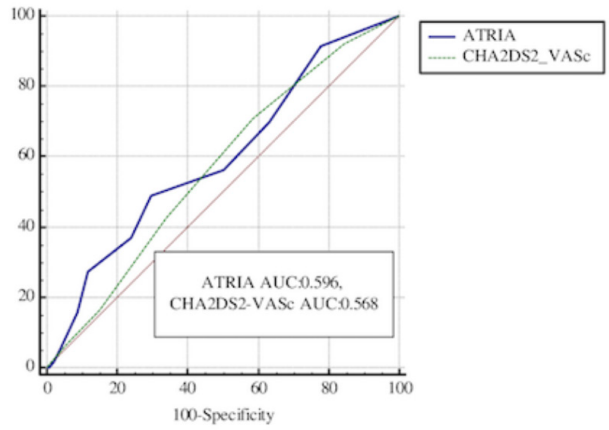


**Figure 2.** ROC curve analysis of ATRIA and CHA2DS2-VASc scores for predicting PE
ROC: Receiver operating characteristics, ATRIA: Anticoagulation and risk factors in atrial fibrillation, PE: Pulmonary embolism

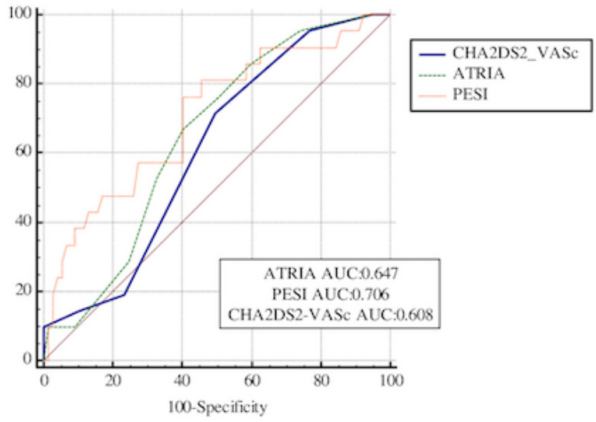


**Figure 3.** ROC curve analysis of PESI, ATRIA and CHA2DS2-VASc scores for predicting mortality in PE
ROC: Receiver operating characteristics, PE: Pulmonary embolism, PESI: Pulmonary embolism severity index, ATRIA: Anticoagulation and risk factors in atrial fibrillation

**Table 2. Clinical and laboratory data of the PE group**

| | Mortality group (n=21) | Non-mortality group (n=177) | p-value |
|---|---|---|---|
| Age, years | 73.7±12.1 | 63.3±16.9 | 0.007* |
| Male, n (%) | 8 (38) | 95 (54) | 0.177 |
| PE type, massive, n (%)<br>Submassive, n (%)<br>Non-massive, n (%) | 5 (24)<br>6 (28)<br>10 (47) | 3 (2)<br>20 (11)<br>154 (87) | <0.001* |
| Hypertension, n (%) | 6 (28) | 79 (45) | 0.160 |
| Diabetes mellitus, n (%) | 4 (19) | 34 (19) | 0.986 |
| Coronary artery disease, n (%) | 5 (24) | 42 (24) | 0.993 |
| Heart failure, n (%) | 3 (14) | 6 (3) | 0.057 |
| Stroke, n (%) | 1 (5) | 1 (1) | 0.201 |
| Malignancy, n (%) | 20 (95) | 0 (0) | <0.001* |
| History of operation, n (%) | 21 (100) | 1 (1) | <0.001* |
| Deep vein thrombosis, n (%) | 21 (100) | 63 (36) | <0.001* |
| HG, g/dL | 11.2±2.8 | 11.6±1.9 | 0.405 |
| WBC, $10^3$/µL | 11.4±4.0 | 10.8±4.9 | 0.580 |
| PLT, $10^3$/µL | 263.9±138.6 | 231.9±103.3 | 0.199 |
| Neutrophil, $10^3$/µL | 9.5±4.2 | 8.3±4.3 | 0.217 |
| Lymphocyte, $10^3$/µL | 1.2±0.6 | 1.8±2.3 | 0.282 |
| D-dimer, µg/L | 12254.0±2014.5 | 11702.0±1443.8 | 0.927 |
| CRP, mg/L | 81.7±72.4 | 68.9±62.0 | 0.441 |
| Troponin, ng/L | 493.6±191.4 | 303.2±98.4 | 0.483 |
| BNP, µg/L | 1045.1±1374.3 | 940.3±1194.4 | 0.826 |
| ATRIA score | 5.2±2.1 | 3.3±2.4 | 0.001* |
| CHA2DS-VASc score | 3.0±1.2 | 2.1±1.3 | 0.004* |
| PESI score | 125.5±36.7 | 93.3±29.7 | <0.001* |

ATRIA: Anticoagulation and risk factors in atrial fibrillation, BNP: Brain natriuretic peptide, CHA2DS2-VASc: C: Congestive heart failure or left ventricular systolic dysfunction, H: Hypertension, A: Age of ≥75 years, D: Diabetes mellitus, S: Previous stroke, V: Vascular disease, A: Age between 65 and 74 years, Sc: Female gender, HG: Hemoglobin, PESI: Pulmonary embolism severity index, PLT: Platelets, WBC: White blood cell count

**Table 3. Pairwise comparison of receiver operating characteristics (ROC) curves of ATRIA, CHA2DS2-VASc and PESI scores for mortality in patients with PE**

| | Difference between AUC | SE | 95% CI | Z statistics | p-value |
|---|---|---|---|---|---|
| ATRIA-PESI | 0.0588 | 0.0561 | -0.0513-0.169 | 1.046 | 0.295 |
| ATRIA-CHA2DS2-VASc | 0.0393 | 0.0479 | -0.0547-0.133 | 0.819 | 0.412 |
| PESI-CHA2DS2-VASc | 0.0980 | 0.0561 | -0.0583-0.254 | 1.229 | 0.219 |

ATRIA: Anticoagulation and risk factors in atrial fibrillation, AUC: Area under curve, CHA2DS2-VASc: C: Congestive heart failure or left ventricular systolic dysfunction, H: Hypertension, A: Age of ≥75 years, D: Diabetes mellitus, S: Previous stroke, V: Vascular disease, A: Age between 65 and 74 years, Sc: Female gender, CI: Confidence interval, PESI: Pulmonary embolism severity index, SE: Standard error

emphasized in many studies evaluating the prognosis in myocardial infarction, no-reflow in STEMI, and end-points in HF, no study investigating the relationship between PE and the ATRIA score has yet been conducted (35-38). Our study is important in that it shows the ATRIA score is higher in patients with PE and can predict mortality. It was found in this study that both ATRIA and CHA2DS2-VASc scores were correlated with the PESI score, and all three scores in the ROC curve analysis had similar results in predicting mortality.

### Study Limitations

The most important limitations of our study are that it was single-centered and the number of participants was low. Second, it was retrospective. Furthermore, we had no data about proteinuria. Since those with a known history of embolism were excluded, it is impossible to provide information on whether the scores used are predictive of PE recurrence or recurrence risk or prognosis. There is a need for multicenter, prospective studies with many participants in this regard. Despite these limitations, our study will contribute to the literature as it is the first study to evaluate the ATRIA score in PE and to compare the CHA2DS2-VASc and ATRIA scores with the PESI score in determining the risk of mortality.

## Conclusion

The easily calculated and more widely used ATRIA and CHA2DS2-VASc scores can be used as an alternative to the PESI score in evaluating the diagnosis of PE and predicting mortality in PE compared to a scoring system such as the PESI score, which is complex and requires many parameters.

### Ethics

**Ethics Committee Approval:** The study protocol was approved by the Adana City Training and Research Hospital Clinical Research Ethics Committee with the date 14.7.2021 and number 1492.

**Informed Consent:** Participants were included in the study after their consent was obtained.

### Authorship Contributions

Concept: O.O.A., A.Y., Design: O.O.A., M.K., S.A., Data Collection and/or Processing: O.O.A., S.A., Analysis and/or Interpretation: O.O.A., A.Y., M.K., F.D., Literature Research: O.O.A., S.A., N.Y.K., F.D., M.D., Writing: O.O.A., S.A., A.Y.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Original Article

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# The Predictive Ability of the C-reactive Protein to Albumin Ratio As A Mortality Predictor in Hospitalized Severe SARS-CoV-2 Infected Patients with Cardiovascular Diseases

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## Abstract

**Aim:** Although there are few studies on the predictive value of C-reactive protein-to-albumin ratio (CAR) in coronavirus disease-2019 (COVID-19) patients, to the best of our knowledge, there are no studies specifically conducted in COVID-19 patients with cardiovascular disease (CVD). This study assessed the use of baseline CAR levels to predict death in hospitalized COVID-19 patients with CVD.

**Methods:** This study was designed as a single-center cross-sectional study. Patients diagnosed with COVID-19 who were admitted to the University of Health Sciences Turkey, Bagcilar Training and Research Hospital between April 16 and May 20, 2020 were analyzed retrospectively. The patients were divided into 2 groups: those who died and those who survived, considering the follow-up period. The CAR values of the study population, as well as patients with CVD, were calculated, and the association of CAR with in-hospital mortality was evaluated.

**Results:** The in-hospital mortality rate was 11.1% (49/442 pts) in all populations. Deceased patients had significantly more frequent CVD ($p < 0.001$) and the mortality rate was 34.4% (30/96 pts) in those patients. Median CAR values were higher in nonsurvivors than among survivors ($p<0.001$). Multivariate analysis demonstrated that CAR was an independent predictor of mortality in patients with CVD [hazard ratio 1.013 (95% confidence interval: 1.002-1.022), $p=0.018$].

**Conclusion:** CAR is an inflammatory risk marker that independently predicts mortality in all COVID-19 hospitalized patients and patients with CVD.

**Keywords:** C-reactive protein, albumin, cardiovascular disease, SARS-CoV-2, COVID-19

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## Introduction

A series of pneumonia cases caused by a novel coronavirus were first identified in China in late 2019 (1). The outbreak of this virus, labeled as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and capable of causing coronavirus disease-2019 (COVID-19), was eventually awarded pandemic status by the World Health Organization in March 2020 (2). In just the short time since, many inflammatory markers such as interleukin-6, cardiac troponin, serum amyloid A, lactate dehydrogenase, D-dimer, ferritin, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio have been studied in an attempt to understand COVID-19, and researchers have discovered some to be related to COVID-19 severity (1). Identifying the risk factors for COVID-19-related mortality is critical because it allows for earlier interventions to prevent deaths during the pandemic (3,4). C-reactive protein (CRP) is a well-known positive acute-phase reactant, whereas albumin is a negative acute-phase reactant (5). Both are valuable markers, associated with systemic inflammation and poor outcome in critically ill patients (5-7). CRP-to-albumin ratio (CAR) is a novel inflammatory indicator, assumed to be more reliable than CRP or albumin alone in determining a patient's inflammatory status and predicting morbidity and mortality (5,8). Accumulating evidence supports the significance of CAR in determining prognosis in various clinical situations such as sepsis, diabetes, coronary artery disease, cancer, and vasculitis (5,8-12).

C- reactive protein is positive and albumin negative is affected in COVID-19 patients. It is prognostic for more severe disease and higher mortality if the CAR rate is elevated in COVID-19 patients (13). Many recent studies have suggested that cardiovascular disease (CVD) in particular is a risk factor for experiencing a more severe COVID-19 disease course. The China Disease Control and Prevention Center reported a mortality rate of 10.5% among those with comorbid CVD disease compared with the overall case fatality rate of 2.4% (14).

Although there are few studies on the predictive value of CAR in COVID-19 patients, to the best of our knowledge, there are no studies specifically conducted in COVID-19 patients with CVD disease. Hence, in this study, we determined the predictive role of baseline CAR values in the determination of death in hospitalized COVID-19 patients, especially patients with CVD.

## Materials and Methods

### Compliance with Ethical Standards

A written informed consent form was signed by each patient or by a first-degree relative of those patients who died. This study was conducted in accordance with the Declaration of Helsinki. The local institutional ethics committee of University of Health Sciences Turkey, Bagcilar Training and Research Hospital approved the study (protocol no. 2020.09.1.04.121).

### Study Design

This study was designed as a single-center cross-sectional study. COVID-19 patients who were hospitalized between April 16 and May 20, 2020 and who were recorded as having either died in the hospital or survived hospital discharge as of June 1, 2020, were consecutively included. Patients under the age of 18 years old, pregnant, who died at admission, were transferred to another hospital, or who lacked baseline data were excluded. Finally, 442 of 475 admitted patients were included in the study cohort. A flow diagram of the study enrollment process is shown in Figure 1.

Patients were divided into two groups: group 1, those who lost their lives in the hospital, and group 2, those who were discharged after recovery. Clinical, demographic, comorbidity, and laboratory data of the study population were obtained by accessing the patient files and the electronic information system of the hospital. A positive laboratory finding for SARS-CoV-2 infection was defined as a positive result on high-throughput sequencing or a real-time reverse-transcriptase polymerase chain reaction assay of nasal or pharyngeal swab specimens. Acute respiratory distress syndrome was defined using the Berlin criteria (15). CVD was defined as any cardiovascular pathology, including coronary heart disease, cerebrovascular disease (stroke), peripheral vascular disease, heart failure, rheumatic heart disease, congenital heart disease, and cardiomyopathies (16).

### Laboratory Assessment

Laboratory data collected within the first 24 hours of hospitalization were considered. Fluorescence flow cytometry was used to analyze complete blood count data using the Sysymex XN-2000 hematology analyzer (Sysmex Corporation, Kobe, Japan). CRP, albumin, and uric acid data were analyzed by photometry using the AU 5800 chemistry analyser (Beckman Coulter, Brea, CA, USA). High-sensitivity troponin I (hs-TnI) and ferritin levels were analyzed by a chemiluminescent assay using a UniCel DxI 800 immunoassay analyzer (Beckman Coulter). D-dimer levels were recorded by photometry using the Succeeded SF-8200 fully automated coagulation analyzer (Beijing Succeeder Technology Inc., Beijing, China). A COVID-19 diagnosis was established by real-time polymerase chain reaction (Bio-Speedy COVID-19 RT-qPCR kit; Bioeksen R&D Technologies Ltd., Istanbul, Turkey) of viral nucleic acids from throat swab samples. All patients underwent simultaneous testing for CRP and albumin levels. CAR

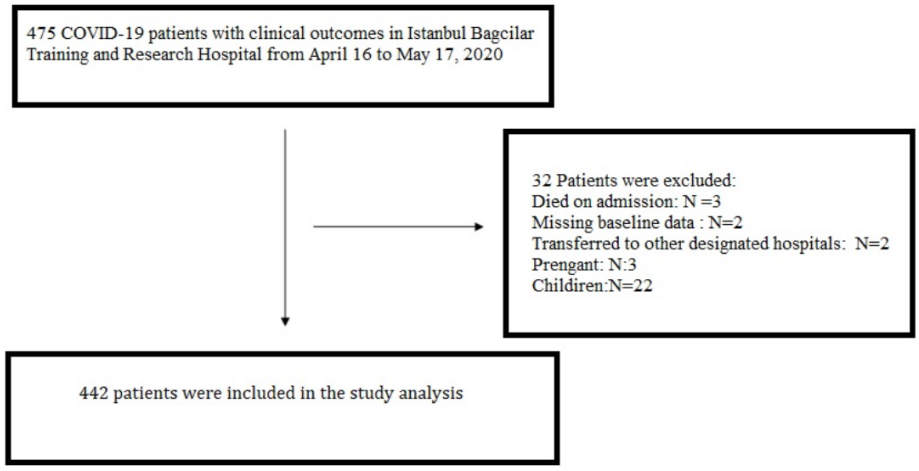



**Figure 1.** Study population chart
COVID-19: Coronavirus disease-2019

values were calculated by dividing the CRP level by the serum albumin level. Estimated glomerular filtration rates were measured using the Modification of Diet in Renal Disease study equation.

### Statistical Analysis

Categorical variables are given as frequencies and percentages. Dichotomous variables were examined using chi-square tests or Fisher's exact tests as appropriate for categorical data, and continuous variables were examined with the Student's t-test or Mann-Whitney U test. The normality of distribution was assessed by the Kolmogorov-Smirnov test. To identify the independent risk factors for in-hospital mortality, univariate and multivariable Cox regression analyses were performed. Only variables with p-values of less than 0.05 in the univariate analysis were included in the multivariate Cox regression analysis. Results of the Cox regression analysis were reported with hazard ratios (HRs) and 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curve analysis was performed to determine the discriminatory performance of parameters found to be independent predictors of mortality. Discriminatory power was classified as 'good' if the area under curve (AUC) was 0.70 or greater and as "inadequate" if the AUC was less than 0.70 (17). To compare the discriminatory performance of the parameters, a pairwise comparison of ROC curves using DeLong et al. (18) was performed. Survival evaluations were conducted by Kaplan-Meier and long-rank tests. Statistical significance was defined as $p<0.05$. All statistical analyses were conducted using IBM Corporation's Statistical Package for the Social Sciences version 24.0 software (IBM Corporation, Armonk, NY, USA). Moreover, the ROC curves of the models were compared using the MEDCALC software (Software bvba 13, Ostend, Belgium).

## Results

A total of 442 of 475 admitted patients (n=247 men) were enrolled in this study. Forty-nine patients died in the hospital (n=29). Detailed demographic, clinical, and laboratory parameters of all study participants, as compared the survivors and non-survivors, are given in Table 1.

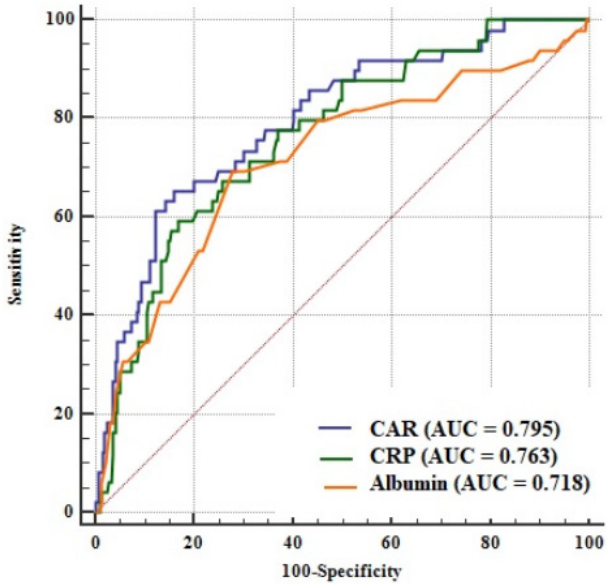
i) Parameters associated with the in-hospital mortality in all study population

In all multivariable analysis models, age, the presence of CVD, a lower estimated glomerular filtration rate, and a higher uric acid level independently predicted mortality (Tables 2 and 3). In the model 1 analysis, CRP was found to be an independent predictor of mortality. Additionally, model 2 cox regression analyses revealed that CAR was an independent predictor of mortality (HR: 1.017, 95% CI: 1.008-1.026; $p<0.003$).

While the discriminatory power of CRP and albumin is similar ($p=0.191$), CAR was statistically superior to both, with P-values of 0.018 and 0.017, respectively. The CAR cut-off value was also determined to be >2.2 with 74% sensitivity and 70% specificity (Figure 2). Kaplan-Meier survival curve analysis revealed that low CAR scores (≤2.2) are associated with a greater chance for survival ($p<0.001$) (Figure 3).

ii) Parameters associated with the in-hospital mortality in patients with CVD

CVD was present in 21.7% of the study population, and nonsurviving patients had more frequent CVD than those who survived (61.2% vs. 16.8%, $p<0.001$). Moreover, patients with CVD had approximately a 3-fold greater mortality compared to the study population (34.4% vs. 11.1%). Compared to survivors those, deceased




| | DBA | 95 % CI | Z-statistic | *p*-Value |
|---|---|---|---|---|
| **CAR vs. CRP** | 0.031 | 0.005 – 0.057 | 2.367 | 0.018 |
| **CAR vs. albumin** | 0.077 | 0.014 – 0.140 | 2.393 | 0.017 |
| **CRP vs. albumin** | 0.046 | -0.023 – 0.114 | 1.308 | 0.191 |

**Figure 2.** Comparison of the ROC curves of the CAR (AUC: 0.795, CI 95% 0.754-0.831, p<0.001), CRP (AUC: 0.763, CI 95% 0.721-0.802, p<0.001), and albumin (AUC: 0.718, CI 95% 0.673-0.759, p<0.001) for detecting the in-hospital mortality

ROC: Receiver operating characteristic, CAR: C-reactive protein-to-albumin ratio, AUC: Area under curve, CI: Confidence interval, CRP: C-reactive protein

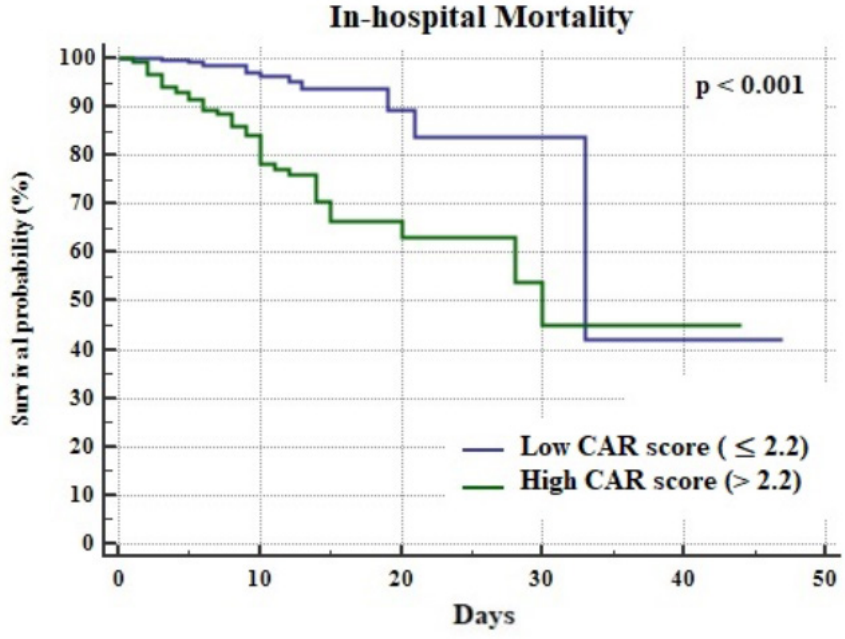



**Figure 3.** Kaplan-Meier plots of survival curves of patients with low (blue line) and high CAR (green line)

CAR: C-reactive protein-to-albumin ratio

**Table 1. Demographic, admission clinical and laboratory parameters of the study cohort**

| Variables | All population (n=442) | Survivors (n=393) | Non-survivors (n=49) | P |
|---|---|---|---|---|
| Male gender, n (%) | 247 (55.9) | 218 (55.6) | 29 (59.2) | 0.622 |
| Age, year, median (max-min) | 58 (18-99) | 56 (18-92) | 79 (46-99) | <0.001 |
| CVD, n (%) | 96 (21.7) | 66 (16.8) | 30 (61.2) | <0.001 |
| Hypertension, n (%) | 204 (46.2) | 168 (42.7) | 36 (73.5) | <0.001 |
| Diabetes mellitus, n (%) | 146 (33) | 124 (31.6) | 22 (44.9) | 0.061 |
| Current smoking, n (%) | 128 (29) | 113 (28.8) | 15 (30.6) | 0.787 |
| COPD, n (%) | 50 (11.3) | 41 (1048) | 9 (18.4) | 0.098 |
| Cancer, n (%) | 26 (5.9) | 19 (4.8) | 7 (14.3) | 0.008 |
| CVA, n (%) | 18 (4.1) | 11 (2.8) | 7 (14.3) | <0.001 |
| Needing ICU, n (%) | 90 (20.4) | 51 (11.7) | 39 (79.6) | <0.001 |
| ARDS, n (%) | 70 (15.8) | 36 (9.2) | 34 (69.4) | <0.001 |
| Hospitalization period, days, median, [IQR] | 9 [5-12] | 9 [5-12] | 9 [4-13] | 0.802 |
| Uric acid, mg/dL | 5.1±2.1 | 4.8±1.8 | 7.3±2.9 | <0.001 |
| eGFR, mL/min/1.73m$^2$, median, [IQR] | 94 [67-105] | 97 [78-106] | 45 [30-70] | <0.001 |
| WBC, 10$^9$/L, median, [IQR] | 6.2 [4.8-8.6] | 6.0 [4.5-7.8] | 9.9 [7.1-13.7] | <0.001 |
| Neutrophil, 10$^9$/L, median, [IQR] | 4.4 [3.0 -6.7] | 4.1 [2.8-6.0] | 8.4 [5.8-11.9] | <0.001 |
| Lymphocyte, 10$^9$/L, median, [IQR] | 1.1 [0.8-1.5] | 1.2 [0.9-1.5] | 0.8 [0.6-1.1] | <0.001 |
| Haemoglobin, g/L | 126±19 | 127±18 | 112±24 | <0.001 |
| Platelet, 10$^9$/L | 231±95 | 232±95 | 223±95 | 0.514 |
| D-Dimer, µg FEU/L, median, [IQR] | 400 [200-900] | 300 [200-700] | 1200 [800-2100] | <0.001 |
| Ferritin, µg/L, median, [IQR] | 213 [98-406] | 198 [95-385] | 360 [148-638] | <0.001 |
| CRP, mg/L, median, [IQR] | 37 [15-104] | 32 [15-104] | 134 [61-215] | <0.001 |
| Albumin, g/L | 34.9±5.1 | 35.2±4.8 | 31.6±5.5 | <0.001 |
| CAR, median, [IQR] | 1.08 [0.42-3.0] | 0.95 [0.36-2.58] | 4.4 [1.9-7.0] | <0.001 |
| hs-TnI, pg/mL, median, [IQR] | 3.1 [1.3-8.0] | 2.9 [1.1 -6.9] | 5.5 [3.2-17.5] | 0.364 |

CVD: Cardiovascular disease, COPD: Chronic obstructive pulmonary disease, CVA: Cerebrovascular accident, ARDS: Acute respiratory distress syndrome; eGFR: Estimated glomerular filtration rate, WBC: White blood count, CRP: C-reactive protein, CAR: CRP to albumin ratio, hs-TnI: High-sensitivity troponin I, IQR: Interquartile range

patients were older (mean 77.9±11.2 years vs. 66.8±11.5 years; p<0.001) and had lower eGFR (median 48 mL/min/1.73m$^2$ vs. 80 mL/min/1.73m$^2$; p<0.001), lower hemoglobin (mean 113±17 g/L vs. 127±19 g/L; p=0.003), higher white blood cell (median 9.9 10$^9$/L vs. 7.2 10$^9$/L; p< 0.001), lower albumin (mean 31.5±5.5 g/L vs. 34.3±4.8 g/L; p=0.013), higher CRP (median 130 mg/L vs. 37 mg/L; p<0.001), higher D-dimer (median 1.0 µg FEU/L vs. 0.4 µg FEU/L; p=0.037), higher ferritin (median 336 µg/L vs. 231 µg/L; p=0.017), and higher hs-TnI levels (median 9.8 pg/mL vs. 143 pg/mL; p<0.001) at admission.

Multivariate analysis revealed that, anemia, high admission hs-TnI values, high admission CRP levels, and high admission CAR values were independent predictors of mortality in COVID-19 patients with CVD (Table 4). Moreover, ROC analysis showed that CAR had a better AUC than CRP (AUC: 0.809 (95% CI=0.712- 0.905; p<0.001 vs. AUC: 0.763 (95% CI=0.695-0.831; p<0.001) and adequate discrimination ability to predict in-hospital mortality with 76% sensitivity and 75% specificity for >2.2 cut-off value (Figure 4).

## Discussion

The main findings of this study are as follows: Patients who died had higher baseline CAR values, baseline CRP levels, and lower albumin levels compared with those who survived; (ii) while high CAR values and increased CRP levels were found to be independent predictors of mortality, the presence of hypoalbuminemia was not; (iii) the predictive ability of CAR was significantly better than that of both CRP and albumin; (iv) patients with CAR values of greater than 2.2 were at greater risk of in-hospital mortality; and (v) CAR was also found to be an independent predictor of in-hospital mortality in patients with CVD.

CRP is well-known today as a marker of systemic inflammation and severe infection. C- reactive protein is a non-specific acute-phase reactant classically related to

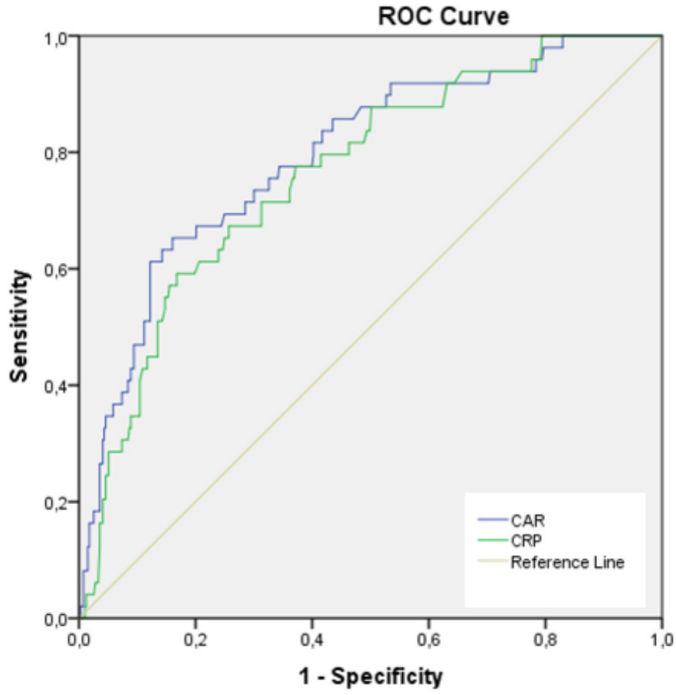



**Figure 4.** ROC curves of the CAR (AUC: 0.809 (95% CI=0.712- 0.905; p<0.001) and CRP (AUC: 0.763 (95% CI=0.695- 0.831; p<0.001) in patients with CVD for detecting the in-hospital mortality

ROC: Receiver operating characteristic, CAR: C-reactive protein-to-albumin ratio, AUC: Area under curve, CI: Confidence interval, CRP: C-reactive protein, CVD: Cardiovascular disease

inflammation (19). Additionally, in providing host defense against invading pathogens, CRP plays an important role by activating the complementary system (19). It has been suggested that CRP can be a marker in the early diagnosis of pneumonia and that patients with severe pneumonia have high CRP levels (20). Recently, CRP levels were found to be positively correlated with lung lesions and may reflect disease severity in the early stages of COVID-19 (21). In a large-scale study involving 2782 COVID-19 patients, CRP was strongly associated with venous thrombo-embolism, acute kidney injury, critical illness, and in-hospital mortality (22). In our study, in line with the available data, CRP independently predicted in-hospital mortality.

Serum albumin, as a negative acute-phase reactant, is a marker of systemic inflammation and hypoalbuminemia is common in many inflammatory diseases (23). There is ample evidence to address the importance of reduced albumin levels in severe COVID-19 (24). In parallel with the findings of previous studies, in our investigation, hypoalbuminemia was detected more frequently among patients who died. Although the exact mechanism of hypoalbuminemia in COVID-19 is not yet understood, systemic inflammation may be a reason. Moreover, The systemic inflammatory response that occurs because of SARS-CoV-2 infection may increase capillary permeability, causing serum albumin to escape into the interstitial space and thus increase the volume of albumin distribution. This may contribute to the development of hypoalbuminemia beyond the negative acute-phase response to the systemic inflammatory response. Serum albumin levels are affected by various factors, such as vascular injury, renal injury, various cytokine levels, free fatty acid concentrations, and steroid hormones (25). Therefore, it is difficult to establish a direct relationship between the serum albumin level and the mortality rate, and, hence, the exact mechanism of this relationship, beyond serum albumin being a marker associated with mortality, remains unknown. As such, albumin alone may not be a reliable prognostic marker in the context of a complex disease like COVID-19.

The CRP to albumin ratio, as a reflection of equilibrium between CRP and albumin, was first described by Fairclough et al. (26) and is an emerging inflammatory indicator suggested to be a better option than either the serum CRP or albumin level alone in predicting poor prognosis in patients with acute medical conditions (5,13). Several previous studies have emphasized the significance of taking pretreatment CAR measurements on clinical outcomes in patients severe inflammation (27,28). In a study by Sun et al. (27), CAR was revealed to be a better prognostic tool than just CRP or albumin level alone in

**Table 2. Factors that were found to be independently associated with in-hospital mortality in unadjusted univariate cox regression analysis**

| Variables | Univariate HR (95% CI) | P |
|---|---|---|
| Age | 1.090 (1.064-1.116) | <0.001 |
| CVD | 5.260 (2.891-9.572) | <0.001 |
| Hypertension | 2.517 (1.331-4.758) | 0.005 |
| Cancer | 2.243 (1.003-5.016) | 0.049 |
| CVA | 2.631 (1.165-5.016) | 0.020 |
| Uric acid | 1.343 (1.219-1.480) | <0.001 |
| eGFR | 0.973 (0.965 - 0.981) | <0.001 |
| Haemoglobin | 0.743 (0.648-0.851) | <0.001 |
| Neutrophil | 1.132 (1.078-1.189) | <0.001 |
| Lymhocyre | 1.023 (1.017-1.030) | 0.002 |
| CRP | 1.007 (1.004-1.010) | <0.001 |
| Albumin | 0.330 (0.176-0.619) | 0.001 |
| Ferritin | 1.001 (1.000 -1.000 | 0.049 |
| CAR | 1.025 (1.016-1.034) | <0.001 |

CVD: Cardiovascular disease, CVA: Cerebrovascular accident, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, CAR: CRP to albumin ratio, CI: Confidence interval, HR: Hazard ratio

patients with sepsis. Furthermore, Karayiannis et al. (28) concluded that higher CAR values are positively correlated with an increased risk of postoperative complications, especially infections. Furthermore, the potential significance of CAR on long-term prognosis was also investigated recently. Park et al. (29) showed that higher CAR values were an independent predictor of 28-day mortality risk in critically ill patients. Similarly, Oh et al. (8) demonstrated the importance of calculating the CAR at the time of ICU admission for long-term mortality prediction in a mixed ICU patient population (8). Moreover, Kim et al. (30) cited CAR level at admission as an independent predictor of 180-day mortality in patients with severe sepsis or septic shock who received early goal-directed treatment.

In patients hospitalized with a diagnosis of COVID-19, high CAR levels were associated with disease severity, 30-day and postdischarge mortality (13). Additionally, in two other studies, a high CAR value was associated with prognosis in patients hospitalized with the diagnosis of hypertensive COVID-19 (31,32). Karakoyun et al. (33) reported that pretreatment CAR levels were statistically higher among those with severe disease than in those with non-severe disease, which is similar to what was reported by Wang et al. (34). In a single study by El-Shabrawy et al. (35) where prognostic importance was evaluated, CAR independently predicted the 30-day mortality rate in 116 patients with COVID-19. Our study, which has a relatively higher number of patients, supports the results of this previous study.

Moreover, CAR has been found to be a more valuable predictive biomarker than either CRP or albumin alone due to its incorporation of two measures (increased CRP and decreased albumin) to predict inflammatory status and prognosis in various CVDs such as coronary artery disease, carotid artery disease, heart failure, valvular heart disease (11,12,36-38). In this study, mortality was higher in COVID-19 patients with CVD, consistent with the literature. Additionally, high CAR levels were also found to be an independent predictor of death in this subset of patients with CVD and COVID-19. Considering literature data, this is the first study to examine the association of high CAR level and mortality in COVID-19 patients with CVD.

### Study Limitations

The current study has several limitations that should be mentioned. First, this study was unicentric and thus subject to bias. We only calculated CAR at admission. However, serial CAR measurements would facilitate more powerful analysis concerning mortality, as such would allow us to understand CAR kinetics in response to therapy. Additionally, we did not compare the CAR with well-established ICU prognostic scores such as the

**Table 3. Factors that were found to be independently predicted the in-hospital mortality in model 1 and 2 multivariate cox regression analysis models**

| Variables | Multivariate 1* HR (95% CI) | P | Multivariate 2* HR (95% CI) | P |
|---|---|---|---|---|
| Age | 1.060 (1.030-1.091) | <0.001 | 1.057 (1.027-1.087) | <0.001 |
| CVD | 2.097 (1.094-4.022) | 0.026 | 2.122 (1.111-4.055) | 0.023 |
| Uric acid | 1.156 (1.027-1.301) | 0.016 | 1.151 (1.023-1.294) | 0.017 |
| eGFR | 0.983 (0.971-0.995) | 0.007 | 0.984 (0.972-0.996) | 0.009 |
| CRP | 1.004 (1.001-1.007) | 0.012 | - | - |
| CAR | - | - | 1.013 (1.005-1.022) | 0.003 |

*T the variables with a p-value of less than 0.05 in the univariate analysis were incorporated into the multivariate cox regression analysis by using Backward LR method. Parameters that are not found to be statistically significant by using the Backward-LR method are not included in the table.
CVD: Cardiovascular disease, CVA: Cerebrovascular accident, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, CAR: CRP to albumin ratio, CI: Confidence interval, HR: Hazard ratio

**Table 4. Factors that were found to be independently predicted the in-hospital mortality in multivariate cox regression analysis in patients with CVD**

| Variables | Multivariate 1* HR (95% CI) | P | Multivariate 2* HR (95% CI) | P |
|---|---|---|---|---|
| Haemoglobin | 0.742 (0.645-0.855) | <0.001 | 0.764 (0.663-0.880) | <0.001 |
| hs-TnI | 1.000 (1.000-1.001) | 0.008 | 1.000 (1.000-1.001) | 0.007 |
| CRP | 1.007 (1.004-1010) | <0.001 | - | - |
| CAR | - | - | 1.024 (1.015-1.033) | <0.001 |

*T the variables with a p-value of less than 0.05 in the univariate analysis were incorporated into the multivariate cox regression analysis by using Backward LR method. Parameters that are not found to be statistically significant by using the Backward-LR method are not included in the table.
CVD: Cardiovascular disease, hs-TnI: High-sensitivity troponin I, CAR: C-reactive protein to albumin ratio, CI: Confidence interval, HR: Hazard ratio

Sequential Organ Failure Assessment or Acute Physiologic Assessment and Chronic Health Evaluation scores. The contribution of these scores should be evaluated on a larger scale. Multicentre prospective studies including more patients are still required to evaluate the predictive accuracy of CAR in determining mortality in the COVID-19 population.

## Conclusion

Our study revealed that admission CAR levels independently predicted the in-hospital mortality in both the study population and the subgroup of patients with CVD. Therefore, we think that CAR, which is an inexpensive indicator, easily accessible and does not require any calculator to use, may allow for the identification of high-risk COVID-19 patients so that they may be stratified early on.

### Ethics

**Ethics Committee Approval:** The local institutional ethics committee of University of Health Sciences Turkey, Bagcilar Training and Research Hospital approved the study (protocol no. 2020.09.1.04.121).

**Informed Consent:** A written informed consent form was signed by each patient or by a first-degree relative of those patients who died.

### Authorship Contributions

Concept: F.K., M.K., F.N.T.C., E.O., Design: F.K., M.K., F.N.T.C., E.O., Data Collection and/or Processing: F.K., S.K., S.O., Z.A.T., S.H.K., Analysis and/or Interpretation: F.K., M.K., F.N.T.C., Literature Research: F.K., M.K., F.N.T.C., U.K., A.G., H.I.B., Writing: F.K., M.K., F.N.T.C., E.O.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Original Article

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# The Predictive Value of Nutritional Indexes for Developing Ascending Aortic Aneurysm in Elderly Patients with Hypertension

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## Abstract

**Aim:** Ascending aorta aneurysm (AsAA) is common in patients with hypertension. There is an increased rate of malnutrition in old age, which can be reliably examined with the Controlling Nutritional Status (CONUT) and Prognostic Nutritional Index (PNI) scoring systems. This study determined the predictive value of the nutritional indexes on the development of AsAA in elderly patients with hypertension.

**Methods:** This retrospective study included 302 patients with hypertension, aged 65 years and older, who presented at the cardiology outpatient clinic approximately 2019-2021. The patients were separated into AsAA developing (n=202) and non-developing (n=100). The nutritional status was determined by the CONUT and PNI scores.

**Results:** Of the 302 patients, 49% were male, the mean age was 72 years (68-77), and the AsAA (+) group was significantly older ($p<0.01$). The CONUT score was similar in both groups ($p=0.06$). The PNI score was found to be significantly lower in the AsAA (+) group than in the AsAA (-) group ($p<0.001$). Logistic regression analyses showed that the PNI score was an independent predictor of AsAAs in elderly patients with hypertension (Odds ratio: 0.92, 95% confidence interval: 0.87-0.98, $p=0.01$).

**Conclusion:** Low nutritional status (determined by PNI) increases the risk of developing AsAA in elderly hypertensive patients. Therefore, determining the nutritional status in elderly hypertensive patients may achieve better clinical outcomes.

**Keywords:** Ascending aorta aneurysm, nutritional index, hypertension, elderly

## Introduction

Ascending aortic aneurysm (AsAA) is defined as an increase of more than 50% in the standard diameter of the thoracic aorta (1). AsAA is common in patients with hypertension, affecting approximately 15% of patients and is related to cardiovascular end-organ damage. Although AsAA progresses slowly, it can cause fatal complications such as aortic dissection (2).

Malnutrition increases at an older age according to several factors such as lower food intake, sarcopenia, and gastrointestinal tract problems (3,4). The Controlling Nutritional Status (CONUT) and the Prognostic Nutritional Index (PNI) scoring systems are reliable tools that are used to examine malnutrition in elderly patients (5).

Studies examining the effect of nutritional status on the prognosis of cardiovascular diseases have become more frequent recently. Nutritional status has been shown to be a predictor of short- and long-term mortality in elderly patients with acute heart failure, Type-A aortic dissection, and non-ST elevation myocardial infarction patients who have undergone percutaneous coronary intervention (6-8). Furthermore, it has been demonstrated that malnutrition in elderly patients affects embolic hemorrhagic processes due to atrial fibrillation and is a predictor of mortality in hypertensive patients. (9,10). However, studies examining the relationship between malnutrition and aortic aneurysm are limited. The relationship between malnutrition and prognosis has been shown in patients with arcus aortic aneurysm undergoing endovascular aneurysm repair (11). However, no study has been conducted on the relationship between ascending AsAA and malnutrition. Therefore, this study aimed to determine the predictive

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value of the nutritional indexes on the development of AsAAs in elderly patients with hypertension.

## Methods

This retrospective study included 302 patients aged 65 years and older who presented at the cardiology outpatient clinic approximately 2019-2021 and were diagnosed with hypertension. Patients were excluded from the study if they were aged under 65 years, had diseases that cause malnutrition such as malignancy, heart failure with reduced ejection fraction (EF<40%), kidney failure, liver failure, or severe infection, or had diseases that caused AsAAs such as the bicuspid aorta, Marfan syndrome, Ehler-Danlos syndrome, and hypothyroidism, which may affect plasma albümin levels.

Heart failure with reduced EF is defined as the inability to pump the heart to tissues and organs, which cause insufficiency to meet metabolic needs and left ventricular EF<40 (12).

Renal failure is defined as the presence of both of these factors [glomerular filtration rate (GFR) less than 60 mL/min and albumin greater than 30 mg per gram of creatinine] along with abnormalities of kidney structure or function for greater than three months signifies chronic kidney disease (13).

Ascending thoracic aortic aneurysm is defined as a dilatation of the ascending aorta producing a cross-sectional diameter more than 1.5 times its normal value (14). Ascending aorta diameter >38 mm in transthoracic echocardiography was accepted as the cut-off value for AsAA for this study cohort.

### Study Design

The patients were separated into two groups those who developed AsAA [AsAA (+), n=202] and those who did not develop AsAA [AsAA (-), n=100]. Medical history, demographic data, height, body mass index, medications, and echocardiographic parameters were obtained from the hospital database. The patients who developed aortic dissection, cardiac death, and death were also recorded. The nutritional status of the patients was determined from the CONUT and PNI scores.

Ethical approval for this study was obtained from the Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital Regional Ethics Committee (approval no: 2022-15, date: 03.01.2022). All patient rights were protected, and written informed consent was obtained before the procedures, according to the Helsinki Declaration (2013).

### Nutritional Score Systems

The CONUT score was calculated using the serum albumin, total cholesterol, and total lymphocyte count (Table 1) (15). The PNI score was calculated using the following formula: 10 x serum albumin value (g/dL) + 0.005 x total lymphocyte count (per $mm^3$). A score greater than 38 points was defined as normal (16).

### Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS 22.0 software (IBM, Armonk, NY, USA). The demographic, clinical, and laboratory values of the two groups were compared using the t-test or Mann-Whitney U test for continuous variables according to the distribution pattern of the data. A chi-square test was used to compare categorical data. The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Univariate and logistic regression analyzes were used to determine the predictors of ascending aorta aneurysms. For all analyses, the statistical significance was set at 2-sided p<0.05.

## Results

Of the 302 patients, 49% were male, and 51% were female. The mean age was 72 years (68-77), and the AsAA (+) group was significantly older (p<0.01). The mean aortic diameter was 42 mm (40-45) in the AsAA (+) group and 36 mm (35-37) in the AsAA (-) group (p<0.001). Age, height, the incidence of coronary artery disease, and atrial fibrillation values were significantly higher in the AsAA (+) group (p<0.01, p=0.001, p=0.001, and p=0.02, respectively).

Total platelet count, lymphocyte count, total protein, and albumin levels were significantly lower in the AsAA (+) group (p=0.001, p=0.002, p<0.001, and p=0.003, respectively). Demographic characteristics and laboratory results of the patients are summarized in Table 2.

**Table 1. Assessment of malnutrition with the CONUT score**

| | Normal | Light | Moderate | Severe |
|---|---|---|---|---|
| Albumin (g/dL)<br>-Score | 3.5-4.5<br>**0** | 3.0-3.49<br>**2** | 2.5-2.9<br>**4** | <2.5<br>**6** |
| Total lymphocytes ($10^9$/L)<br>-Score | >1.60<br>**0** | 1.20-1.59<br>**1** | 0.80-1.19<br>**2** | <0.80<br>**3** |
| Total cholesterol (mg/dL)<br>-Score | >180<br>**0** | 140-180<br>**1** | 100-139<br>**2** | <100<br>**3** |
| Total score | **0-1** | **2-4** | **5-8** | **9-12** |

CONUT: Controlling nutritional status

Patients with AsAA determined to have a larger left atrium (p=0.002), larger left ventricular diastolic dimension (p<0.001), lower ejection fraction (p<0.001), thicker interventricular septum and posterior wall (p=0.001, p=0.003) than the group without AsAA (Table 3).

The CONUT score was similar in both groups. Although moderate and severe malnutrition was higher in the AsAA (+) group than in the AsAA (-) group, it did not reach statistical significance (p=0.06). The PNI score was found to be significantly lower in the ASAA (+) group than in the AsAA (-) group (p<0.001) (Figure 1) (Table 3).

Univariate and logistic regression analyses were performed for the predictors of AsAA (Table 4 and 5). Logistic regression analyses showed that the PNI score was an independent predictor of ascending aorta aneurysms in elderly patients with hypertension [Odds ratio (OR): 0.92, 95% confidence interval (CI): 0.87-0.98, p=0.01]. Age (OR: 1.09, 95% CI: 1.04-1.13, p<0.001), smoking (OR: 2.50, 95% CI: 1.36-4.57, p=0.003), and coronary artery disease (OR: 2.17, 95% CI: 1.14-4.13, p=0.01) were found to be independent predictors of the development of AsAA in elderly patients with hypertension (Table 5).

The median follow-up of the patients was 3.32 years (2.72-4.13). During the follow-up period, aortic dissection, percutaneous aortic intervention, surgery, and mortality did not develop in any case in the AsAA (-) group. In the AsAA (+) group, 4 (2.0%) patients developed aortic dissection, 6 (3%) patients underwent aortic surgery, and 8 (4%) patients died. Only two of the patients died from an aortic dissection.

## Discussion

This study demonstrated that nutritional status determined by the PNI score was an independent predictor of the development of AsAA in elderly patients with hypertension.

The patients with AsAA in this study were found to be older and taller, with a greater frequency of atrial fibrillation and coronary artery disease, as expected. The use of antihypertensive and oral anticoagulant drugs was also higher in the AsAA (+) group. These results were compatible the findings of previous studies (17,18).

PNI is a practical, validated nutritional score, which objectively reveals the nutritional status according to lymphocyte count and albumin level. Several studies have demonstrated the relationship between PNI score and cardiovascular diseases (19-21). Studies on the relationship between aortic pathologies and nutritional status have been conducted on patients with aortic dissection and patients who had undergone percutaneous intervention or surgery to the aorta (7,11,22-24). In all of these studies, it has been shown that malnutrition adversely affects long-term survival and complications in patients undergoing intervention to the aorta. However, these data did not indicate clinical results regarding aneurysms that did not require intervention. The current study may be novel in demonstrating the role of nutritional status in AsAAs without percutaneous and surgical intervention.

Leone et al. (25) showed that AsAA significantly increased the frequency of cardiovascular events in hypertensive patients according to age, gender, and body surface area adjusted risk analysis. Therefore, diagnosing

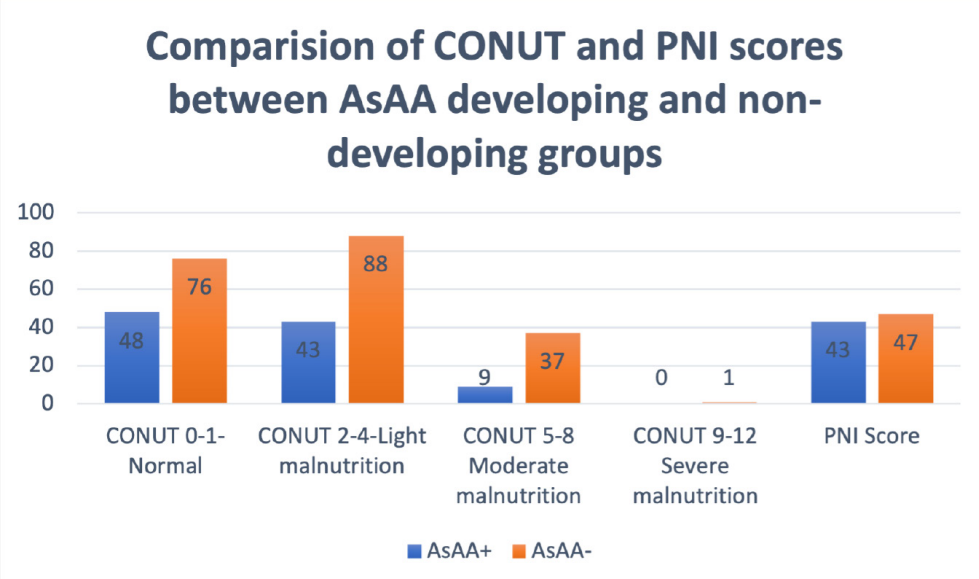


**Figure 1.** Comparision of CONUT and PNI scores between AsAA developing and non-developing groups

CONUT: Controlling Nutritional Status, PNI: Prognostic nutritional, AsAA: Ascending aorta aneurysm

**Table 2. Demographic characteristics and laboratory results of the patients**

| | Total n=302 | Normal aorta n=100 (33.1%) | Aortic aneurysm 202 (66.9%) | p-value |
|---|---|---|---|---|
| Sex (male) | 148 (49.0%) | 45 (45.0%) | 103 (51.0%) | 0.32 |
| Age (years) (median- Q1-Q3) | 72 (68-77) | 71 (63-73) | 74 (69-79) | **<0.01*** |
| Height, cm, (median) | 166 (161-172) | 163 (159-170) | 167 (162-172) | **0.001*** |
| Body mass index (kg/m$^2$), (SD) | 25.5 (2.1) | 25.3 (1.7) | 25.6 (2.2) | 0.15 |
| Diabetes mellitus, n% | 102 (33.8%) | 38 (38.0%) | 64 (31.7%) | 0.27 |
| Smoking, n% | 104 (34.4%) | 27 (27.0%) | 77 (38.1%) | 0.056 |
| Hyperlipidemia, n% | 157 (52.0%) | 46 (46.0%) | 111 (55.0%) | 0.14 |
| Coronary artery disease | 89 (29.7%) | 17 (17.3%) | 72 (35.6%) | **0.001**** |
| CABG, n% | 34 (11.3%) | 8 (8.0%) | 26 (12.9%) | 0.20 |
| PCI | 45 (14.9%) | 15 (15.0%) | 30 (14.9%) | 0.97 |
| Heart failure, n% | 32 (10.6%) | 8 (8.0%) | 24 (11.9%) | 0.30 |
| CVE | 25 (8.3%) | 5 (5.0%) | 20 (9.9%) | 0.14 |
| Atriyal fibrillation, n% | 105 (34.8%) | 26 (26.0%) | 79 (39.1%) | **0.02** |
| Peripheral vascular disease, n% | 15 (5.0%) | 3 (3.0%) | 12 (5.9%) | 0.26 |
| **Medications** | | | | |
| Beta blocker, n% | 253 (83.8%) | 72 (72.0%) | 181 (89.6%) | **<0.001**** |
| Calcium channel blocker, n% | 110 (36.4%) | 24 (24.0%) | 86 (42.6%) | **0.002**** |
| ACEI, n% | 92 (30.7%) | 35 (35.0%) | 57 (28.5%) | 0.25 |
| ARB, n% | 139 (46.0%) | 55 (55.0%) | 84 (41.6%) | **0.02**** |
| Diuretic, n% | 124 (41.1%) | 50 (50.0%) | 74 (36.6%) | **0.02**** |
| Spiranolactone, n% | 36 (11.9%) | 7 (7.0%) | 29 (14.4%) | 0.06* |
| Alfa blocker, n% | 19 (6.3%) | 2 (2.0%) | 17 (8.4%) | **0.03**** |
| OAD-Insulin, n% | 90 (29.8%) | 34 (34.0%) | 56 (27.7%) | 0.26 |
| Statin, n% | 145 (48.0%) | 51 (51.0%) | 94 (46.5%) | 0.46 |
| ASA, n% | 131 (43.4%) | 43 (43.0%) | 88 (43.6%) | 0.92 |
| Clopidogrel, n% | 24 (8.0%) | 6 (6.0%) | 18 (9.0%) | 0.37 |
| Oral anticoagulant, n% | 82 (27.2%) | 17 (17.0%) | 65 (32.2%) | **0.005**** |
| Monotherapy, n% | 63 (20.9%) | 20 (20.0%) | 43 (21.3%) | 0.79 |
| Dual therapy, n% | 79 (26.2%) | 29 (29.0%) | 50 (24.8%) | 0.40 |
| Triple therapy, n% | 102 (33.8%) | 32 (32.0%) | 70 (34.7%) | 0.64 |
| More, n% | 49 (16.2%) | 15 (15.0%) | 34 (16.8%) | 0.68 |
| **Laboratory** | | | | |
| Hemoglobin, (g/dL) | 13.5 (12.1-14.6) | 13.6 (12.8-14.1) | 13.3 (11.9-14.6) | 0.09 |
| Platetelet (x10$^3$/mm$^3$) | 246 (216-281) | 259 (231-287) | 239 (201-269) | **0.001***** |
| Leukocyte (x10$^3$/mm$^3$) | 7.5 (1.9) | 7.6 (1.7) | 7.4 (1.9) | 0.60 |
| Neutrophil (x10$^3$/mm$^3$) | 4.5 (1.5) | 4.4 (1.4) | 4.5 (1.6) | 0.57 |
| Lymphocyte (x10$^3$/mm$^3$) | 1.9 (1.5-2.4) | 2.2 (1.6-2.5) | 1.9 (1.4-2.3) | **0.002***** |
| Monocyte (x10$^3$/mm$^3$) | 0.6 (0.8) | 0.7 (1.4) | 0.6 (0.2) | 0.08 |
| Total protein, (mg/dL) | 6.6 (6.1-7.0) | 6.9 (6.5-7.1) | 6.5 (6.0-6.8) | **<0.001***** |
| Albumin, (mg/dL) | 3.4 (3.0-3.9) | 3.6 (3.3-4.1) | 3.4 (2.9-3.8) | 0.003*** |
| AST, (mg/dL) | 27.6 (11.2) | 27.1 (9.9) | 27.9 (11.8) | 0.56 |
| ALT, (mg/dL) | 21.8 (9.6) | 21.2 (7.8) | 22.1 (10.4) | 0.46 |
| Glucose, (mg/dL) | 114.4 (36.5) | 111.6 (22.7) | 115 (41.7) | 0.35 |
| Creatinine, (mg/dL) | 0.9 (0.7-1.1) | 0.8 (0.6-1.0) | 0.9 (0.8-1.2) | <0.001*** |

| Table 2. Continued | | | | |
|---|---|---|---|---|
| | **Total n=302** | **Normal aorta n=100 (33.1%)** | **Aortic aneurysm 202 (66.9%)** | **p-value** |
| Na, (mg/dL) | 138.9 (3.6) | 138.8 (3.8) | 139.0 (3.6) | 0.59 |
| K, (mg/dL) | 4.2 (3.9-4.5) | 4.1 (3.9-4.4) | 4.3 (4.0-4.5) | **0.004***** |
| CRP, (mg/dL) | 0.3 (0.1-0.9) | 0.3 (0.1-0.8) | 0.3 (0.1-1.1) | 0.34 |
| Uric acid, (mg/dL) | 5.8 (5.0-6.7) | 5.5 (4.9-6.5) | 6.0 (5.1-6.9) | 0.01*** |
| Total cholesterol, (mg/dL) | 202 (40) | 206 (38) | 200 (40) | 0.19 |
| HDL cholesterol, (mg/dL) | 50 (16) | 53 (17) | 49 (15) | 0.052 |
| LDL cholesterol, (mg/dL) | 127 (36) | 131 (42) | 125 (33) | 0.14 |
| Triglyceride, (mg/dL) | 164 (74) | 165 (61) | 164 (80) | 0.87 |

*Mann-Whitney U test, **Chi-square, ***t-test
CABG: Coronary artery bypass grafting, PCI: Percutaneous coronary intervention, CVE: Cerebrovascular event, OAD: Oral antidiabetic, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

and controlling AsAA in hypertensive elderly patients is crucial for protection against organ damage. The results of the current study support the view that improving nutritional status may be effective in preventing aortic and vascular damage in elderly hypertensive patients.

A striking result of this study was that, unlike the PNI score, there was no significant difference between the groups in the CONUT score. It was thought that the possible reason for this was the relatively small number of patients. Moderate-severe malnutrition determined by the CONUT score was higher in the AsAA group, and this difference would probably have reached a statistically significant level with more patients.

In this study, age, smoking, and coronary artery disease were other independent predictors of AsAA. These results are compatible with a similar study by Otaki et al. (26).

### Study Limitations

The main limitation of this study was the single-center, retrospective, and cross-sectional design. Additionally, the change of AsAA in the echocardiography could not

| Table 3. Nutritional status, echocardiographic findings, and long-term clinical outcomes of the patients | | | | |
|---|---|---|---|---|
| **Nutritional Indexes** | | | | |
| **CONUT score** | | | | |
| | **Total** | **Normal Aorta** | **AsAA** | |
| Normal (0-1) | 124 (41.2%) | 48 (48.0%) | 76 (37.8%) | 0.06 |
| Light malnutrition (2-4) | 131 (43.5%) | 43 (43.0%) | 88 (43.8%) | |
| Moderate & severe malnutrition (5-8) | 46 (15.3%) | 9 (9.0%) | 37 (18.4%) | |
| Severe malnutrition (9-12) | 1 (0.3%) | 0 | 1 (0.5%) | |
| **PNI score (>38=normal nutrition)** | 44.7 (7.4) | 47.1 (8.0) | 43.5 (6.7) | **<0.001***** |
| **Echocardiographic findings** | | **Normal Aorta** | **AsAA** | |
| LA, mm | 40.0 (38.0-43.0) | 39.0 (38.0-41.0) | 41.0 (39.0-43.0) | **0.002***** |
| LVEDD, mm | 49.0 (48.0-51.0) | 49.0 (46.0-50.7) | 50.0 (48.0-52.0) | **<0.001***** |
| EF % | 55.0 (50.0-55.0) | 55.0 (55.0-60.0) | 51.0 (50.0-55.0) | **<0.001***** |
| IVS, mm | 12.8 (1.2) | 12.5 (1.0) | 12.9 (1.2) | **0.001***** |
| PW, mm | 12.1 (0.7) | 11.9 (0.6) | 12.1 (0.7) | **0.003***** |
| Aortic annulus, mm | 24.0 (23.0-26.0) | 23.0 (22.0-24.0) | 25.0 (24.0-27.0) | **<0.001***** |
| Sinus valsalva, mm | 32.0 (30.0-36.0) | 30.0 (29.0-31.0) | 34.0 (31.0-36.0) | **<0.001***** |
| Ascending aorta, mm | 40.0 (37.0-43.0) | 35.0 (33.0-37.0) | 42.0 (40.0-45.0) | **<0.001***** |
| **Long-term clinical outcomes** | | | | |
| Aortic disssection | 4 (1.3%) | 0 | 4 (2.0%) | 0.15 |
| Aortic surgery/percutaneous intervention | 6 (2.0%) | 0 | 6 (3.0%) | 0.08 |
| All-cause mortality | 8 (2.7%) | 0 | 8 (4.0%) | **0.04*** |

CONUT: Controlling Nutritional Status, PNI: Prognostic Nutritional Index, LA: Left atrium, LVEDD: Left ventricle end-diastolic dimension, IVS: Interventricular septum, EF: Ejection fraction, PW: Posterior wall, AsAA: Ascending aorta aneurysm
*Mann-Whitney U test, ***t-test

**Table 4. Univariate regression analysis for the predictors of ascending aorta aneurysm**

| | OR | 95% CI | p-value |
|---|---|---|---|
| PNI score | 0.93 | 0.89-0.96 | **<0.01** |
| CONUT score | 2.59 | 1.15-5.85 | **0.02** |
| Gender | 1.27 | 0.78-2.05 | 0.32 |
| Age | 1.07 | 1.04-1.11 | **<0.01** |
| Smoking | 1.66 | 0.98-2.81 | **0.04** |
| Coronary artery disease | 2.63 | 1.45-4.79 | **<0.01** |

CONUT: Controlling Nutritional Status, PNI: Prognostic Nnutritional, CI: Confidence interval, OR: Odds ratio

**Table 5. Logistic regression analysis for the predictors of ascending aorta aneurysm**

| | OR | 95% CI | p-value |
|---|---|---|---|
| PNI score | 0.92 | 0.87-0.98 | **0.01** |
| CONUT score | 0.59 | 0.16-2.06 | 0.40 |
| Gender | 1.41 | 0.82-2.41 | 0.21 |
| Age | 1.09 | 1.04-1.13 | **<0.001** |
| Smoking | 2.50 | 1.36-4.57 | **0.003** |
| Coronary artery disease | 2.17 | 1.14-4.13 | **0.01** |

CONUT: Controlling Nutritional Status, PNI: Prognostic nutritional, CI: Confidence interval, OR: Odds ratio

be obtained. This valuable finding shows the aneurysm expansion rate and prognosis. Finally, the relationship between morbidity, mortality, and nutritional status could not be demonstrated because the AsAA-related morbidity and mortality rates were very low.

## Conclusion

Low nutritional status increases the risk of developing AsAA in elderly hypertensive patients. Therefore, determining nutritional status by risk scores and supporting with natural dietary complements or medically the high-risk elderly hypertensive patients may achieve better clinical outcomes in AsAA patients. Nevertheless, there is a need for further multicenter studies with larger patient numbers and longer follow-up periods to confirm these results.

### Ethics

**Ethics Committee Approval:** Ethical approval for this study was obtained from the Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital Regional Ethics Committee (approval no: 2022-15, date: 03.01.2022).

**Informed Consent:** All patient rights were protected, and written informed consent was obtained before the procedures, according to the Helsinki Declaration (2013).

### Authorship Contributions

Concept: U.K., Design: U.K., Data Collection and/or Processing: U.K., Analysis and/or Interpretation: K.K., Literature Research: K.K., Writing: U.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# Laboratory Parameters Predict Complications in Primary Hyperparathyroidism: A Multicenter Cross-sectional Study

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## Abstract

**Aim:** There is no study predicts the development of complications with laboratory parameters in patients with primary hyperparathyroidism (PHPT). We aimed to determine the laboratory parameters that predict the development of osteoporosis or nephrolithiasis in patients with PHPT and identify high-risk patients.

**Methods:** This multicenter retrospective cross-sectional study was conducted between January 2018 and January 2020. The study group consisted of 389 patients who were diagnosed with PHPT (68 patients without surgical indications and 321 patients with PHPT who underwent surgery), and 451 individuals without any additional disease as a control group. Patients' data was obtained from the hospital automation system. All patients were divided into three groups (control, unoperated and operated), and laboratory parameters were compared.

**Results:** The Wisconsin index (WIN), which is used to detect hyperfunctional glands in addition to parathyroid adenoma in PHPT, and the Parathyroid functional index (PFIndex), which is used to differentiate HPT secondary to vitamin D deficiency, can identify patients at high risk of nephrolithiasis or osteoporosis in patients with PHPT. In patients who have been operated on due to PHPT-related complications, the WIN value of 283.29 showed 95% sensitivity and 72% specificity in predicting osteoporosis, while the PFIndex of 36.43 had 86% sensitivity and 68% specificity for predicting nephrolithiasis.

**Conclusion:** The WIN and PFIndex can be used to refer patients with PHPT for surgery before the onset of osteoporosis or nephrolithiasis. Although no risk factor could be found for nephrolithiasis, WIN was found as an independent risk factor for osteoporosis.

**Keywords:** Hyperparathyroidism, nephrolithiasis, osteoporosis, parathyroid functional index, Wisconsin index

## Introduction

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder that causes abnormalities in serum calcium (Ca) and phosphorous (P) levels (1). An increase is observed in serum parathormone (PTH) and Ca levels, and hypophosphatemia may occur at a rate of 10-20% (2,3). Because it is converted to 1.25-(OH)2-Vit D with an increase in renal alpha-hydroxylase activity, 25-OH-Vit D levels can be lower than normal (4). PTH activity is suppressed with 25-OH-Vit D replacement without an increase in serum Ca levels (5,6).

Changes caused by serum PTH levels in Ca, P, and 25-OH-Vit D levels have been used in the diagnosis of PHPT in several studies. Madeo et al. (1) reported that the ratio of serum Ca level to P (Ca/P) level was revealed to be an important marker in the diagnosis of PHPT. Guo et al. (7) developed the parathyroid function index (PFIndex), which is obtained by multiplying the Ca level by

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the PTH level and then dividing the product by the serum P level (Ca×PTH/P), to differentiate secondary vitamin D deficiency HPT (VD-SHPT) from normocalcemic PHPT (NC-PHPT) (7,8). This term was used for the first time in their study in 2020. Mazeh et al. (9) developed the Wisconsin index (WIN) by multiplying the PTH level by the Ca level. This index has been used as an intraoperative index to predict further gland hyperfunctioning (9). However, none of these parameters has been associated with surgical indications.

In addition to all these studies, no study predicts the development of complications with laboratory parameters in patients with PHTH. Thus, this study used the close relationships between Ca, P, PTH, and 25-OH-Vit D levels as parameters that could predict the presence of osteoporosis and nephrolithiasis. Therefore, we investigated the ratio of Ca, P, PTH, Ca/P and serum PTH levels at the time of presentation to the 25-OH-Vit D level (PTH/VitD), the ratio of serum PTH and Ca levels to the serum 25-OH-VitD level (PTH×Ca/Vit D), and the relationship between WIN and PFIndex in patients with and without surgical indications for osteoporosis and nephrolithiasis to identify the parameters that could refer these patients for surgery before the onset of osteoporosis and nephrolithiasis.

## Methods

### Ethical Approval

This study was approved by the local ethics committee of Yozgat Bozok University, Faculty of Medicine (Ethics Committee no: 2017-KAEK-189_2020.10.14_01).

### Study Design and Sample Size

This multi-centre cross-sectional study was conducted between January 2018 and January 2020. Data of patients were obtained from Yozgat City Hospital, Hitit University, Erol Olcok Training and Research Hospital, and Amasya Serefeddin Sabuncuoglu Training and Research Hospital. The study group consisted of 389 patients who were diagnosed with PHPT, and the control group consisted of the first 451 individuals who were admitted to the outpatient clinic with no comorbid diseases. Patients' age, sex, comorbid diseases, and drugs used were obtained from the hospital database and then recorded. The first recorded laboratory values were included in the analysis.

The diagnosis was NC-PHPT if the serum Ca level was within the laboratory reference range and the PTH level was above the reference range, PHPT if the serum Ca and PHT levels were above the reference range, and normohormonal PHPT if the serum Ca level was high, but the PTH level was within the normal range. The exclusion criteria were as follows: pregnant women: patients aged <18 years; patients with 25-OH-Vit D deficiency; renal failure (GFR<90 mL/min); chronic liver failure; congestive heart failure; malabsorption syndrome and malignancy history; patients with hypercalciuria; patients who used drugs such as thiazide, lithium, bisphosphonate, and denosumab; patients with familial hypocalciuric hypercalcaemia; and patients whose serum Ca level was more than 1 mg/dL above the upper normal limit of the laboratory reference range. The criteria stated in the Guideline for the Management of Asymptomatic PHPT in the Fourth International Workshop were accepted as indications for surgery in patients included in the study. These criteria are as follows: age <50 years, serum Ca level >1 mg/dL according to the upper bound of the laboratory reference range, 24-h urinary Ca excretion >400 mg/day, GFR <60 mL/min, dual-energy X-ray absorptiometry (DEXA), and a T-score ≤−2.5 or the presence of fracture in vertebral imaging and the presence of nephrolithiasis or nephrocalcinosis in renal imaging (10). Patients who did not meet these criteria were not operated.

### Laboratory Assessment

Venous blood samples of the patients were collected after a mean of an 8 h fast. Xylidyl blue methods (Beckman Coulter AU 5800 analyser, Beckman Coulter Inc., USA) were used to measure serum creatinine (Cr, 0.6-1.17 mg/dL), Ca (8.5-10.5 mg/dL), 24-h urinary Ca (photometric), albumin (3.5-5.2 mg/dL), bromocresol green, and P (2.5-4.5 mg/dL). Serum Ca levels were corrected using the formula of [0.8 × (4.0-albumin) + serum calcium] according to serum albumin measurements. Serum intact PTH (1-84) (12-88 pg/mL) and 25-OH-D (ng/mL) levels were measured using chemiluminescent immunologic tests (Beckman Coulter DXI 800 device).

The PFIndex was calculated by dividing the product of serum PTH level (pmol/L) and the corrected Ca level (mmol/L) by the serum P level (mmol/L) (PFIndex=Ca×PTH/P) (7). WIN was calculated by multiplying the serum PTH level (pg/mL) by the corrected Ca level (mmol/L) (WIN=Ca×PTH) (8).

The indices we developed for the study were the serum PTH (pg/mL) level to 25-OH-Vit D (ng/mL) ratio (PTH25-OH-VitDR) and the ratio of multiplying the serum PTH (pg/mL) level and serum Ca (mg/dL) level, divided by the 25-OH-Vit D level (ng/mL) (PTH×Ca/25-OH-Vit D).

### Imaging Methods

Renal ultrasound (US) was performed by radiologists for nephrolithiasis and nephrocalcinosis. Bone mineral density (BMD) was measured using DEXA (Hologic QDR4500 device, Hologic Inc., Waltham, MA, USA). L1-4, total hip, femoral neck, and the distal one-third of the radius were evaluated. T-score <-2.5 was considered to have osteoporosis (11).

### Statistical Analysis

Data analysis was performed using the SPSS 20 (IBM Corp, Armonk, NY, USA) software. The data is presented in the form of a mean, standard deviation, and percentiles. The normality distribution of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, and that of numerical data was assessed using the non-parametric Kruskal-Wallis tests. A parametric one-way analysis of variance (ANOVA) was used for normally distributed variables, and post hoc assessment was performed using Bonferroni correction. The non-parametric Mann-Whitney U test was used for two-group comparisons of non-normally distributed numerical data, and the parametric Student's t-test was used for normally distributed numerical data. In the multivariate analysis, possible factors detected in the univariate analyses were analyzed in the logistic regression analysis to further identify independent parameters that could predict the onset of osteoporosis. The threshold value affecting osteoporosis and nephrolithiasis was determined using receiver operating characteristic (ROC) curve analysis. A p-value <0.05 was set as a significant result.

## Results

The patients were divided into three groups: the control group, the PHPT group with surgical indications and the PHPT group without surgical indications. Laboratory parameters were compared among the groups in Table 1. PTH, PTH/VitD, PFIndex, PTH×Ca/Vit D, and WIN values were significantly higher in the PHPT group with surgical indications than in the PHPT group without surgical indications ($p<0.001$) (Table 1).

Laboratory parameters of those with osteoporosis or nephrolithiasis and those without surgical indications among patients with PHPT were compared separately. Compared with the group without surgical indications, significant differences were found in all parameters other than serum P level in patients with osteoporosis ($p<0.05$) (Table 2). Serum Ca, PTH, and urinary Ca levels, as well as Ca/P, PTH/VitD, PFIndex, and PTH Ca/Vit D and WIN values, were significantly higher in nephrolithiasis patients, while age and serum P levels were significantly lower (Table 2).

Indicators that could predict the development of osteoporosis and nephrolithiasis were assessed in the ROC curve analysis, and the calculated area under the curve values are shown in Table 3. The cut-off value of 283.29 for WIN had a sensitivity of 95% and a specificity of 72% for detection of osteoporosis. Moreover, the cut-off value of 36.43 for the PFIndex had a sensitivity of 86% and specificity of 68% to predict concomitant nephrolithiasis (Table 3, Figure 1). The values were considered in the multivariate logistic regression analysis for osteoporosis and nephrolithiasis. Although no risk factor could be found for nephrolithiasis, WIN was found as an independent risk factor for osteoporosis (odds ratio of 1.507, 95% confidence interval: 1.01-1.71) (Table 4, Figure 2).

## Discussion

The prevalence of asymptomatic PHPT in the general population is 80%, and it may cause complications in the bones and kidneys (4). However, predicting these complications is difficult, and no laboratory parameters have been confirmed to predict the development of complications. In this study, WIN and PFIndex demonstrated high sensitivity and specificity in predicting osteoporosis and nephrolithiasis. Additionally, multivariate logistic analysis of laboratory parameters that showed potential risk in the development of osteoporosis revealed WIN as an independent risk factor. These findings can be used as important markers in decision-making when referring patients for surgery before the onset of osteoporosis and nephrolithiasis. The low and high-risk groups in terms of nephrolithiasis and osteoporosis can be determined by the obtained results. Therefore, patients in the low-risk group can be followed up only with routine blood parameters and urinary Ca excretion instead of BMD and renal US. Complications can be evaluated for patients in that high-risk group, or they can be referred for surgery.

Mazeh et al. (9) recommended using WIN as a parameter during parathyroid surgery to predict additional gland hyperfunctioning. They concluded that this parameter was more practical and useful than waiting for intraoperative PTH results in terms of the presence of an additional functional gland after minimally invasive parathyroidectomy. However, in a recent study, WIN was not found to be more successful than intraoperative PTH in patients with multi-glandular parathyroid disease (12). Guo et al. (7) used the PFIndex to successfully differentiate NC-PHPT from VD-SHPT. Guo et al. (7) used WIN in the differential diagnosis of PHPT and NC-PHPT, but it was not as successful as the PFIndex. There is no other study in the literature about PFIndex for predicting operation indications in patients with PHPT. None of these indices have been associated with the presence of complications. Previous studies have identified demographic and laboratory data as risk factors in the development of complications. However, no cut-off value that could predict the existence of complications has been proposed. Thus, the parameters identified in this study can be used to decide which patients can undergo surgery among those without complications.

The presence of osteoporosis in PHPT is associated with the resorption of Ca from the bones, as well as

the direct effects of increased PTH and fibroblast growth factor 23 (FGF-23) levels on the bones (13). Abnormalities in the cortical structure are often observed in bones. The incidence of osteoporosis can be as high as 39-62% (14). Bone fractures are present in 21% of patients at the time of diagnosis of PHPT (15). This was linked to the decrease in the trabecular bone score and was associated with the deterioration in bone microarchitecture. BMD improves in all regions, and vertebral fractures decrease with surgery in patients with PHPT and osteoporosis (4,16). In the study by Lundstam et al. (16), although no vertebral fractures developed

**Table 1. Comparison of laboratory data of the control group, the PHPT group without a surgical indication, and the PHPT group that underwent surgery**

| | Control group n=451 | PHPT n=389 | | |
|---|---|---|---|---|
| | F/M: 351/100 | Unoperated n=68 F/M: 58/10 | Operated n=321 F/M: 278/43 | p |
| Age (years) | 54.7±5.6 | 60.4±7[a,c] | 55.4±12.1 | <0.001[&] |
| Ca (mg/dL) | 9.4±0.4[b,c] | 10.8±0.4 | 11±0.4 | <0.001[µ] |
| P (mg/dL) | 3.3±0.5[b,c] | 2.7±0.5 | 2.5±0.5 | <0.001[&] |
| Cr (mg/dL) | 0.9±0.3[b,c] | 0.8±0.2 | 1±5 | <0.001[µ] |
| PTH (pg/mL) | 56.2 24.9[b,c] | 148.3±60.7[c] | 223.4±147.2 | <0.001[µ] |
| 25-OH-VitD (ng/mL) | 17±10.9[b,c] | 14.9±10.6 | 13.2±10.6 | <0.001[µ] |
| Urinary Ca (mg/day) | - | 246.5±72 | 415±221.5 | <0.001[µ] |
| Urinary Cr (mg/day) | - | 1171.5±399.2 | 1351±927.7 | 0.371[µ] |
| Ca/P | 2.9±0.4[b,c] | 4.1±0.9 | 4.6±1.1 | <0.001[µ] |
| PTH/VitD | 4.6±3.7[b,c] | 17.5±17.9[c] | 29.4±34.7 | <0.001[µ] |
| PFI | 13.5±7.2[b,c] | 51.5±27[c] | 89.4±76.2 | <0.001[µ] |
| PTH*Ca/Vit D | 43.4±34.6[b,c] | 189.4±192.4[c] | 325.3±387.4 | <0.001[µ] |
| WIN | 131.9±58.2[b,c] | 400.7±165.9[c] | 618.2±414.5 | <0.001[µ] |

Data presented as mean ± SD. [&]: One-way ANOVA, [µ]: Kruskal -Wallis test.
[a] There was a significant difference compared with the normal group in post-hoc comparison.
[b] There was a significant difference compared with the unoperated group in post-hoc comparison.
[c] There was a significant difference compared with the operated group in post-hoc comparison.
Ca: Calcium, P: Phosphorus, Cr: Creatinine, PTH: Parathyroid hormone, Ca/P: Calcium phosphorus ratio, PFI: Parathyroid functional index, PTH/VitD: Parathyroid hormone 25-OH-VitD ratio, WIN: Wisconsin index, SD: Standard deviation, PHPT: Primary hyperparathyroidism

**Table 2. Comparison of laboratory parameters of the PHPT group without a surgical indication and the PHPT group that underwent surgery for osteoporosis or nephrolithiasis**

| | Unoperated group (n=68) | Operated group for osteoporosis (n=174) | p | Unoperated group (n=68) | Operated group for kidney stones (n=105) | p |
|---|---|---|---|---|---|---|
| Age (years) | 60.4±7 | 58.6±11 | 0.012[&] | 60.4±7 | 55.6±12.4 | 0.010[&] |
| Ca (mg/dL) | 10.8±0.4 | 11±0.4 | <0.001[µ] | 10.8±0.4 | 11±0.4 | <0.001[µ] |
| P (mg/dL) | 2.7±0.5 | 2.5±0.5 | 0.140[&] | 2.7±0.5 | 2.5±0.5 | 0.002[&] |
| Cr (mg/dL) | 0.8±0.2 | 0.7±0.2 | <0.001[µ] | 0.8±0.2 | 1.6±8.2 | 0.444[µ] |
| PTH (pg/mL) | 148.3±60.7 | 249±165.7 | <0.001[µ] | 148.3±60.7 | 220±133.2 | <0.001[µ] |
| 25-OH-VitD (ng/mL) | 14.9±10.6 | 13.4±11.3 | <0.001[µ] | 14.9±10.6 | 12.6±7.6 | 0.353[µ] |
| Urinary Ca (mg/day) | 246.5±72 | 402±233.1 | <0.001[&] | 246.5±72 | 426±202.7 | <0.001[&] |
| Ca/P | 4.1±0.9 | 4.6±1.1 | <0.001[µ] | 4.1±0.9 | 4.7±1.3 | 0.001[µ] |
| PTH/VitD | 17.5±17.9 | 34.6±41.5 | <0.001[µ] | 17.5±17.9 | 27.1±29.8 | 0.016[µ] |
| PFI | 51.5±27 | 100.6±87.9 | <0.001[µ] | 51.5±27 | 89.6±68.6 | <0.001[µ] |
| PTH*Ca/Vit D | 189.4±192.4 | 382.4±463.2 | <0.001[µ] | 189.4±192.4 | 299.3±326.6 | 0.011[µ] |
| WIN | 400.7±165.9 | 687.7±466.1 | <0.001[µ] | 400.7±165.9 | 607±367.9 | <0.001[µ] |

Data presented as mean ± SD. [&]: Student's t-test, [µ]: Mann-Whitney U test. Ca: Calcium, P: Phosphorus, Cr: Creatinine, PTH: Parathyroid hormone, Ca/P: Calcium phosphorus ratio, PFI: Parathyroid functional index, PTH/VitD: Parathyroid hormone 25-OH-Vit D ratio, WIN: Wisconsin index

during the 5-year follow-up of patients with PHPT who underwent surgery, vertebral fractures developed in patients who did not undergo surgery; however, no significant difference was found between the two groups. Risk factors for fracture development include advanced age, low BMD, low 25-OH-Vit D levels, high bone turnover markers, and high PTH levels (4,17). In our study, a statistically significant relationship was found in all laboratory parameters except serum P levels in the PHPT group with osteoporosis compared with the PHPT group without surgical indications. In the ROC analysis, a WIN value of 283.2 had a sensitivity of 95% and a specificity of 72% in predicting osteoporosis, and it was identified as an independent risk factor in the regression analysis. In the study by Reid et al. (18), no independent risk factor could be detected in the analysis between laboratory values and low BMD among patients with PHPT. Although WIN was found to be an independent risk factor, no independent risk factors among laboratory parameters such as Ca, P, and PTH were associated with the variability of these values, and indices obtained from these values were considered more decisive parameters.

PHPT causes complications in the kidneys such as nephrolithiasis (prevalence, 10-20%), hypercalciuria, and GFR decline (prevalence, 15-17%) (4,8). Although a decrease in the new onset of kidney stones was observed with parathyroid surgery, nephrocalcinosis and renal failure persisted (13,19). Huang et al. (20) stated that the recurrence of nephrolithiasis despite parathyroidectomy is an important problem. The development of nephrolithiasis was associated with young age, male sex, high plasma Ca and PTH levels, a lower plasma P level, and hypercalciuria grade (18). Marchini et al. (21) revealed that the development of renal calculi in patients with PHPT was associated with serum PTH and Ca levels. In this study, the serum P level was significantly lower and although no significant difference was found in serum Cr and 25-OH-VitD levels, other laboratory parameters were significantly higher in patients with nephrolithiasis compared with the group without surgical indications. In the ROC analysis of indices that could predict the development of nephrolithiasis, the cut-off value of 36.43 for the PFIndex had a sensitivity of 86% and a specificity of 68%. However, no independent risk factor was detected in the regression analysis.

Complications develop in the long term in 25% of patients with PHPT in whom surgical treatment is not required (22). Untreated disease can sometimes silently progress with bone demineralization and increased calcium load in tissues until complications arise. Moreover, an increase in FGF-23 levels in PHPT has negative effects on the skeletal, renal, and cardiovascular systems (13). Therefore, when patients with asymptomatic PHPT should be referred for parathyroid surgery, there is still a matter of debate. For reasons such as the progression of renal failure and nephrocalcinosis after parathyroid surgery and the further occurrence of vertebral fractures in patients who do not undergo surgery, it is important to refer these patients for surgery before the development of complications. Given their high sensitivity and specificity, the WIN value of 283.2 and the PFIndex value of 36.43 can be appropriately used as surgical indications in patients with PHPT in whom osteoporosis and nephrolithiasis have not yet developed, respectively. Patients whose values are below these levels may be followed up with these parameters without performing BMD or renal US, with the advantage of low costs.

### Study Limitations

This study has some limitations. Firstly, it was a retrospective study, and the number of patients without surgical indications was low. Secondly, it was impossible to obtain laboratory parameters in patients just before and after the development of complications. Therefore, the

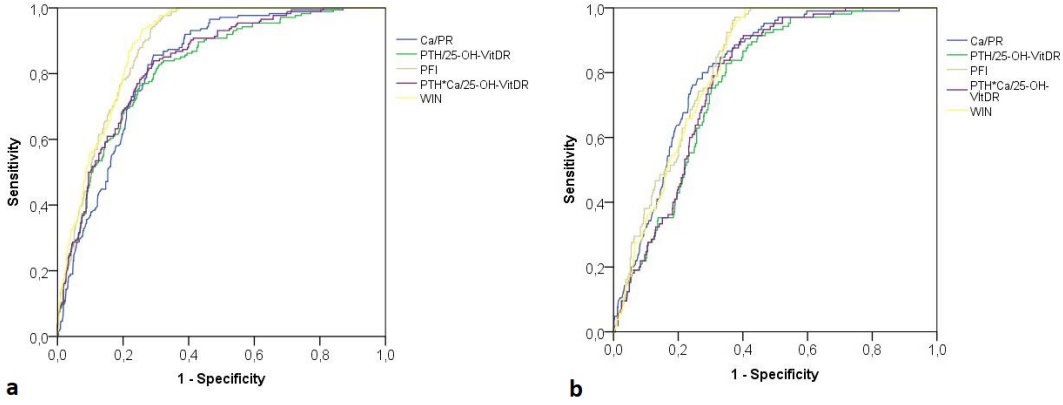


**Figure 1.** ROC curve analysis for indices that can predict the development of osteoporosis and nephrolithiasis
ROC: Receiver operating characteristic

| Table 3. Receiver operating characteristics curve analyses of patients with osteoporosis or nephrolithiasis | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Osteoporosis** | | | | | | | |
| | **AUC** | **SD** | **p** | **95% CI** | **Cut-off value** | **Sensitivity %** | **Specificity %** |
| **Ca/P** | 0.822 | 0.015 | <0.001 | 0.793-0.852 | 3.49 | 87% | 68% |
| **PTH/VitD** | 0.818 | 0.017 | <0.001 | 0.785-0.851 | 13.11 | 82% | 70% |
| **PFI** | 0.879 | 0.011 | <0.001 | 0.857-0.902 | 35.63 | 90% | 74% |
| PTH*Ca/VitD | 0.829 | 0.016 | <0.001 | 0.798-0.861 | 70.93 | 87% | 64% |
| **WIN** | 0.886 | 0.011 | <0.001 | 0.864-0.908 | 283.29 | 95% | 72% |
| **Nephrolithiasis** | | | | | | | |
| | **AUC** | **SD** | **p** | **95% CI** | **Cut-off value** | **Sensitivity %** | **Specificity %** |
| **Ca/P** | 0.812 | 0.018 | <0.001 | 0.777-0.847 | 3.79 | 82% | 70% |
| **PTH/VitD** | 0.767 | 0.019 | <0.001 | 0.729-0.805 | 8.68 | 83% | 65% |
| **PFI** | 0.825 | 0.016 | <0.001 | 0.794-0.855 | 36.43 | 86% | 68% |
| **PTH*Ca/VitD** | 0.779 | 0.018 | <0.001 | 0.743-0.815 | 96.33 | 82% | 68% |
| **WIN** | 0.818 | 0.016 | <0.001 | 0.787-0.849 | 299.12 | 84% | 67% |

AUC: Area under the curve, SD: Standard deviation, CI: Confidence interval, Ca/P: Calcium phosphorus ratio, PFI: Parathyroid functional index, PTH/VitD: Parathyroid hormone 25-OH-VitD ratio, WIN: Wisconsin index

| Table 4. Multivariate and univariate logistic regression analyses of parameters effective in predicting osteoporosis in patients with PHPT | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Multivariate** | | | | **Univariate** | | | |
| | **B** | **p** | **OR** | **95% CI** | **B** | **p** | **OR** | **95% CI** |
| **Ca/P** | 0.300 | 0.371 | 1.35 | 0.70-2.60 | 0.507 | 0.002 | 1.66 | 1.21-2.28 |
| **PTH/VitD** | 0.201 | 0.192 | 0.82 | 0.61-1.11 | 0.025 | 0.002 | 1.03 | 1.01-1.04 |
| **PFI** | 0.018 | 0.401 | 0.98 | 0.94-1.02 | 0.024 | <0.001 | 1.02 | 1.01-1.04 |
| **PTH*Ca/VitD** | 0.017 | 0.224 | 1.02 | 0.99-1.05 | 0.002 | 0.002 | 1.00 | 1.00-1.01 |
| **WIN** | 0.007 | 0.031 | 1.51 | 1.01-1.71 | 0.004 | <0.001 | 1.58 | 1.00-1.81 |

OR: Odds ratio, CI: Confidence interval, Ca/P: Calcium phosphorus ratio, PFI: Parathyroid functional index, PTH/VitD: Parathyroid hormone 25-OH-Vit D ratio, WIN: Wisconsin index, PHPT: Primary hyperparathyroidism

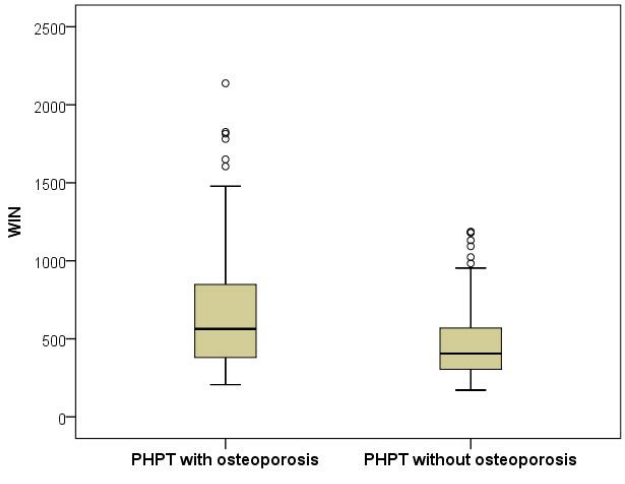


**Figure 2.** WIN results of patients with PHPT who were operated for osteoporosis and patients with PHPT who did not have an operation indication
WIN: Wisconsin index, PHPT: Primary hyperparathyroidism

values of patients at the time of presentation were used in the study. However, our study is important because it is the first study to identify an independent predictor of osteoporosis and present a cut-off value with relatively high sensitivity and specificity values for the presence of both osteoporosis and nephrolithiasis.

## Conclusion

In our study, it has been shown that WIN and PFIndex can properly predict the presence of nephrolithiasis and osteoporosis. WIN can be used specifically as an independent predictor of osteoporosis. With these results, low-risk patients according to WIN and PFIndex may be followed up with routine blood tests and urinary Ca excretion, whereas BMD and renal US may be reserved for high-risk patients. WIN and PFIndex can be calculated with routine blood tests for PHPT, and no extra cost is required. With these indices, low-risk patients are detected, and there is no additional cost and time loss for renal US and BMD. Our findings should be supported by further prospective studies, including larger sample sizes.

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**Ethics**

**Ethics Committee Approval:** This study was approved by the local ethics committee of Yozgat Bozok University, Faculty of Medicine (Ethics Committee no: 2017-KAEK-189_2020.10.14_01).

**Informed Consent:** This multicenter retrospective cross-sectional study.

**Authorship Contributions**

Concept: O.O.B., D.K., Z.C., M.C., Design: O.O.B., Data Collection and/or Processing: O.O.B., D.K., Z.C., Analysis and/or Interpretation: O.O.B., Literature Research: O.O.B., Writing: O.O.B., D.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# Prognostic Role of Current Nutritional Indicators on Early and Late Postoperative Survival After Geriatric Hip Fracture Surgery

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## Abstract

**Aim:** Malnutrition is reported to be related to higher mortality rates following geriatric hip fracture, and new malnutrition indicators are currently being identified. The aim of this study is to analyze prognostic nutritional index (PNI), C-reactive protein (CRP)/albumin ratio (CAR) and CRPI/PNI ratio (CPR) as prognostic factors for first-month, six-month, one-year and overall mortality following hip fracture surgery.

**Methods:** This study was designed as a cross-sectional study. We reviewed the medical records of patients older than 75 years with osteoporotic hip fracture surgery between January 2012 and October 2019. Preoperative serum albumin, total lymphocyte count, and CRP levels were evaluated as laboratory values. PNI, CAR, and CPR were calculated and analyzed as prognostic factors for mortality.

**Results:** Four hundred and thirty patients were included in the study. High American Society of Anesthesiology (ASA) score (p=0.01) and admission to the intensive care unit (ICU) (p=0.016) were found to be independently associated with worse survival in the first month. The admission to the ICU (p=0.004) was independently related to poor survival in the first six months. High ASA score (p=0.018) and admission to the ICU (p=0.016) were independently associated with a poor survival in the first year. High ASA score (p<0.001) and admission to the ICU (p<0.001) were found to be independent prognostic factors for poor overall survival.

**Conclusion:** PNI, CAR, and CPR were not significantly related to poor survival in the first month, six months, one year, and overall follow-up period after geriatric hip fracture surgery.

**Keywords:** Prognostic nutritional index, C-reactive protein/prognostic nutritional index, CRP to albumin ratio, mortality, hip fracture, elderly population

## Introduction

Hip fractures in older adults are also associated with a high mortality rate, as reported by 8-37% in the literature (1), and the increased mortality risk can last for years after a hip fracture (2). Various risk factors may be related to the mortality following a surgically treated hip fracture in the geriatric population. Age, gender, high American Society of Anaesthesiologists (ASA) score, duration of hospitalization, delayed surgery, and malnutrition are some of these factors (3-5).

Malnutrition is a common clinical problem in geriatric patients who have hip fractures, and it is reported to be related to lower functional results and higher mortality rates (6). Serum albumin level and lymphocyte count, considered as serum biomarkers used to define the nutritional status of the patient, are reported as prognostic factors in osteoporotic hip fracture in geriatric patients (7). The prognostic nutritional index (PNI) is also found to be a prognostic factor in malignancies and is calculated using the formula: 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (8,9). C-reactive protein (CRP), which is

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a marker of infection and inflammation, is also reported as a prognostic factor for survival after hip fracture surgery (10). In different studies, PNI, CRP/albumin ratio (CAR), and CRP/PNI ratio (CPR) are investigated as prognostic factors for mortality after osteoporotic hip fracture surgery, but the literature has a lack of data and needs more studies on this issue (11,12).

The purpose of this study is to evaluate PNI, CAR, and CPR as prognostic factors for first-month, six-month, one-year, and overall mortality after hip fracture surgery.

## Methods

### Compliance with Ethical Standards

This study was approved by the University of Health Sciences Turkey, Haseki Training and Research Hospital Ethics Commitee (IRB number: 2020-221) and was conducted in accordance with the Declaration of Helsinki. Informed consent was routinely obtained from all patients before surgery.

### Design of the Study

The study was designed as a cross-sectional study. We reviewed the medical records of patients older than 75 years who were diagnosed with femoral neck (FNF) and intertrochanteric femur fractures (ITFF) and underwent surgical treatment between January 2012 and October 2019. Patients' demographic and medical data were obtained from the institutional database system and phone calls. Time to surgery was determined as the time between admission to the hospital and surgery. The mortality of the patients and the date of their death were evaluated using the National Death Report System. Follow-up periods were recorded from patient files. Survivorship of the patients was assessed according to the National Population Registry System, which was checked for all patients in October 2020.

Patients with high energy or major trauma, a history of malignancy or pathological femoral fractures, subtrochanteric fractures, neglected fractures (more than four weeks), diagnosed with any systemic infection at the time of the fracture, and incomplete information on the registries were all excluded from the study. Finally, 430 patients were included in the study (Figure 1).

Patients' data concerning age, gender, type of fracture, the type of anesthesia, implant type used in the surgery, ASA classification, time of surgery, delay to surgery, duration of hospital stay, and history of intensive care unit (ICU) admission were collected. An ASA score was used to determine the preoperative general health status of the patients according to their comorbidities. The preoperative ASA classification was determined by the anesthesiologists' preoperative evaluation. The patients' ASA scores were categorized as low (ASA 1-2) or high (ASA 3-4) (13).

Preoperative serum albumin, total lymphocyte count, and CRP levels were evaluated as laboratory values. PNI, CAR, and CPR were calculated and analyzed as prognostic factors for mortality. Laboratory values obtained on the first admission to the hospital were used for preoperative evaluation to get an idea about the long-term health status of the patients.

### Operation Data

All the patients included in the study were treated in a single, fully equipped training and research hospital. All the patients with FNF were operated on using hemiarthroplasty (HA), while patients with ITFF were treated using HA, intramedullary nailing, and dynamic hip screws. All patients were operated on as soon as possible upon completion of the preoperative preparations.

### Outcome Measurements

The primary outcome was survival, determined as the time from the surgery to death or the end of the study. The

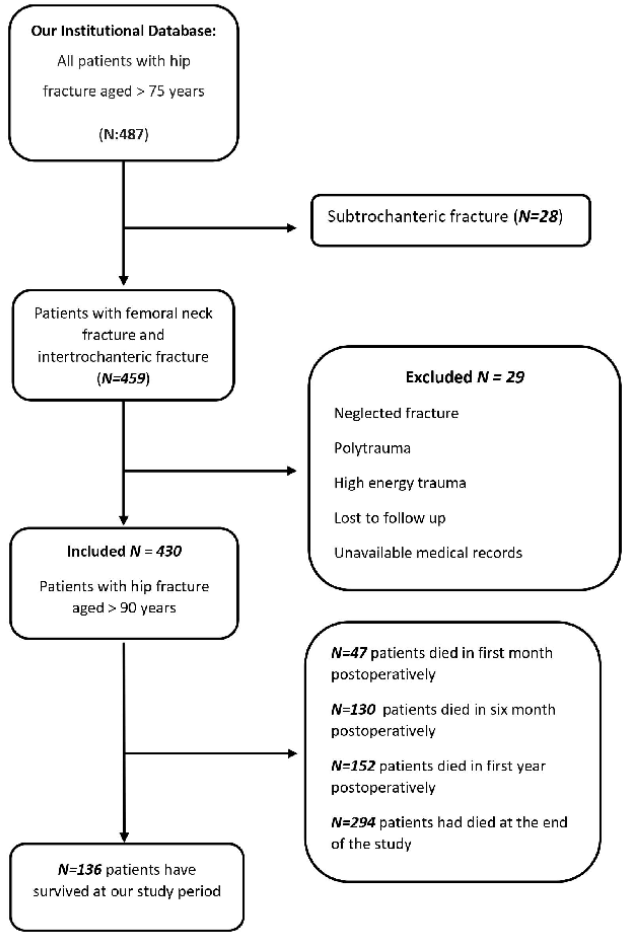


**Figure 1.** Flowchart of our study

patients' survival was evaluated in four different periods according to survival time: in the first month, six months, the first year, and overall survival. Demographic and laboratory values were analyzed for validity as prognostic factors for mortality following geriatric hip fracture surgery in each period.

### Statistical Analysis

SPSS (for Microsoft, v. 22.0, SPSS Inc., Chicago, IL, USA) was used as a statistical software. The survival of the patients was evaluated using Kaplan-Meier survival analysis. Furthermore, univariate Cox regression analysis was used to determine potential prognostic factors for the survival of the patients. The prognostic factors with p-values (two-sided) ≤0.05 were chosen for inclusion in the multivariate Cox proportional hazard model to identify independent variables in a stepwise fashion. Variables with p-values of 0.05 or less in multivariate analysis were retained as independent risk factors. A p-value <0.05 was set as statistically significant.

## Results

The mean age of the patients was 84.3±7 years. Two-hundred eighty-two patients were female (65.5%), and 148 patients were male (35.5%). Two-hundred seventy-four patients (%63.7) had ITFF, while 156 patients (36.3%) had FNF. The mean follow-up period was 25.6±23.4 months. The mean delay to surgery was 5.8±3.6 days. The average length of hospital stay was 12.2±8.4 days. One-hundred thirty-two patients (30.6%) had postoperative ICU admissions.

Forty-seven patients (10.9%) died in the first month after surgery. One hundred thirteen patients (26.3%) were dead in six months, while one hundred fifty-two patients (35.3%) were dead in the first year following surgery. The overall mortality rate was 68.4% (Figure 2). According to the Kaplan-Meier analysis, the mean survival period was 37.7 months and the survival rate was 11.2% at the end of the study (Figure 3).

The average preoperative CRP value was 68.6±62.2 mg/dL. The mean PNI was 42.4±8.4. The mean CPR was 1.72±1.67. The mean CAR was 20.8±2.4. Baseline demographic data of the patients included in the study are presented in Table 1.

### Analysis for first-month survival

In the first month, PNI, CPR, and CAR were not significantly associated with worse survival in the first month. The other analyzed items are shown in Table 2.

### Analysis for six-month survival

PNI, CPR, and CAR were not significantly associated with poorer survival in the first six months. The other analyzed items are shown in Table 3.

### Analysis for first-year survival

In the first year, PNI, CPR, and CAR were not significantly associated with worse survival in the first year. The other analyzed items are shown in Table 4.

### Analysis for overall survival

PNI, CPR and CAR was not found to be independent prognostic factors for overall survival. The other analyzed items are shown in Table 5.

## Discussion

The incidence of hip fractures will gradually increase with the increase in life expectancy. The 1-year mortality rate in hip fractures in patients over 65 years of age has been reported to be between 8% and 35% in the literature (1,14). It was reported in the literature that patients' postoperative mortality and morbidity were affected by their age, higher ASA score, comorbid diseases, and preoperative nutritional status (11,12,15-17).

**Table 1. Demographic data of the all patients**

| | Patients with hip fracture aged more than 75 years (n: 430) | |
|---|---|---|
| | Mean ± SD | Min.-Max. |
| Age, years | 84.3±7 | 75-104 |
| Gender, female/male | 282/148 | |
| Side, Right/Left | 229/201 | |
| Fracture type, Int./C | 274/156 | |
| Treatment method IMN/HA/DHS | 188/189/53 | |
| Survive, months | 25.6±23.4 | 0.1-113.4 |
| Delay to surgery, day | 5.8±3.6 | 1-20 |
| Hospital stay, day | 12.2 ± 8.4 | 2-108 |
| History of intensive care unit, n (%) | 132 (30.6%) | |
| Type of anesthesia G, R | 65/365 | |
| ASA score | | |
| Low (1-2), n (%) | 237 (55.1%) | |
| High (3-4), n (%) | 193 (44.9%) | |
| Mortality | | |
| In first months, n (%) | 47 (10.9%) | |
| In six months, n (%) | 113 (26.3%) | |
| In first years, n (%) | 152 (35.3%) | |
| Overall, n (%) | 294 (68.4%) | |
| C-reactive protein, mg/dL | 68.6±62.2 | 0.01-272 |
| Preoperative prognostic nutritional index (PNI) | 42.4±8.4 | 22.5-90 |
| CRP/PNI ratio | 1.72±1.67 | 0.1-11.4 |
| CRP/albumin ratio | 20.8±2.4 | 0.1-137 |

SD: Standard deviation, Min.: Minimum, Max.: Maximum, Int.: Intertrochanteric fracture, C: Collum fracture, IMN: Intramedullary nailing, HA: Hemiarthroplasty, DHS: Dynamic hip screws, G: General, R: Regional, ASA: American Society of Anesthesiology, CRP: C-reactive protein, PNI: Prognostic nutritional index

| Table 2. Univariate and multivariate Cox regression analysis for patients who died in first month after surgery | | | |
|---|---|---|---|
| **Factors** | | **Hazard ratio and the 95% CI** | **p-value** |
| ***Univariate Cox regression analysis*** | | | |
| **Age** | | **1.025 (0.986-1.066)** | **0.211** |
| **Sex** | | | |
| | Female | Reference | Reference |
| | Male | 1.424 (0.799-2.539) | 0.231 |
| **ASA Score** | Low | Reference | Reference |
| | High | 2.479 (1.356-4.532) | 0.033* |
| **Side** | Right | Reference | Reference |
| | Left | 0.831 (0.466-1.482) | 0.532 |
| **Delay to surgery** | | 1.156 (0.980-1.133) | 0.156 |
| **Hospital stay** | | 1.018 (0.997-1.039) | 0.09 |
| **Intensive care** | No | Reference | Reference |
| | Yes | 3.864 (1.529-9.767) | 0.004* |
| **Type of anesthesia** | Spinal | Reference | Reference |
| | General | 0.975 (0.437-2.177) | 0.951 |
| **Type of fracture** | Intertrochanteric | Reference | Reference |
| | Collum | 1.098 (0.610-1.977) | 0.756 |
| **Preoperative C-reactive protein** | | 1.004 (1.000-1.008) | 0.041* |
| **Prognostic nutritional index** | | 0.966 (0.928-1.005) | 0.088 |
| **CRP/PNI Ratio** | | 1.185 (1.038-1.352) | 0.012* |
| **CRP/Albumin ratio** | | 1.014 (1.003-1.025) | 0.014* |
| ***Multivariate Cox regression analysis*** | | | |
| **ASA Score** | Low | Reference | Reference |
| | High | 2.275 (1.219-4.245) | 0.010** |
| **Intensive care** | | 3.163 (1.239-8.075) | 0.016** |
| **Preoperative C-reactive protein** | | 0.993 (0.976-1.010) | 0.417 |
| **CRP/PNI ratio** | | 1.260 (0.477-3.329) | 0.641 |
| **CRP/Albumin ratio** | | 1.012 (0.931-1.101) | 0.773 |

* These p -values were less than 0.05 (Univariate analysis)
** These p -values were less than 0.05 (Multivariate analysis)
CI: Confidence interval, ASA: American Society of Anesthesiology, CRP: C-reactive protein, PNI: Prognostic nutritional index

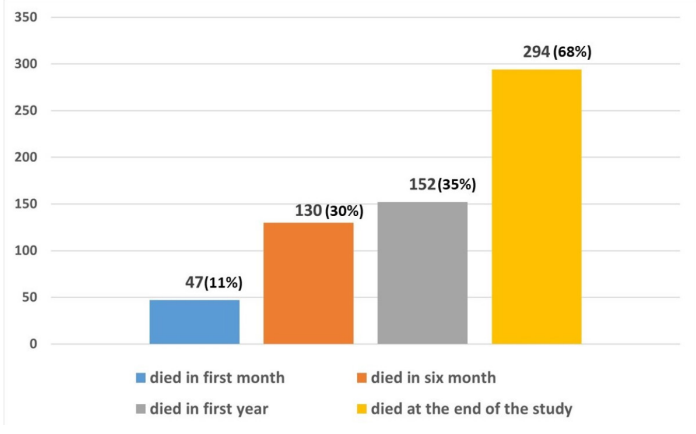


**Figure 2.** Illustration of the number of died patients in the study

| Table 3. Univariate and multivariate Cox regression analysis for patients who died in six months after surgery | | | |
|---|---|---|---|
| **Factors** | | **Hazard ratio and the 95% CI** | **p-value** |
| ***Univariate Cox regression analysis*** | | | |
| **Age** | | 1.012 (0.987-1.037) | 0.367 |
| **Sex** | | | |
| | Female | Reference | Reference |
| | Male | 1.437 (0.989-2.089) | 0.06 |
| **ASA Score** | Low | Reference | Reference |
| | High | 1.864 (1.283-2.708) | 0.001* |
| **Side** | Right | Reference | Reference |
| | Left | 1.176 (0.813-1.701) | 0.389 |
| **Delay to surgery** | | 1.024 (0.975-1.076) | 0.349 |
| **Hospital stay** | | 1.018 (1.004-1.032) | 0.01* |
| **Intensive care** | No | Reference | Reference |
| | Yes | 2.348 (1.448-3.809) | <0.001* |
| **Type of anesthesia** | Spinal | Reference | Reference |
| | General | 1.256 (0.775-2.037) | 0.355 |
| **Type of fracture** | Intertrochanteric | Reference | Reference |
| | Collum | 1.192 (0.818-1.737) | 0.361 |
| **Preoperative C-reactive protein** | | 1.006 (1.003-1.008) | <0.001* |
| **Prognostic nutritional index** | | 0.973 (0.948-0.998) | 0.036* |
| **CRP/PNI ratio** | | 1.257 (1.154-1.369) | <0.001* |
| **CRP/Albumin ratio** | | 1.019 (1.012-1.026) | <0.014* |
| ***Multivariate Cox regression analysis*** | | | |
| **ASA Score** | Low | Reference | Reference |
| | High | 1.701 (1.160-2.494) | 0.07 |
| **Hospital stay** | | 1.013 (0.996-1.031) | 0.144 |
| **Intensive care** | | 2.060 (1.262-3.362) | 0.004** |
| **Preoperative C-reactive protein** | | 0.993 (0.981-1.005) | 0.269 |
| **Prognostic nutritional index** | | 1.005 (0.973-1.037) | 0.781 |
| **CRP/PNI ratio** | | 1.312 (0.652-1.071) | 0.446 |
| **CRP/Albumin ratio** | | 1.015 (0.963-1.071) | 0.568 |

* These p -values were less than 0.05 (Univariate analysis)
** These p -values were less than 0.05 (Multivariate analysis)
CI: Confidence interval, ASA: American Society of Anesthesiology, CRP: C-reactive protein, PNI: Prognostic nutritional index

Malnutrition is linked to lower postoperative survival, delayed bone healing, increased surgical site infection, and higher rates of postoperative complications (18). Recently, PNI, CAR, and CPR have been investigated to assess patients' nutritional status. To our knowledge, this is the first study to examine these three items as a prognostic factor for mortality following surgically treated osteoporotic hip fractures in elderly patients. Ren et al. found that PNI was not associated with poorer survival, but the CPR was an independent predictor for 1-year mortality in their study (11). Capkin et al. (12) concluded that preoperative CAR can be used as a prognostic factor for 1-year mortality in patients over 65 years old who had a hip fracture. Belangero et al. (19) showed low preoperative albumin levels and high preoperative CRP levels were related to significantly higher mortality rates following surgically treated ITFF. But the results of our study were incompatible with the results in the current literature. This may be because the lower age limits of the patient groups evaluated in the studies were different, and the postoperative rehabilitation and follow-up protocols used in the studies were different as well.

Several studies studied mortality rates in different time periods after geriatric hip fracture surgery. Foss and Kehlet (20) showed a 13% mortality rate in the first month postoperatively after hip fracture surgery. The six-month mortality rates of elderly patients with hip fractures were reported to be 19.5% in the study by Zaki et al. (21) and

**Table 4. Univariate and multivariate Cox regression analysis for patients who died in first year after surgery**

| Factors | | Hazard ratio and the 95% CI | p-value |
|---|---|---|---|
| ***Univariate Cox regression analysis*** | | | |
| **Age** | | 1.002 (0.981-1.024) | 0.857 |
| **Sex** | | | |
| | Female | Reference | Reference |
| | Male | 1.234 (0.888-1.713) | 0.210 |
| **ASA Score** | Low | Reference | Reference |
| | High | 1.606 (1.167-2.209) | 0.004* |
| **Side** | Right | Reference | Reference |
| | Left | 1.049 (0.763-1.442) | 0.770 |
| **Delay to surgery** | | 1.034 (0.992-1.078) | 0.117 |
| **Hospital stay** | | 1.016 (1.003-1.030) | 0.014* |
| **Intensive care** | No | Reference | Reference |
| | Yes | 1.895 (1.288-2.788) | 0.002* |
| **Type of anesthesia** | Spinal | Reference | Reference |
| | General | 1.217 (0.798-1.856) | 0.363 |
| **Type of fracture** | Intertrochanteric | Reference | Reference |
| | Collum | 1.158 (0.610-1.605) | 0.377 |
| **Preoperative C-reactive protein** | | 1.005 (1.003-1.007) | <0.001* |
| **Prognostic nutritional index** | | 0.985 (0.964-1.007) | 0.170 |
| **CRP/PNI ratio** | | 1.234 (1.139-1.337) | <0.001* |
| **CRP/Albumin ratio** | | 1.017 (1.010-1.024) | <0.001* |
| ***Multivariate Cox regression analysis*** | | | |
| **ASA Score** | Low | Reference | Reference |
| | High | 1.482 (1.069-2.054) | 0.018** |
| **Intensive care** | | 1.631 (1.096-2.429) | 0.016** |
| **Hospital stay** | | 1.012 (0.996-1.028) | 0.136 |
| **Preoperative C-reactive protein** | | 0.993 (0.983-1.028) | 0.135 |
| **CRP/PNI Ratio** | | 1.231 (0.743-2.038) | 0.420 |
| **CRP/Albumin ratio** | | 1.020 (0.975-1.068) | 0.392 |

* These p-values were less than 0.05 (Univariate analysis)
** These p-values were less than 0.05 (Multivariate analysis)
CI: Confidence interval, ASA: American Society of Anesthesiology, CRP: C-reactive protein, PNI: Prognostic nutritional index

**Table 5. Univariate and multivariate Cox regression analysis for overall survival of the patients after surgery**

| Factors | | Hazard ratio and the 95% CI | p-value |
|---|---|---|---|
| ***Univariate Cox regression analysis*** | | | |
| **Age** | | 1.016 (1.001-1.031) | 0.040* |
| **Sex** | | | |
| | Female | Reference | Reference |
| | Male | 1.200 (0.945-1.523) | 0.135 |
| **ASA Score** | Low | Reference | Reference |
| | High | 1.584 (1.258-1.994) | <0.001* |
| **Side** | Right | Reference | Reference |
| | Left | 1.029 (0.819-1.295) | 0.804 |
| **Delay to surgery** | | 1.033 (1.003-1.064) | 0.033* |
| **Hospital stay** | | 1.018 (1.007-1.030) | 0.002* |
| **Intensive care** | No | Reference | Reference |
| | Yes | 1.088 (1.401-2.375) | <0.001* |
| **Type of anesthesia** | Spinal | Reference | Reference |
| | General | 1.159 (0.842-1.594) | 0.365 |
| **Type of fracture** | Intertrochanteric | Reference | Reference |
| | Collum | 1.065 (0.840-1.351) | 0.602 |
| **Preoperative C-reactive protein** | | 1.004 (1.002-1.005) | <0.001* |
| **Prognostic nutritional index** | | 0.986 (0.970-1.003) | 0.101 |
| **CRP/PNI ratio** | | 1.167 (1.091-1.248) | <0.001* |
| **CRP/Albumin ratio** | | 1.012 (1.007-1.018) | <0.001* |
| ***Multivariate Cox regression analysis*** | | | |
| **Age** | | 1.005 (0.989-1.022) | 0.528 |
| **ASA Score** | Low | Reference | Reference |
| | High | 1.520 (1.191-1.940) | <0.001** |
| **Intensive care** | | 1.590 (1.212-2.085) | <0.001** |
| **Delay to surgery** | | 1.015 (0.982-1.050) | 0.382 |
| **Hospital stay** | | 1.012 (0.997-1.027) | 0.128 |
| **Preoperative C-reactive protein** | | 0.994 (0.986-1.003) | 0.199 |
| **CRP/PNI ratio** | | 1.238 (0.814-1.884) | 0.318 |
| **CRP/Albumin ratio** | | 1.520 (1.191-1.940) | 0.555 |

*These p-values were less than 0.05 (Univariate analysis)
**These p-values were less than 0.05 (Multivariate analysis)
CI: Confidence interval, ASA: American Society of Anesthesiology, CRP: C-reactive protein, PNI: Prognostic nutritional index

25.0% in the study by Prodovic et al. (22). In their study, Bilsel et al. (15) reported a 35% 1-year mortality rate following hip fracture surgery. The mortality rates found in this study for the first month, six months, and one year following geriatric hip fracture surgery, were consistent with the literature.

Quach et al. (23) reported that the ASA score was independently associated with one-year mortality following hip fracture surgery. Paksima et al. (24) found that patients with a higher ASA score had a higher mortality rate following hip fracture. Bilsel et al. (15) showed that patients with high 3 or 4 ASA status had a significantly increased risk of mortality. We found a high ASA (3-4) score was independently related to poor survival in the first month, six months, one year, and overall follow-up period. Hasan et al. (25) found that the mortality rate of patients

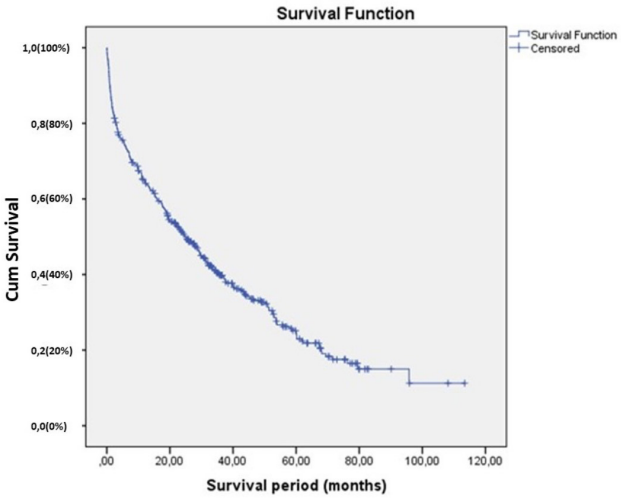


**Figure 3.** Kaplan-Meier survival curve of the patients included in the study

with postoperative ICU admission was significantly higher than those without admission to the ICU. Our findings were compatible with the current literature.

### Study Limitations

There are some limitations in the study. Firstly, our study includes a small number of patients. Secondly, there are several factors affecting mortality rates, such as dementia, dialysis, and preoperative mobilization status of the patient. They were not investigated in our study. Thirdly, we could not also assess the postoperative complications in detail because of the retrospective nature of our study. However, the nutritional indicators examined in our study have recently started to be used in clinical practice, and they are not frequently used in clinical orthopedic practice. The evaluation of these three new markers is the most important strength of our study. Because each of these indicators has been evaluated separately in the literature.

## Conclusion

Our results suggest that PNI, CAR, and CPR were not associated with poor survival in the first month, six months, one-year, and overall follow-up period following geriatric hip fracture surgery. Patients with a high ASA (3-4) score and those admitted to the postoperative ICU, on the other hand, should be closely monitored because they are more likely to die.

### Ethics

**Ethics Committee Approval:** This study was approved by the University of Health Sciences Turkey, Haseki Training and Research Hospital Ethics Commitee (IRB number: 2020-221).

**Informed Consent:** Informed consent was routinely obtained from all patients before surgery.

### Authorship Contributions

Concept: M.E., S.B., Design: M.E., S.B., E.G., M.Er., Data Collection and/or Processing: M.E., S.B., E.G., K.A.C., S.O.S., Analysis and/or Interpretation: M.E., S.B., M.Y., Literature Research: M.E., S.B., E.G., K.A.C., M.Er., Writing: M.E., S.B., M.Y.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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Case Report

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# Giant Pseudoangiomatous Stromal Hyperplasia of the Adolescent Breast: A Case Report with Emphasis on Image Findings and Literature Review

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**Abstract**

Pseudoangiomatous stromal hyperplasia (PASH) is a rare benign mesenchymal proliferation of the breast with unclear etiology. It is diagnosed in a wide spectrum from incidental microscopic findings to palpable breast mass. Diagnosis is generally made in the premenopausal age group. PASH cases seen in adolescents reported in the literature are very rare and none of them has mentioned the radiologic features in detail. In this case report, we present a 12-year-old patient with giant (150x100x127 mm in size) PASH in her right breast, giving emphasis to the findings of the ultrasonography and magnetic resonance imaging, including contrast-enhanced dynamic and diffusion-weighted imaging sequences. To the best of our knowledge, the present case is the second biggest giant PASH seen in the adolescent age.

**Keywords:** Pseudoangiomatous stromal hyperplasia, breast neoplasms, adolescent

## Introduction

Pseudoangiomatous stromal hyperplasia (PASH) is a rare benign mesenchymal proliferation of the breast that was first described by Vuitch et al. (1) in 1986. Even though the pathogenesis is unclear, either endocrine or exocrine stimulation may play a role in abnormal mesenchymal proliferation. PASH is diagnosed in a wide spectrum from incidental microscopic findings to palpable breast mass (2). It is most commonly seen in middle-aged premenopausal women (3). Only 25 of 200 cases reported as PASH in the literature were seen in the adolescent age group so far, with only 2 of them being more than 10 cm (4-6). In this case report, we presented a giant PASH case in an adolescent, giving emphasis to imaging findings. To the best of the authors' knowledge, this is the second biggest giant PASH seen in the adolescent age.

## Case

Informed consent was obtained verbally from the family of the child. A 12-year-old girl was admitted to the hospital with a palpable mass in her right breast that had grown rapidly in the last 8 months. Her menarche age was 11 with normal menstrual cycles. The right breast was asymmetrically big and sensitive on physical examination with no accompanying erythema, temperature change, or nipple retraction. The family history was unremarkable regarding breast cancer. On ultrasonographic (US) examination, a giant hypoechoic heterogeneous giant solid mass with scattered cystic areas inside (Figure 1). In short-tau inversion recovery (STIR) images, the lesion was heterogeneous hyperintense (Figure 2), and in the obtained axial T1W, contrast-enhanced image with a maximum intensity projection, the feeding artery was obviously seen (Figure 3). On performed gadolinium-enhanced magnetic resonance imaging (MRI), a Ta1-weighted image (T1WI) isointense mass lesion with sharp and lobulated contours and 150 x 100 x 127 mm in size was observed. The lesion showed persistent enhancement beginning from the early arterial phase (Figure 4) and no diffusion restriction with an ADC value of 1,327x10$^{-3}$ mm$^2$/s. MRI features were concordant with the BIRADS-3 lesion.

Due to the rapid increase in size, a tru-cut biopsy under US guidance was performed with a 14-gauge needle after obtaining a written consent form. In the pathology specimens, stromal proliferation with hyalinization around

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scattered sparse ducts was observed (Figure 5). Cells wrapping the pseudovascular spaces showed staining for CD34, vimentin, and alpha-smooth muscle actin and were negative for CD31 and Factor VIII. The pathology report revealed the diagnosis of PASH.

## Discussion

PASH is generally seen in premenopausal or postmenopausal women who are under hormone replacement therapy (2). A positive response to anti-estrogen medication like tamoxifen supports the hormonal effect in the pathogenesis of PASH (6). The size of PASH lesions commonly varies between 0.6 and 12 cm (7). However, PASH can present with giant breast lesions in the child age group, as seen in this study. Juvenile fibroadenoma, hamartoma, phyllodes tumors, and less frequent PASH and angiosarcoma were considered in the initial diagnosis of our case. Differential diagnosis with angiosarcoma is critical because it affects treatment.

The diagnosis of PASH radiologically is difficult as imaging features are generally nonspecific. Only 40% of the cases were diagnosed incidentally by imaging (2,7). PASH is generally seen as a hypoechoic, well-circumscribed solid lesion in the US. Solid lesions may contain scattered cystic areas seen as lace-like reticular components (6). Mammographic features of PASH vary from a well-defined mass to an asymmetrical density. The most common mammographic appearance is a noncalcified solid mass or localized increase in stromal composition. However, PASH was identified in only 31% of the patients with palpable masses in their breasts (8). Due to the age of the patient, we did not perform mammography in this study.

In parallel to mammographic imaging, PASH is seen varying from focal and segmental enhancing non-mass areas to well-defined circumscribed masses on MRI. Non-specific T1, T2 weighted imaging contrast enhancement patterns have been described in the literature. Reticular lines seen inside the mass are relatively diagnostic for PASH. This imaging feature was first described by Teh et al. (5) as high signal slit-like spaces on T2-weighted imaging and STIR. In our opinion; this pattern, if evident, is useful for the diagnosis, as it matches with dense collagen deposits that surround the less dense ducts on pathologic examination. Regarding contrast kinetic curves, a study with the largest case series of PASH so far demonstrated persistent (Type I) in 65%, washout (Type III) in 25%, and plateau-type (Type II) enhancement in 6% (9). The mass in this study had a Type I kinetic curve. Diffusion-weighted imaging characteristics and clear diffusion coefficient (ADC) values of PASH have not been defined in the literature so far. In this study, the ADC value was $1{,}327 \times 10^{-3}\ mm^2/s$, which corresponded to benign lesions. This value may

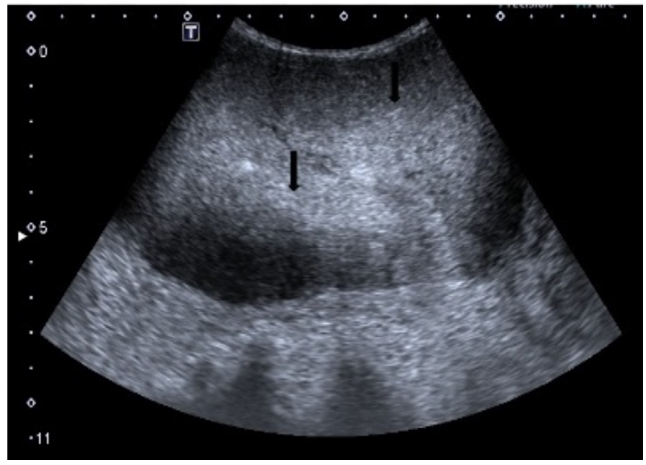

**Figure 1.** Ultrasonography shows lace like hyperechoic areas inside the mass lesion (black arrows)

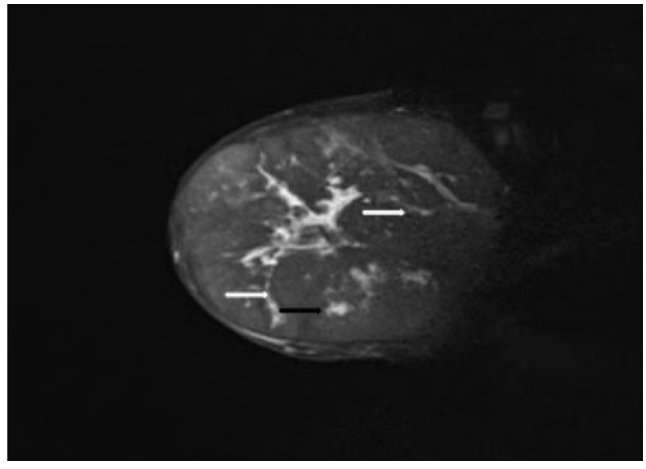

**Figure 2.** Sagittal T2WI of the right breast shows an abundant hyperintense linear lacelike network (white arrows) and cystic spaces (black arrow)

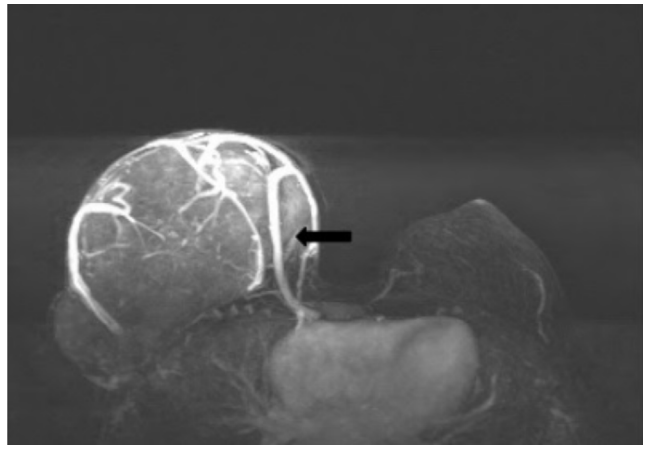

**Figure 3.** Axial MIP reveals a feeding vessel sign (black arrow)
MIP: Maximum intensity projection

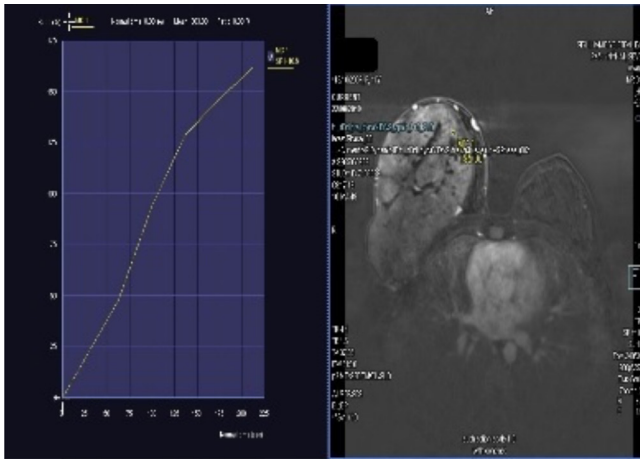

**Figure 4.** The kinetic curve shows persistent contrast enhancement

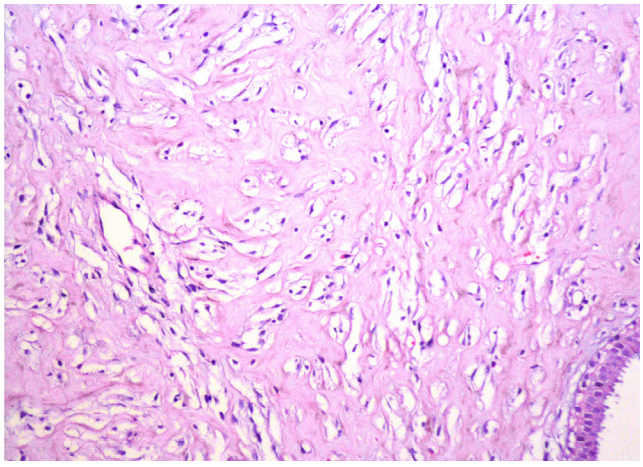

**Figure 5.** Anastomosing endothelial vascular like structures (pseudovascular spaces) scattered in hyalinised stroma (haematoxylin and eosin, magnification ×100)

exclude phyllodes tumors, angiosarcomas, or malignant mesenchymal tumors. Hamartomas and fibroadenomas can be included in the differential diagnosis. However, hamartomas typically contain intralesional fat and fibroadenomas have T2 hypointense septations inside.

This case highlights the radiological findings of a very rare and complex entity in the pediatric age group. Radiologists should be aware of the imaging findings of PASH. The differential diagnosis of PASH and angiosarcoma is crucial as these two lesions have similarities in clinical presentation, especially in giant sizes.

### Ethics

**Informed Consent:** Informed consent was obtained verbally from the family of the child.

### Authorship Contributions

Concept: B.D., B.A.U., Design: B.D., B.A.U., Data Collection or Processing: B.D., B.A.U., Analysis or Interpretation: B.D., B.A.U., Literature Research: B.A.U., Writing: B.A.U.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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Case Report

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# Management of Luc´s Abscess with Extraordinary Clinical Features Resulting in Bilateral Preseptal Cellulitis and Intracranial Complication: A Case Report and Current Literature Review

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**Abstract**

Luc's abscess is rarely seen complications of otitis media with case reports from the literature despite being known as a benign course. A few cases have been reported combined with chronic suppurative otitis media, unlike other subperiosteal abscesses due to otitis media. Although Luc's abscess is remarkable with its distinctive clinical features, early diagnosis may require high suspicion and sufficient clinical experience of clinicians. In case of clinical doubt, the clinician should not hesitate to request further research. A High-resolution computed tomography scan is necessary for determining the extent of disease and treatment planning as soon as possible. Here we present the case of a twelve-year-old boy with Down syndrome diagnosed with Luc's abscess involving the mastoid bone and developed preseptal cellulitis in both eyes progressed to life-threatening processes. We discussed the clinic features and decision of treatment options of the patients in the light of the literature.

**Keywords:** Otitis media, complication, preseptal cellulitis, Down syndrome

## Introduction

The complication process begins with bone destruction secondary to acute mastoiditis and then spreads the infection to the subperiosteal plane in patients with otitis media. A subperiosteal abscess is called depending on its location (1). Luc's abscess is only encountered in the case reports, even though it was presented as a relatively benign course compared to other subperiosteal abscesses (2,3). Another feature distinguishing Luc's abscess from other complications is the possibility of delay in differential diagnosis due to its rare nature (1). In order to prevent the process of life-threatening complications, early identification is vital. We have experienced that if adequate treatment is not given in time, its aggressive course may be inevitable and behave like a locally aggressive tumor.

This case is presented to guide the routes of infection, show the clinical symptoms that cause a life-threatening process, and emphasize the importance of timely surgical intervention in possible similar pathologies. In the light of the literature, we wanted to review the clinical approach and surgical planning process in these cases, especially during the pandemic.

## Case Report

A twelve-year-old boy with Down syndrome was consulted to our ENT clinic with suspicion of a preliminary diagnosis of sinusitis complication caused by swelling in the right eyelid by the Opthalmology department. He had a history of purulent, foul-smelling ear discharge from time to time for the last five years. Physical examination revealed inflammatory swelling of the mastoid area with anterior-inferior protrusion of the pinna. The inflammation extended from the temporo-zygomatic region to the right eye, and the examination was painful. The tympanic membrane was not evaluated due to the existing fragile polypoid tissue and edema of the external auditory canal on otoscopic

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examination. Another ENT examination excluding the narrow left external auditory canal was regular.

Laboratory analysis revealed increased C-reactive protein (CRP: 171,4 mg/L; normal<10.0) and leukocytosis (13,8K/uL). Covid PCR tests were done at 24-hour intervals, and they were all negative. Vital signs were within normal limits. There were no pathological findings in the Paranasal sinus computed tomography (CT) imaging.

However, contrast-enhanced high-resolution computed tomography (HRCT) of the temporal bone revealed a few interconnected abscess foci in which the most prominent diameter was 27x18 mm with ring enhancement patterns. Edema and cellulitis extended to the right eyelid and cheek above the temporo-zygomatic region. Both mastoid and middle ear cavities are filled by soft tissue density, and a linear bone defect on the tegmen tympany with existing pathological contrast enhancement was observed (Figure 1). The contrast-enhanced Magnetic Resonance Imaging (MRI) scan showed limited filling defect on the right sigmoid sinüs and hypoplasic contralateral sigmoid sinus.

Based on these findings, the patient was hospitalized with the diagnosis of Luc's abscess caused preseptal cellulitis. He was commenced on intravenous (IV) empirical antibiotherapy. In addition, the infectious diseases department suggested adding vancomycin to medical treatment because bilateral preseptal cellulitis occurred with clinical progression despite being treated for three days (Figure 2). The culture of the purulent discharge did not allow a microbiological differential diagnosis. Following clinic regression, a right radical mastoidectomy, repair of CSF leakage, and meatoplasty were performed under general anesthesia after written informed consent was obtained from the patient's parents. During the surgery, we encountered a mastoid bone defect in the Macewen triangle with pus discharge together with widespread destruction of all mastoid cells, middle ear structures, lateral semicircular canal, tympanic segment through the facial nerve's second bend, and the tympanic tegmen caused a visible CSF leak. In addition, the peri-sinusoidal extradural abscess was observed with filled hemorrhagic granulation tissue and cholesteatoma in the mastoid cavity. Following surgery, our patient made an uneventful recovery. Postoperative facial nerve functions were normal. He was discharged with microbiological advice on a two-week oral and topical antibiotics course on the 10$^{th}$ postoperative day. The patient was well and asymptomatic (Figure 3). He completed the 15$^{th}$ month postoperatively with healing and is still under close monitoring and follow-up.

## Discussion

Henri Luc, in 1913 first described a subperiosteal abscess spreading to the temporo-zygomatic region

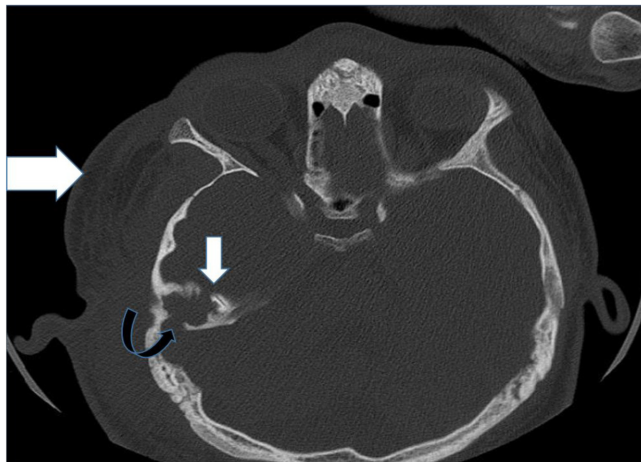

**Figure 1.** An axial plan CT scan of the temporal bone. Soft tissue density completely filling the right external ear canal, middle ear, mastoid bone, marked edema, the right temporo-zygomatic region (white wide arrow), tegmen defect area (white thin arrow), and defect of the parasigmoidal sinus region (black arrow)

CT: Computed tomography

**Figure 2.** The right temporal swelling extended anteriorly to the right zygoma and bilateral preseptal cellulitis in a patient with Down syndrome (black arrow). The picture was published with the permission of the patients' parents

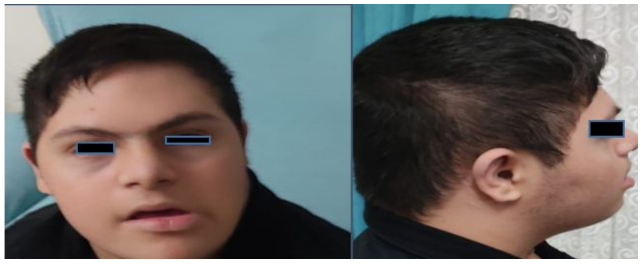

**Figure 3.** In the current image of the patient after 15 months postoperatively, it is seen that there is no sign of temporal swelling and preseptal cellulitis. The picture was published with the permission of the patients' parents

after acute otitis media without mastoid involvement. He claimed that the infection in the middle ear reaches the temporo-zygomatic region through the Rivinus notch from the submucosa of the middle ear or branches of the deep auricular artery. He also argued that the cases of Luc's abscess showed a more benign clinical course since there was no mastoid bone involvement and mastoidectomy was not necessary for their treatment. Although it is already an infrequent clinical entity, we found that case reports supported this theory when we scanned the literature (4). As in our case, Luc abscess cases accompanied by chronic otitis media and mastoid involvement were limited to only a few cases (2,3,5,6). However, we did not find a case report with bilateral preseptal cellulitis accompanied by severe life-threatening complications as a clinical course.

Fernandez et al. (2) reviewed English-language literature to evaluate clinical features and management of Luc's abscess cases from 1989 to 2018. A total of 21 cases (17 children and four adults) were found in the literature. It was observed that only one patient had no signs of mastoiditis in his own CT scan. These patients have been treated with abscess drainage alone, myringotomy with abscess drainage, or mastoidectomy. Although the clinical features of Luc's abscess are relatively stable, it has been emphasized that clinical and radiological evaluation is absolutely necessary before deciding to avoid mastoidectomy, especially in a pediatric patient.

Temporal space abscesses usually originate from an odontogenic infection or acute otitis media. Whereas the most frequent cause of ocular signs is seen in children with an orbital complication of acute sinusitis, the first clinical sign of Luc's abscess may be cellulitis extending from the temporo-zygomatic region to the eye (2,3,7). When examining a child with Down syndrome, difficulties are performing a radiological examination and physical examination due to poor patient cooperation and various structural anomalies such as stenosis of the external auditory (8,9). Therefore, clinical diagnosis can only rely on the physical examination and imaging techniques in a mentally challenged patient. Unfortunately, our patient with Down syndrome was consulted to our clinic after Luc's abscess had already developed clinically for many possible reasons.

Only 14% of Luc's abscess cases are associated with cholesteatoma (2). We have not encountered such an uncontrolled case of CSOM with cholesteatoma in our routine practice for decades. The conditions of the pandemic period may have caused several challenges to the priorities of both patients and clinicians, even though the only effective treatment for cholesteatoma is still on-time surgery (7,10). We encountered widespread pathological damage caused by cholesteatoma during the surgery in our patient. This case reminds us that CSOM with cholesteatoma behaves like a locally aggressive tumor and should not be considered an elective case, especially during the pandemic.

HRCT temporal bone scan is necessary to confirm the disease's diagnosis and extension, exclude mastoid involvement, intracranial or extracranial complications. It should not be forgotten that extradural abscess is one of the intracranial complications of CSOM that can only be diagnosed during the surgery as seen in our patient (10,11). The necessary surgical interventions should be decided by considering each child's benefit/loss ratio. It was learned that temporal CT was not requested in clinical follow-ups until the consultation was requested from our clinic with a pre-diagnosis of sinusitis complication in our case.

We encountered the child patient with Luc's abscess and an aggressive clinical course. Moreover, this case was perhaps the most advanced form with multiple CSOM complications and bilaterally preseptal cellulitis in the literature. Therefore, clinicians must remain alert for clinical signs and symptoms to examine these patients for the presence of more than one complication. It should be kept in mind that cholesteatoma deprived of early diagnosis and appropriate treatment shows a locally aggressive tumor behavior by its nature.

In conclusion, in case of any doubt during clinical follow-up, evaluating these patients with contrast-enhanced temporal CT may be a vital decision. It should be kept in mind that the clinical course may be more aggressive, especially in comorbid patients who remain uncontrolled with a prolonged suppuration phase.

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**Authorship Contributions**

Concept: M.U., Design: M.U., Data Collection or

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