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Original Article

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The Effect of Post-extubation Nasal HFOV Support on Extubation Success in Premature Babies in the Neonatal Intensive Care Unit

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Abstract

Aim: Currently, it is recommended to use the nasal intermmittent positive pressure ventilation (NIPPV) mode after extubation. The nasal high-frequency oscillator ventilation (NHFOV) mode, which does not require synchronization, is being investigated to be used as a non-invasive ventilation mode. We aimed to compare the effect of NHOFV and NIPPV used after extubation.

Methods: Our study was a randomized controlled study, and according to the power analysis results, 82 patients were included. The study was performed between September 2022 and March 2023. Post-extubation, the patients were randomly assigned to the NHFOV and NIPPV modes. Patients reintubated within the first 72 hours were considered extubation failures. The extubation success rate, demographic and clinical data, and blood gas values of the patients were analyzed.

Results: A total of 82 patients were evaluated. No statistically significant difference was found when the extubation success rate was compared in the NHFOV and NIPPV groups (respectively, 80.5% and 73.2%, p=0.432). The partial carbon dioxide pressure was found to be statistically significantly lower in the NHFOV group [respectively, 44.156±12.067 mmHg and 50.634±11.886 mmHg (p=0.017)].

Conclusion: Nasal high-frequency oscillator ventilation is at least as effective as NIPPV for use after extubation. Normalization of blood gas and fewer side effects are promising for routine use.

Keywords: Nasal intermittent positive-pressure ventilation, non-invasive high-frequency oscillatory ventilation, preterm infant, extubation success

Introduction

Respiratory support is a lifesaving practice for newborns, especially for premature infants. Non-invasive ventilation (NIV) is positive pressure ventilation support, without intubation, provided using various interfaces to patients with adequate respiratory effort. Non-invasive ventilation support plays an important role in the management of respiratory distress in premature infants. Despite NIV support and surfactant therapy, some patients may still require invasive mechanical ventilation (1). Prolonged invasive ventilation increases the risk of morbidity and mortality in these infants (2,3). Therefore, the management of such patients should focus on minimizing intubation and reducing its duration as much as possible (1).

Various NIV strategies have been developed to reduce the need for invasive mechanical ventilation. Providing NIV support to patients after extubation reduces the reintubation rate. Non-invasive ventilation can be applied in various ways such as nasal continuous positive airway pressure (NCPAP), nasal intermittent positive-pressure ventilation (NIPPV), and high-flow nasal cannula. Nasal continuous positive airway pressure has been used successfully for nearly 50 years (4). Recent

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studies have shown the use of NIPPV after extubation reduces reintubation, the need for surfactant, and air leaks compared to NCPAP (5). High-frequency oscillator ventilation (HFOV) is a mode of ventilation that employs tidal volumes less than dead space and is effective in eliminating carbon dioxide by providing constant lung expansion (6). Today, the increase in the successful use of invasive HFOV has led to the consideration of using nasal high-frequency oscillator ventilation (NHFOV). Although there are studies in the literature showing that the use of NHFOV post-extubation is as effective as the NIPPV mode, it is not sufficient to recommend it for routine use (7-10).

In this study, we aimed to investigate the effectiveness of post-extubation NHFOV on extubation success compared to NIPPV. In this way, we hope to decrease the reintubation rates among premature infants and protect them from the harms associated with long-term intubation.

Materials and Methods

Compliance with Ethical Standards

This study was conducted in the Neonatal Intensive Care Unit of Sanliurfa Harran University Training and Research Hospital. Ethical approval from Harran University Clinical Research Ethics Committee was obtained prior to the study (approval no.: HRÜ/22.14.18, date: 25.07.2022).

Study Design and Patients

This randomized controlled study was performed between September 2022 and March 2023. The study was carried out in accordance with the Helsinki Declaration. Infants with a gestational age of 26-34 weeks were included in the study. Infants who were intubated within first hour after birth and remained intubated for at least 12 hours were included in the study. Patients with severe central, cardiac and chromosomal anomalies were not included in the study. Informed consent was obtained from the parents before the study.

Demographic and clinical characteristics of the patients (birth weight, gestational age, gender, mode of delivery, 1st and 5th minute APGAR score, surfactant requirement, postnatal day of extubation) were obtained. Post-extubation, patients were placed on NIV support using NIPPV and NHFOV modes. Extubation patients who were reintubated within 72 hours of NIV support was considered unsuccessful. The nutritional status of the patients was also recorded while under NIV support. During follow-up with NIV, any deterioration in the nutritional plan of the patients due to vomiting, gastric residue, or abdominal distension (reducing the nutritional volume by at least half or skipping 2 consecutive nutrition feeds) was considered feeding intolerance (11). In addition, blood gases taken 1 hour after extubation of the patients were evaluated.

Randomization and Bliding

Infants who met the inclusion criteria and were extubated on nasal respiratory support were randomly divided into two groups. As a randomization method, the "Simple Randomization (or Complete Randomization)", which is known as the assignment of individuals who meet the criteria for participation in the study to the groups with equal chance, completely randomly and regardless of the previous assignment, was used (12). An open-label study design was used (13). Using sealed envelopes for randomization, patients were divided into two groups: NIPPV and NHFOV, according to the nasal respiratory support mode used after extubation.

NIV Protocol

All patients were taken to NIV support with the Leoni Plus ventilator (Löwenstein Medical, Bad Ems, Germany), device, and nasal mask (Medin Medical Innovations GmbH, Olching, Germany). In our clinic, initial NIPPV values are set at positive end-expiratory pressure 5-7 cmH_2O, peak inspiratory pressure 15-20 cmH_2O, frequency 30-40/min, inspiratory time 0.4 sec, and fraction of inspired oxygen (FiO_2) at 0.21-0.50 according to the target oxygen saturation range (90-95%). Initial NHFOV values include: frequency 10-12 Hz, inspiration: expiration ratio 1:1, amplitude 20-30 cmH_2O, pressure mean 8-10 cmH_2O, and FiO_2 is set to 0.21-0.50 according to the target oxygen saturation range (90-95%). In NHFOV mode, we do not expect a visible tremor like in invasive HFOV. The machine sound can be detected while listening to the patients' respiratory sounds. Also, in NIPPV mode, detecting the PEEP by listening to the patient's respiratory sound shows that nasal support has started effectively. In the follow-ups, the settings are changed according to the patient's clinical condition, chest X-ray, and blood gas values. Patients with clinical signs of severe respiratory distress (tachypnea, retraction) on NIV support, patients with the partial carbon dioxide (PCO_2) pressure value above 65 mmHg, patients with a persistent FiO_2 requirement of more than 0.50 to reach the target oxygen saturation level, and patients who experience frequent apnea attacks or need positive pressure ventilation more than twice a day were reintubated.

Statistical Analysis

The method used to determine the sample population of the study is "Systematic Sampling". When Type 1 error amount (alpha) was 0.05, test power (1-beta) was 0.90, effect size was 0.65 (large), and alternative hypothesis (H1) was two-sided, the required minimum sample size to find a statistically significant difference between the NIPPV and NHFOV groups was determined. The study should include a total of 82 individuals, with 41 participants in each group. Sample size calculations

were performed using G*Power version 3.1.9.7 (14). The Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, USA) was used for statistical analysis of the research data. The Shapiro-Wilk test was used to check the conformity of continuous variables with normal distribution. Independent Student's t-test was used for two independent group comparisons of normally distributed variables, and Mann-Whitney U test was used for two independent group comparisons of non-normally distributed variables. Normally distributed continuous data were expressed as mean ± standard deviation, and non-normally distributed continuous data were expressed as median (minimum-maximum). The relationship between categorical variables was tested with chi-square and Fisher's exact analysis. P<0.05 was considered statistically significant.

Results

Our study group, consisting of 82 patients, was all infants who were intubated due to respiratory distress within the first hour after birth. The median gestational age of our patients was 29 weeks (26-33) and the median birth weight was 1265 grams (800-2350). Patients were divided into NIPPV and NHFOV groups, with 41 patients in each group. Both groups had statistically similar characteristics in terms of gestational age, birth weight, gender, mode of delivery, and APGAR scores. Patients were extubated on nasal respiratory support on the median day 2, with a range of 1-15, and postnatal extubation days were statistically similar in both groups. The extubation success rate was 76.8% in our patients extubated to nasal respiratory support. No statistically significant difference was found when the extubation success rate was compared in the NHFOV and NIPPV groups [respectively, 80.5% and 73.2%, (p=0.432)]. Feeding intolerance developed in a total of 9 patients, and no statistical difference was found between the two groups (Table 1).

When the blood gas values taken after extubation were compared between the two groups, the PCO_2 was found to be statistically significantly lower in the NHFOV group [respectively, 44.156±12.067 mmHg and 50.634±11.886 mm/Hg (p=0.017)] (Table 2).

Table 1. Demographic and clinical data of patients

	All patients (n=82)	NIPPV group (n=41)	NHFOV group (n=41)	p-value†
Gestational age week*	29 (26-33)	29 (26-33)	29 (26-33)	0.260
Birth weight g*	1265 (800-2350)	1180 (800-2070)	1400 (830-2350)	0.066
Gender (Female) n (%)	39 (47.6)	19 (46.3)	20 (48.8)	0.825
Mode of delivery (Caesarean) n (%)	73 (89)	36 (87.8)	37 (90.2)	1.000
1st min APGAR score*	6 (2-8)	6 (2-8)	7 (2-8)	0.247
5th min APGAR score*	8 (4-10)	8 (5-10)	8 (4-9)	0.550
Need for surfactant n (%)	57 (69.5)	27 (65.9)	30 (73.2)	0.472
Postnatal day of extubated day*	2 (1-15)	2 (1-15)	2 (1-12)	0.625
Extubation success rate n (%)	63 (76.8)	30 (73.2)	33 (80.5)	0.432
Nutritional intolerance n (%)	9 (11)	6 (14.6)	3 (7.3)	0.482

*Values are given as median (minimum-maximum) and Mann-Whitney U test was used
Categorical variables are given as persentages and chi-square/Fisher's exact test was used
†Results of statistical comparisions betwen NIPPV and NHFOV groups
NIPPV: Nasal intermmittent positive pressure ventilation, NHFOV: Nasal high-frequency oscillator ventilation, min: Minute

Table 2. Blood gas values taken in the first hour after extubation

	All patients (n=82)	NIPPV group (n=41)	NHFOV group (n=41)	p-value†
Ph**	7.309±0.090	7.296±0.091	7.322±0.089	0.185
The partial pressure of carbon dioxide** mmHg	47.395±12.340	50.634±11.886	44.156±12.067	0.017
Bicarbonate** mmol/L	20.172±2.483	20.404±2.441	19.940±2.533	0.399
Base excess** mmol/L	-4.814±2.903	-4.530±2.76	-5.100±3.046	0.377
Lactate*	1.8 (0.5-7)	1.6 (0.5-6.3)	1.90 (0.79-7)	0.138

*Values are given as median (minimum-maximum) and Mann-Whitney U test was used
**Values are given mean ± standard deviation and the Independent Samples t-test was used
†Results of statistical comparisions betwen NIPPV and NHFOV groups
NIPPV: Nasal intermmittent positive pressure ventilation, NHFOV: Nasal high-frequency oscillator ventilation

Discussion

Successful extubation strategies represent an important issue, and are under continuous investigation. Early and successful extubation prevents mortality and many morbidities (1). In our study, we investigated the effect of NHFOV and NIPPV modes used in NIV ventilatory support after extubation on extubation success. We found that NHFOV was at least as effective as NIPPV in the first 72 hours after extubation.

Nasal intermittent positive-pressure ventilation is recognized as the best modality after extubation for successful transition of infants from invasive to non-invasive modes. However, the lack of synchronization may reduce the success of NIV support (6). The idea that NHFOV will be more effective in extubation success is currently being considered. Research on this subject continues. Nasal high-frequency oscillator ventilation can be viewed as a combination of invasive HFOV and NCPAP. It increases the effectiveness of NIV support by reaching higher pressure values due to overlapping vibrations of the gas. It is also an important advantage that it does not require synchronization (15,16). In a study comparing NHFOV and NCPAP, NHFOV was proven to have better extubation success than NCPAP (8). A recent meta-analysis published in 2023 found that NHFOV reduced intubation and reintubation rates in premature infants compared to NCPAP. Additionally, it did not lead to an increase in complications potentially associated with NIV (17). In a study of infants with RDS born below 32 weeks, the NIPPV and NHFOV modes were found to be more appropriate for post-extubation use than NCPAP (18). Seth et al. (10) found that there was no difference between NHFOV and NIPPV modes used post-extubation in terms of extubation failure in their study. A meta-analysis published in 2023 included eight studies comparing NIPPV and NHFOV involving 1603 patients. Nasal high-frequency oscillator ventilation was found to reduce reintubation rates without increasing adverse outcomes (19). The meta-analysis, which included 23 studies involving 2331 newborns, determined that the NHFOV mode was the most effective option post-extubation (20). In our patients, we found that the extubation success of the NHFOV group was proportionally higher, although there was no statistical difference.

Carbon dioxide level is an indicator of adequate ventilation. In intensive care patients, blood gas carbon dioxide levels are closely monitored and the patient's ventilation support is adjusted. Hypercarbia is an important cause of reintubation. An advantage over NIPPV in NHFOV mode is that it is more efficient at eliminating carbon dioxide. Studies have found that NHFOV is more effective in reducing pCO_2 and normalizing blood gas levels (16,18,21). In our study group, we found that pCO_2 was lower in the NHFOV group, which is consistent with findings reported in the literature. Nasal high-frequency oscillator ventilation is not routinely used in clinics. For patients who need reintubation due to hypercarbia while in NIPPV mode, trying NHFOV mode before reintubation may help avoid unnecessary intubation.

Complications such as pulmonary air leaks and feeding intolerance may occur with NIV support (15,22). An experimental study involving 8 lambs found that the NHFOV mode significantly inhibited gastroesophageal reflux (23). In a study of 81 infants with RDS, the NHFOV mode was shown to significantly reduce the need for invasive mechanical ventilation compared to NCPAP, without increasing the incidence of side effects (24). During NIV support, abdominal distension due to the passage of gas into the gastrointestinal system may cause feeding intolerance (22). In our study, pulmonary air leakage did not develop in any of our patients. However, feeding intolerance occurred in nine patients, with a lower incidence observed in the NHFOV group, though the difference was not statistically significant. On the other hand, all our patients with feeding intolerance were immature infants, weighing less than 1000 g. Although NHFOV appeared to be safer in terms of nutritional intolerance, it was not possible to directly connect the experienced nutritional intolerance to NIV support.

Study Limitations

Our study was limited due to being single-center and having a limited number of cases. In addition, our patients were only followed for the first 72 hours after extubation, and the lack of long-term results is a limitation of our study. Despite these limitations, It also has strengths such as being a randomized controlled trial and being a current and important issue for premature babies.

Conclusion

We found that NHFOV was at least as effective as NIPPV in NIV support in the first 72 hours after extubation. Nasal high-frequency oscillator ventilation seems more promising than NIPPV regarding side effects and blood gas values. The carbon dioxide levels of patients placed on NHFOV post-extubation were lower than in patients monitored on NIPPV. It can be speculated that patients monitored on NHFOV mode may need closer carbon dioxide level monitoring. More randomized controlled studies are needed on this subject.

Ethics

Ethics Committee Approval: Ethical approval from Harran University Clinical Research Ethics Committee was obtained prior to the study (approval no.: HRÜ/22.14.18, date: 25.07.2022).

Informed Consent: Informed consent was obtained from the parents before the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.F.D., H.A., M.K., A.B., I.Y., Concept: M.F.D., H.A., Design: M.F.D., H.A., Data Collection or Processing: M.F.D., H.A., M.K., A.B., I.Y., Analysis or Interpretation: M.F.D., Literature Search: M.F.D., Writing: M.F.D.

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Original Article

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Sodium/Potassium-transporting ATPase Subunit Alpha-3 Antibody is not Present in Patients with Idiopathic Intracranial Hypertension

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Abstract

Aim: Increased cerebrospinal fluid (CSF) oligoclonal band prevalence, elevated cytokine levels, glial antibodies, and positive response to steroids have been described in idiopathic intracranial hypertension (IIH), suggesting autoimmune etiology in this disease. Sodium/potassium ATPases have been implicated in CSF production. Our objective was to discern unprecedented autoantibodies specific for sodium/potassium-transporting ATPase subunit alpha-3 (ATP1A3) in IIH.

Methods: Sera obtained from 31 individuals clinically diagnosed with IIH and 20 healthy control subjects were subjected to indirect immunofluorescence staining using live cultured rat brain neurons and HEK293 cells transfected with ATP1A3 cDNA.

Results: Autoantibodies targeting neuronal cell surface antigens were identified in three patients diagnosed with IIH. However, serum samples from IIH patients and healthy controls did not react with ATP1A3-transfected cells.

Conclusion: Our results indicate that ATP1A3 antibodies do not have a primary role in IIH pathogenesis. However, we provide preliminary support for the presence of anti-neuronal autoimmunity.

Keywords: Idiopathic intracranial hypertension, autoimmunity, antibody, sodium/potassium-transporting ATPase

Introduction

Idiopathic intracranial hypertension (IIH) is a disease characterized by elevated intracranial pressure (ICP) without any specified reason (1). Since this disease is a diagnosis of exclusion, it is crucial to evaluate secondary reasons that could cause an increase in ICP (2).

Clinically, headache, transient visual obscurations, pulsatile tinnitus, and neck and low back pain are the most common symptoms of the disease (3). If left untreated, optic atrophy and permanent vision loss may develop due to papilledema (4). While the disease is seen with a frequency of 0.5-2 per 100,000 in the general population, this rate rises to 12-20 per 100,000 in obese women of reproductive age, the population in which the disease is most common (5-8).

Although speculations such as cerebrospinal fluid (CSF) overexpression, deterioration in CSF drainage, and an increase in venous pressure that may cause impairment of CSF dynamics have been put forward, the pathogenesis of the disease is still not clearly identified (1). The strong link between IIH and obesity suggests that inflammation from fat cells might be involved in causing the disease; supporting this idea, levels of CCL2 and leptin were found to be higher in the CSF of IIH patients than in those without the condition (9). Increased prevalence of the disease in women of childbearing age has raised the possibility that hormonal factors may also be important. The activity of the 11β-hydroxysteroid dehydrogenase type 1 enzyme, which is an enzyme in glucocorticoid metabolism, is found to be related to CSF dynamics and may have a role in the pathogenesis of the disease (10).

Detection of oligoclonal bands (OCB) in CSF samples of IIH patients suggested that the disease could have an immunogenic background (11). Aquaporin-4 (AQP-4),

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which is a well-known water channel protein associated with water homeostasis and an antigenic target for neuromyelitis optica, has been investigated as a potential immunogenic target in IIH cases. However, different study groups have failed to establish anti-AQP-4 antibodies in serum and CSF samples of IIH patients (9,12).

Similarly, the screening of antibodies against the myelin oligodendrocyte glycoprotein antigen has also been negative. On the other hand, strong immunoreactivity with membrane antigens of hippocampal and cortical neurons was observed in sera of IIH patients, suggesting that autoantibodies directed against the neuronal surface antigens may have a role in the pathogenesis of IIH. In light of these findings, serum samples from 34 IIH patients were screened for antibodies against common neuronal surface antigens, such as NMDAR, AMPAR, CASPR2, LGI1, and GABABR, with the commercial cell-based assay (CBA) kit, and none of them were positive (13).

The perivascular astrocytic end-feet have received attention due to the close association of their area with water homeostasis in IIH pathogenesis. To establish any potential role of the anti-glial humoral response, antibodies against glial fibrillary acidic protein (GFAP) were screened in the serum samples of 58 IIH patients with live cell CBA and identified in 2 patients (14). Another study group has reported a single case of IIH with anti-GFAP antibodies in the CSF sample (15). However, because the GFAP antigen is an intracytoplasmic antigen, it was thought that anti-GFAP antibodies may not have a pathogenic role; instead, this positivity may occur as a secondary phenomenon. Nevertheless, the findings also suggest that an anti-glial immune response against an as yet unidentified target antigen may play a role in the disease pathogenesis.

Various transporters expressed in the choroid plexus (CP) can participate in CSF production. It is known that in the CP epithelium, sodium potassium (Na/K) ATPase modulates the osmotic gradient and water transport (16). The functionality of the Na/K ATPase is important for CSF production because ouabain, the Na+/K+-ATPase inhibitor, reduces CSF production by 50% (17). Furthermore, autoantibodies against sodium/potassium-transporting ATPase subunit alpha-3 (ATP1A3) have been detected in two clinical cases of paraneoplastic syndrome (18,19).

The aim of the study was to screen autoantibodies specific to ATP1A3 in IIH.

Materials and Methods

Compliance with Ethical Standards

Ethical approval of the study was obtained from the Istanbul University, Istanbul Faculty of Medicine, Clinical Research Ethics Committee (date: 12.12.2023, and approval number: 24). The study followed the guidelines set forth in the Helsinki Declaration II. The informed consent forms of all the subjects who participated in the study were signed by patients.

Participants

All assays employed a control group comprising twenty healthy individuals matched for age and gender. We incorporated thirty-one adult patients who were diagnosed with IIH using the updated diagnostic criteria (20). These individuals were monitored at our headache outpatient clinic for a period exceeding one year. The demographic and clinical characteristics of the patients are detailed in Table 1.

Investigation of Anti-neuronal Antibodies

All participants' sera were stored at -80 °C until analysis. All patients were treatment-naive and symptomatic at the time of sera collection. Antibodies for NMDAR, AMPAR, LGI1, CASPR2, GABABR, GAD, and glycine receptor were investigated by CBAs utilizing human embryonal kidney 293 (HEK293) cells, as described previously (Euroimmun, Luebeck, Germany). ATPase subunit alpha-3 antibodies were investigated in HEK293 cells transfected with ATP1A3 cDNA by immunofluorescence staining, as per the manufacturer's instructions (Euroimmun) (18,19). As a positive control, a murine monoclonal antibody against the cytoplasmic N-terminus of ATP1A3 (Dianova, Hamburg, Germany) followed by anti-mouse IgG-Cy2 (Jackson Research, Suffolk, UK) was used as reported previously (19).

Immunofluorescence on Live Neurons

The immunoreactivity of IgG against neuronal surface antigens was evaluated using a CBA using rat cortical neurons isolated from newborn rat embryos (P1), as

Table 1. Demographic and clinical features of the patients

Clinical characteristics	**n=31**
Age (Mean ± SD)	32.61±9.53
Gender (Female/Male)	28 (90.3%)/3 (9.7%)
BMI (Mean ± SD)	33.46±6.96
Onset of the disease (age) (Mean ± SD)	29.78±8.12
Disease duration (month) (Mean ± SD)	82.15±56.27
First symptom (%) Headache Vision disturbances	 90.48 9.52
Symptoms (%) Blurred vision Tinnitus Diplopia Papilledema Vision lost	 90.48 63.66 9.1 82.61 27.27
CSF opening pressure (mmH_2O) (Mean ± SD)	402.27±160.48

SD: Standard deviation, BMI: Body mass index, CSF: Cerebrospinal fluid

described (21). Cultured neurons were incubated with sera (1:250) in a neurobasal medium for one hour at room temperature. Following this incubation, neurons were fixed using 3% paraformaldehyde and subsequently exposed to a 1:100 dilution of Alexa Fluor 488-conjugated anti-human IgG (Abcam, Cambridge, UK) for 45 minutes. The evaluation of immunostaining was conducted using an inverted fluorescence microscope (Leica Microsystems Ltd., Heerbrugg, Switzerland). Positive outcomes were identified by the presence of a green color, which was generated through the binding of a secondary antibody and displayed a range from moderate to strong intensity.

Statistical Analysis

No statistical analysis was conducted due to the descriptive nature of our study.

The power analysis was conducted based on the antibody positivity rate of 3% detected in our previous GFAP study. In the power analysis, the required number of patients to be included in the study was determined by setting the type 1 error (alpha) at 0.05 and the type 2 error (beta) at 0.20 (14).

Results

Identification of IIH Patients with Neuronal Surface Antibodies

To analyze serum antibodies targeting neuronal surface antigens, we employed a specialized immunocytochemistry method. To prevent antibodies directed against intracellular antigens, sera were added to cell culture before fixation and permeabilization steps. This approach revealed serum IgG specifically reacting with cell surface antigens and axonal-dendritic projections in cultured neurons in 3 out of 31 IIH patients, while none of the 20 healthy controls exhibited such reactivity (Figure 1). None of the IIH, or healthy control, sera tested positive for well-characterized anti-neuronal antibodies investigated through CBAs. This observation indicates that the binding of neuronal surface IgG in IIH sera was not attributable to well-characterized anti-neuronal antibodies associated with autoimmune encephalitis. Likewise, neither the IIH serum nor the healthy control serum reacted with ATP1A3 transfected HEK293 cells. In contrast, the commercial monoclonal antibody for ATP1A3, which served as a positive control, reacted strongly with ATP1A3 transfected cells, but did not react with cells that had other neuronal antigen cDNAs (Figure 2).

Discussion

In our previous study, GFAP and CACNA1H antibodies were detected in two different headache syndromes (14,22). In this study, we exclusively examined neuronal cell-surface antibodies, focusing on their pathogenic effects in autoimmune encephalopathies (23,24). In 9.7% of patients with IIH, we detected rare neuronal surface antibodies, potentially contributing to the pathogenesis of IIH by reacting with neuronal membrane antigens. However, a newly discovered putative neuronal surface antibody targeting ATP1A3 was not found in IIH patients. Previously, we had established that individuals with IIH display CSF OCB, elevated levels of serum/CSF cytokines and pro-inflammatory adipokines, and increased levels of neuron-specific enolase, serving as an indicator of neuronal damage (11,25,26). In addition, we also identified anti-GFAP antibodies in some IIH patients, indicating anti-astrocyte autoimmunity in this disorder (14). Our current findings substantiate the proposition that individuals with IIH may indeed host antibodies targeting neuronal surface proteins. In aggregate, these outcomes strongly imply that inflammation and potentially antigen-specific autoimmunity play a role in the pathogenesis of IIH.

The sodium/potassium transporting ATPase, a pivotal cellular component, consists of a catalytic alpha subunit, an ancillary non-catalytic beta subunit, and an additional regulatory subunit. *ATP1A* genes, encompassing ATP1A3, encode the alpha subunit, serving as the catalytic component behind the active enzyme. This enzyme orchestrates the hydrolysis of ATP, concurrently facilitating the exchange of sodium and potassium ions across the plasma membrane. The ensuing electrochemical gradient of sodium and potassium ions not only fuels the energetic

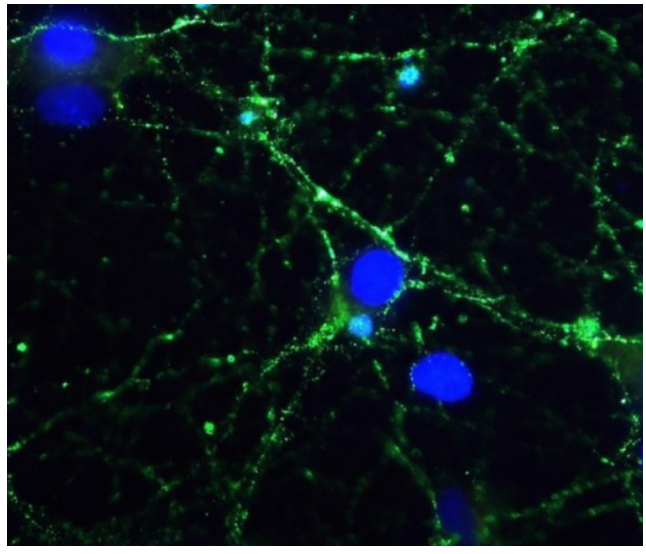

Figure 1. Immunolabeling of cultured live rat neurons with serum IgG of an IIH patient using indirect immunofluorescence. The serum IgGs of the patient show reactivity with the membrane of neuronal cell body and axonal/dendritic protrusions (green). Original magnification (800x, oil lens), counterstained with DAPI (blue)

IIH: Idiopathic intracranial hypertension

dynamics of cellular processes but also underpins the active transport of diverse nutrients (27).

It has been well demonstrated that ATP1A3 is expressed by the neuronal membrane and is thus exposed to potentially hazardous effects of circulating antibodies (28). It was therefore tempting to conclude that ATP1A3 antibodies may disrupt the function of the sodium/potassium-transporting ATPase, which plays a role in osmoregulation, the transport of various nutrient molecules, and the electrical excitability of neurons (29). Osmotic regulation is potentially impaired in IIH, as evidenced by amelioration of symptoms through the use of diuretics acting on Na-K transport, such as acetazolamide and furosemide (30). Given the substantial amino acid identity shared among various ATP1 proteins, there is a likelihood that individuals with IIH may possess antibodies targeting additional ATP1 proteins. This hypothesis warrants further comprehensive investigation.

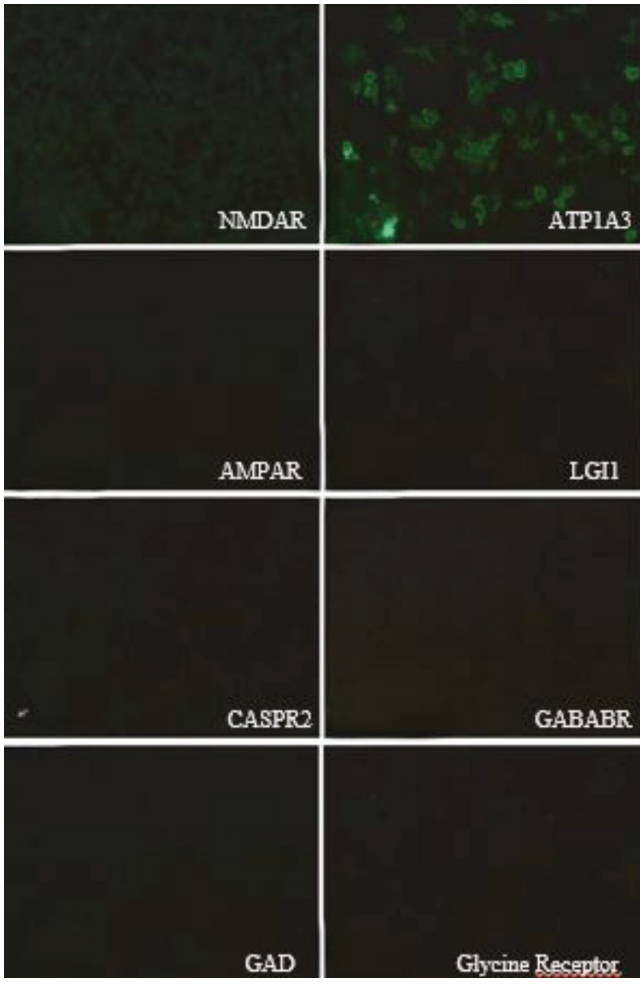

Figure 2. Immunofluorescence assays conducted with HEK293 cells transfected with different neuronal cDNA. The commercial monoclonal antibody against ATP1A3, used as a positive control, strongly immunoreacted with ATP1A3 transfected cells (green) but not with cells transfected with cDNA of other neuronal antigens (NMDAR, AMPAR, LGI1, CASPR2, GAD, Glycine receptor). Original magnification (20x)

ATP1A3: ATPase subunit alpha-3

Headache is the most typical symptom of IIH, and mutations in the *ATP1A* genes are associated with a plethora of neurological disorders, including hemiplegic migraine (31). As a matter of fact, ATP1A3 mutations are associated with epileptic encephalopathy, alternating hemiplegia of childhood, cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss-*CAPOS* syndrome, rapid-onset dystonia-parkinsonism, and recurrent episodes of cerebellar ataxia (32), indicating the remarkable importance of this subunit in neuronal functions. Notably, anti-neuronal antibodies were previously identified in a different headache syndrome, HaNDL, providing evidence for the participation of humoral autoimmunity in specific headache syndromes (22). Intriguingly, ATP1A3 antibodies have already been identified in paraneoplastic neurological syndrome patients presenting with ataxia and gaze palsy, emphasizing the immunogenic action of this particular subunit and potential involvement in the pathogenesis of neurological disorders (18,19).

Study Limitations

We only used sera in this study. Further exploration of CSF samples from IIH patients might yield more clinically relevant anti-neuronal antibodies. Lastly, similar antibody identification assays targeting different Na-K channels need to be conducted with a larger cohort of IIH patients to reliably establish the presence of such antibodies.

Conclusion

We have provided proof-of-concept evidence for the presence of novel neuronal surface antibodies in IIH. The exact pathophysiological significance of these antibodies in IIH needs to be further scrutinized.

Ethics

Ethics Committee Approval: This study was approved by the Istanbul University, Istanbul Faculty of Medicine, Clinical Research Ethics Committee (date: 01.12.2023, approval no.: 24).

Informed Consent: The informed consent forms of all the cases who participated in the study were signed by patients.

Footnotes

Authorship Contributions

Concept: C.I.K., Design: C.I.K., Data Collection or Processing: S.S., C.U., Analysis or Interpretation: C.I.K., E.T., Writing: C.I.K., E.T.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Prognostic Value and Association of Platelet-to-Albumin Ratio with Coronary Artery Ectasia and Severity Classification

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Abstract

Aim: Coronary artery ectasia (CAE) is characterized by abnormal dilation of coronary arteries and is associated with inflammation and thrombotic events. The platelet-to-albumin ratio (PAR) has emerged as a potential biomarker reflecting both inflammatory status and thrombotic activity. This study aimed to evaluate the relationship between PAR and the presence and severity of CAE.

Methods: This retrospective, cross-sectional observational study included 80 patients diagnosed with CAE who underwent coronary angiography between April 2022 and January 2024, as well as 73 age- and sex-matched control participants with normal coronary anatomy. We calculated the PAR and assessed CAE using the Markis classification, which categorizes CAE severity based on the number and distribution of ectatic segments.

Results: There was no significant difference between the two groups in terms of age and sex. Although the PAR was higher in the coronary ectasia group, the difference was not statistically significant. However, PAR was significantly correlated with the Marquis classification (p=0.014).

Conclusion: While PAR values showed no significant difference between patients with CAE and those with normal coronary arteries, there was a notable correlation between PAR values and the Markis classification among patients with CAE, suggesting that PAR could be useful in evaluating the severity of CAE.

Keywords: Coronary artery ectasia, inflammation, platelet/albumin ratio

Introduction

Coronary artery ectasia (CAE) is a distinctive form of coronary artery disease (CAD) characterized by abnormal dilation and expansion of the coronary arteries (1). It is defined as the enlargement of the coronary ectatic segment, which typically ranges from 1.5 to 2 times the diameter of the adjacent normal vessel (2). Although CAE is traditionally considered a variant of atherosclerosis, its pathophysiology remains incomplete, with a range of underlying etiologies including atherosclerosis, congenital abnormalities, inflammatory conditions, and connective tissue disorders (3,4). Coronary artery ectasia is gaining clinical attention because of its potential to cause complications, such as myocardial infarction, coronary thrombosis, and even sudden cardiac death. Recently, various biomarkers have been used to better understand the pathophysiology of CAE and predict disease severity (5).

Platelets play a crucial role in thrombosis, as they not only increase blood coagulability but also trigger

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and intensify inflammatory reactions by interacting with immune cells and producing pro-inflammatory cytokines (6). Platelets also contribute to the onset, progression, and destabilization of atherosclerotic vascular diseases (7). They play a significant role in major adverse cardiac events and peripheral arterial diseases. Low albumin levels have been shown to correlate with adverse events in various chronic inflammatory conditions and (8). Coronary artery disease the role of inflammation in the pathogenesis of CAE has been well documented in previous studies (9). The platelet-to-albumin ratio (PAR) has emerged as a novel indicator of inflammation and oxidative stress, both of which play critical roles in cardiovascular pathogenesis. PAR is calculated by dividing the platelet count by the albumin level (10). The platelet-to-albumin ratio has shown promise as a potential prognostic marker for various cardiovascular conditions; however, its role in CAE remains largely unexplored. We hypothesized that higher PAR values would be associated with CAE, as determined by the Markis classification, reflecting a greater inflammatory and thrombotic burden in patients with extensive ectatic disease.

The aim of this study is to investigate the relationship between PAR and both the presence and severity of CAE, according to the Markis classification. This study may contribute to clinical practice by offering the PAR as a simple, cost-effective, and readily available indicator for predicting CAE severity. In turn, this could provide significant clinical benefits by allowing the early identification of high-risk patients and optimization of follow-up strategies.

Materials and Methods

Compliance with Ethical Standards

The study was reviewed and approved by the Siirt University Ethics Committee (approval no.: 100749, date: 28.02.2024) adhering to the principles of the Helsinki Declaration.

Study Design

This was a single-center, retrospective, cross-sectional observational study. In our investigation, we retrospectively assessed 80 patients diagnosed with coronary ectasia who underwent coronary angiography at our hospital between April 2022 and January 2024. Additionally, we evaluated 73 patients with comparable demographic profiles and normal coronary anatomies.

The inclusion criteria for this study were as follows: Patients aged ≥18 years with a confirmed diagnosis of CAE based on coronary angiography. Patients were required to have complete clinical and laboratory data available, including platelet count and serum albumin levels, measured at the time of coronary angiography. Additionally, CAE severity was classified according to the Markis classification. The exclusion criteria for the study were defined as follows: Acute myocardial infarction, history of prior percutaneous coronary intervention, moderate to severe valvular heart disease, heart failure with reduced ejection fraction, congenital heart disease, hereditary hyperlipidemia, severe liver and kidney dysfunction, and pulmonary hypertension. The control group consisted of age- and sex-matched individuals who underwent coronary angiography during the same period and were found to have normal coronary artery structure, defined as less than 10% stenosis and no evidence of ectasia or significant CAD (Figure 1).

Patient Evaluation

Three invasive cardiologists independently reviewed prior coronary angiograms. Coronary artery ectasia was defined as the dilation of the coronary ectatic segment, reaching 1.5-2 times the diameter of the adjacent normal vessel, while coronary artery aneurysm was characterized by dilation that is 2 times or more. Coronary angiographies were routinely conducted via the femoral route using the Judkins method, excluding cases where nitroglycerin was administered. Computerized quantitative angiography was used for coronary artery diameter measurements, considering the largest diameter in the segments as reference.

Prior to coronary angiography, we analyzed basic biochemical tests and complete blood counts from all patients, taken after overnight fasting. These included lymphocyte, leukocyte, monocyte, hemoglobin, platelet, mean platelet volume, creatinine, estimated glomerular filtration rate, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, systemic immune-inflammation index (SII), and platelet count divided by serum albumin concentration, which yields the PAR.

Statistical Analysis

The obtained results were evaluated using Statistical Package for the Social Sciences (SPSS) 22.0 (SPSS, Inc., Chicago, Illinois, USA) for statistical analysis. Continuous variables were recorded as mean ± standard deviation for parametric data and as median with interquartile range (25^{th}-75^{th} percentiles) for non-parametric data. Categorical variables were expressed as frequencies and percentages. Data distribution was assessed using the Kolmogorov-Smirnov test. Variables showing a normal distribution among groups were compared using the Student's t-test, while those not showing a normal distribution were compared using the Mann-Whitney U test. The chi-square test was used for comparing categorical variables. Finally, correlation analysis was performed using either the Spearman or Pearson correlation test. A significance level

of p<0.05 was considered statistically significant for all analyses.

Results

The groups were found to have similar statistical gender distributions. The mean age was determined to be 58.3 (±10.1) in the coronary ectasia group and 58.6 (±10.6) in the normal coronary group, with no significant difference observed between the groups. No differences were observed between the groups in terms of chronic diseases and smoking habits (Table 1).

There is no noticeable distinction in the echocardiographic parameters between the two groups. Although the estimated systolic pulmonary artery pressure did not reach statistical significance in the coronary ectasia group, it was found to be higher. The hemoglobin level was statistically higher in the coronary ectasia group (p=0.001). There was no significant difference observed between the groups in terms of cholesterol levels. Although the PAR was higher in the coronary ectasia group, the difference did not reach statistical significance (Figure 1, Table 2).

In the correlation analysis, a statistically significant correlation was found between the SII and PAR (p<0.01), while PAR was significantly correlated with the Markis classification (p<0.014) (Table 3). The logistic regression model suggests that when PAR is divided into two groups (corresponding to class 1 and 2 versus class 3 and 4), it has a significant impact on the Markis classification, whereas SII does not show a significant effect in this model (Figures 2 and 3).

Discussion

Our findings also suggest that PAR may be a prognostic differentiator rather than a diagnostic marker. There was no statistically significant difference between the CAE group and the normal coronary artery control group in terms of mean PAR values. Although the PAR was higher in the SSI group, the p-value was not significant. This shows that PAR alone is not sufficient to detect the presence of CAE. However, it is understood that PAR may be valuable in determining the extent and severity of the disease in patients with CAE. In other words, high PAR gives a clue to the extent of the current CAE rather than the diagnosis of CAE.

In recent years, some indices containing key blood parameters have been shown to aid in risk assessment and potential treatment strategies by providing valuable information about the inflammatory and atherosclerotic

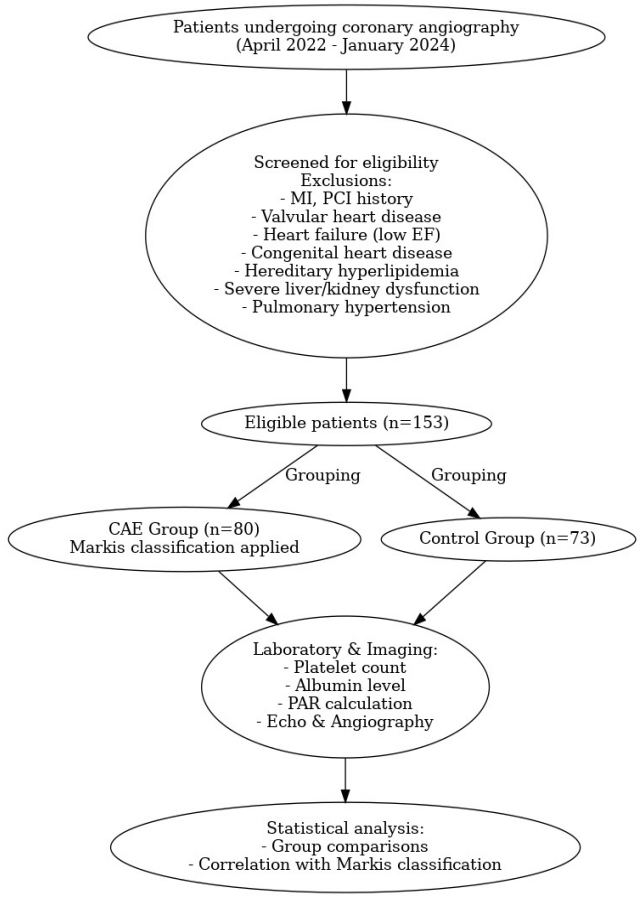

Figure 1. Patients flow charts
PCI: Percutaneous coronary intervention, MI: Myocardial infarction, PAR: Platelet/albumin ratio, CAE: Coronary artery ectasia, EF: Ejection fraction

Table 1. Demographic characteristics and distribution of comorbidities among group

	Normal coronary (n=73)	Coronary ectasia (n=80)	p-value
Sex (women)	38 (52.1%)	37 (46.3%)	0.475*
Age	58.6 (±10.6)	58.3 (±10.1)	0.874+
Diabetes mellitus	11 (15.1%)	13 (16.3%)	0.841*
Hypertension	28 (38.4%)	34 (42.5%)	0.603*
Hyperlipidemia	14 (19.2%)	15 (18.8%)	0.947*
Smoking	15 (20.5%)	21 (26.3%)	0.410*
Rhythm (AF)	3 (4.1%)	4 (5%)	0.794*

*Pearson's chi-squared test, +: Student's t-test, p-value <0.05 indicates statistical significance, AF: Atrial fibrillation

components involved in the pathogenesis and prediction of CAE. For example, SII and the atherogenic plasma index are some of the important indices associated with CAE. Studies have shown that SII, calculated from neutrophil-to-lymphocyte ratio and platelet counts, is independently linked to the presence and severity of isolated CAE, with higher SII values indicating a more severe inflammatory process (11,12). In our study, contrary to the literature, SII was not significant in patients with coronary ectasia. In addition, unlike PAR, there was no significant correlation

Table 2. Distribution of echocardiographic and blood parameters between groups

	Normal coronary (n=73)	Coronary ectasia (n=80)	p-value
LVEDD (mm)	46.4 (±3.4)	46.7 (±3.8)	0.712
LVESD (mm)	27.7 (±3.7)	28.0 (±4.2)	0.705
IVS (mm)	10.9 (±1.2)	11.1 (±1.2)	0.433
PW (mm)	10.1 (±0.9)	10.2 (±0.8)	0.751
E/A	0.9 (±0.3)	1.0 (±0.4)	0.366
sPAP (mmHg)	28.9 (21-40)	30.25 (20-47)	0.174*
Urea (mg/dL)	30.2 (±11.2)	30.9 (±9.5)	0.666
Creatinin (mg/dL)	0.99 (0.37-8.86)	0.93 (0.62-2.1)	0.342*
Sodium (mmol/L)	139.0 (133-143)	140.1 (135-149)	0.007*
Potassium (mmol/L)	30.2 (±11.2)	30.9 (±9.5)	0.732
Hemoglobin (g/dL)	13.1 (±1.8)	14.1 (±1.8)	0.001
Albumin (g/dL)	42.5 (±2,8)	41.9 (±3.6)	0.310
CRP (mg/L)	4.1 (±0-14)	5.3 (0.3-81)	0.176*
WBC (10^3/μL)	7.7 (±2.5)	7.5 (±2.0)	0.532
Neutrophil (10^3/μL)	4.9 (±2.2)	4.6 (±1.5)	0.252
Leukocytes (10^3/μL)	2.21 (±0.8)	2.24 (±0.8)	0.830
Platelet (10^3/μL)	259.9 (±78.7)	271.5 (±71.4)	0.343
Monocytes (10^3/μL)	0.44 (±0.5)	0.55 (±1.1)	0.480
LDL (mg/dL)	108.4 (40-238)	111.2 (44-268)	0.854*
HDL (mg/dL)	46.2 (±12.4)	45.5 (±11)	0.721
Total cholesterol (mg/dL)	177.8 (±37.5)	187.4 (±41)	0.156
Triglycerides (mg/dL)	176.4 (71-1104)	155.6 (51-486)	0.273*
SII	770.0 (159.1-9183)	644 (178-2409)	0.991*
PAR	6.13 (±1.84)	6.51 (±1.85)	0.201

p<0.05 indicates statistical significance, p-values with an asterisk indicate variables that were compared using the Mann-Whitney U test due to non-normal distribution, non-normally distributed variables are presented as median (minimum-maximum), other variables were compared using the Student's t-test and values are expressed as mean ± standard deviation
LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diamater, IVS: Interventricular septum, PW: Posterior wall, E/A: E wave/a wave ratio, sPAP: Systolic pulmonary artery pressure, CRP: C-reactive protein, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, SII: Systemic immune-inflammation index, PAR: Platelet/albumin ratio, WBC: White blood cell

Table 3. Correlation analysis of Platelet/Albumin ratio with Markis classification and SII

	PAR		SII	
Parameters	**r**	**p***	**r**	**p***
Markis classification	-0.273	0.014	-0.002	0.987
PAR			0.446	<0.01

p<0.05 indicates statistical significance
PAR: Platelet/albumin ratio, SII: Systemic immune-inflammation index

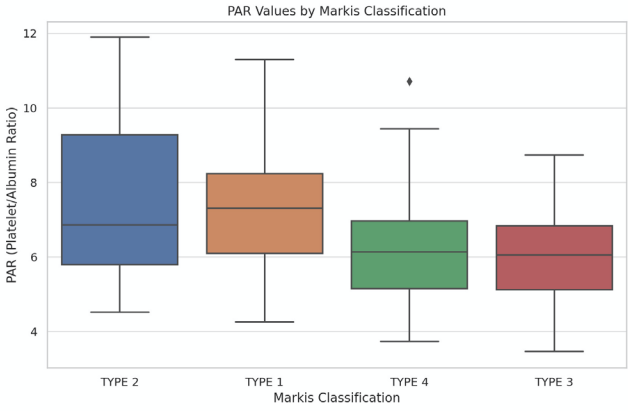

Figure 2. Distribution of PAR values across Markis classification groups
PAR: Platelet/albumin ratio

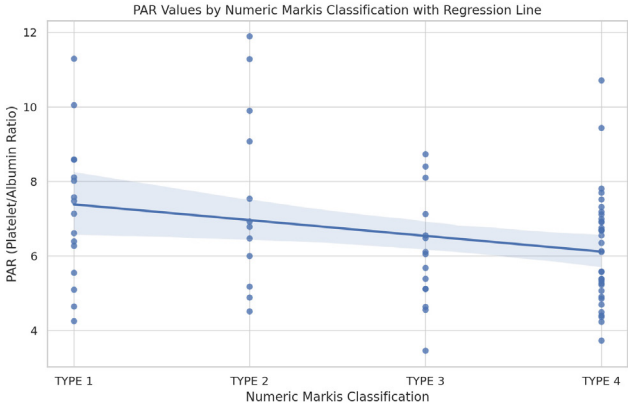

Figure 3. Correlation between PAR value and Markis classification with regression line
PAR: Platelet/albumin ratio

with the Marquis classification. This may be due to the multifaceted nature of CAE. Additionally, recent evidence from Alıcı et al. (13) has shown that hematological ratios, such as the platelet-to-white blood cell ratio, can serve as novel prognostic biomarkers in acute coronary settings, further supporting the potential utility of simple blood-based indices like PAR in cardiovascular prognostication. Another study using platelets showed that the mean platelet volume-platelet count ratio was significantly associated with the presence and severity of CAE and that platelet count had a potential role in this disease (14). Research conducted revealed that the proportion of white blood cells to average platelet volume is significantly linked to CAE and could be a cost-efficient approach to monitor CAE (15).

Coronary artery ectasia is also associated with albumin levels in the context of inflammation and endothelial dysfunction. Studies have shown a significant relationship between CAE and the C-reactive protein-to-albumin ratio (CAR) (16). In addition, CAE has been associated with microalbuminuria, a marker of endothelial dysfunction, suggesting a potential association with increased cardiovascular risk (17). Furthermore, the importance of CAR and CAE in predicting the phenomenon of non-reflow in patients with acute ST-segment elevation myocardial infarction has been compared, and CAR has emerged as a more reliable predictor (18). These findings highlight the complex interplay between CAE, inflammation, endothelial dysfunction, and albumin levels, emphasizing the importance of monitoring these parameters in patients with CAE. Recent research has shown a strong correlation between elevated PAR values and unfavorable outcomes in patients with certain diseases and malignancies (19,20). A recent study on patients with on ST-segment elevation acute coronary syndromes who received percutaneous coronary intervention showed that higher PAR quartiles were linked with higher rates of non-fatal myocardial infarction, ischemia-driven revascularization, and Major Adverse Cardiovascular Events (MACE). A high PAR value was found to be directly associated with an increased risk of MACE (21).

The Markis classification system is a widely accepted method for categorizing CAE based on the number and severity of ectatic segments in the coronary arteries (22). It includes four distinct types: Type I (diffuse ectasia in two or three coronary arteries), Type II (diffuse ectasia in one artery and localized ectasia in another), Type III (diffuse ectasia in one artery), and Type IV (localized or segmental ectasia in one artery). This classification scheme helps clinicians gauge the extent of CAE and can provide insights into the risk of complications such as thrombosis and coronary artery occlusion. Our analysis revealed an intriguing finding regarding the relationship between PAR and the Markis classification of coronary ectasia. This unexpected result suggests that while PAR may not be useful in distinguishing between patients with or without CAE, it could have value in predicting the severity or extent of ectasia among those with the condition. A higher PAR in individuals with lower Markis classifications (indicating fewer ectatic segments) could reflect underlying differences in platelet activation or albumin levels, which may decrease as CAE progresses.

While our study did not find a significant relationship between PAR and the presence of coronary ectasia, the correlation between PAR and the Markis classification highlights the need for further investigation into the role of PAR in predicting CAE severity. Understanding this relationship could have important clinical implications, potentially aiding in risk stratification and guiding treatment strategies for CAE patients.

Study Limitations

Our study has limitations, including a relatively small sample size and a focus on a specific cohort, which may limit the generalizability of the results. Future studies with larger cohorts and more diverse populations could provide more profound insights into the potential role of PAR in CAE and help identify additional markers that could complement PAR in assessing ectasia severity. Despite these limitations, the study has strengths such as a well-defined patient group, rigorous statistical analysis, the use of the widely accepted Markis classification for severity assessment, and the inclusion of comparisons with established inflammatory indices, which add value to the literature.

Conclusion

Our findings suggest that PAR could serve as a monitoring tool for identifying CAE patients at higher risk of disease progression or adverse outcomes, despite not differentiating them from healthy individuals. Its significant correlation with the Markis classification highlights its potential as a severity marker, bridging a gap in the biomarker utility for CAE. Further large-scale studies are needed to validate its role in predicting long-term clinical outcomes and guiding disease management.

Ethics

Ethics Committee Approval: The study was reviewed and approved by the Siirt University Ethics Committee (approval no.: 100749, date: 28.02.2024).

Informed Consent: Informed consent forms were obtained from the patients and control group.

Footnotes

Authorship Contributions

Concept: Y.E.Y., H.S., Design: Y.E.Y, M.A., Data Collection or Processing: M.A., H.S., Ş.A.K., Analysis or Interpretation: M.A., A.T.Ş., Literature Search: A.T.Ş., Ş.A.K., H.S., Writing: Y.E.Y., A.T.Ş.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Investigation of Anti-neutrophil Cytoplasmic Antibody by Indirect Immunofluorescence Assay in COVID-19 Patients

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Abstract

Aim: Coronavirus disease-2019 (COVID-19) has been suggested to trigger the production of autoimmune antibodies and contribute to the development of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. This study aims to investigate the presence of ANCA among COVID-19 patients.

Methods: This cross-sectional, prospective analysis included 200 COVID-19 patients with positive polymerase chain reaction test results for severe acute respiratory syndrome-coronavirus-2 and no history of autoimmune disease, recruited between June 2021 and November 2022. The control group included 50 age-matched healthy blood donors. The ANCA profile was assessed using the indirect immunofluorescence assay method with the EUROPLUS Granulocyte Mosaic EUROPattern test kit (EUROIMMUN, Germany) on sera samples of the patient and control groups.

Results: Perinuclear ANCA (p-ANCA) was detected in 12 of 200 COVID-19 patients (6.0%) and cytoplasmic ANCA (c-ANCA) was detected in 15 of 200 patients (7.5%). No ANCA positivity was observed in the control group (0/50). ANCA positivity among COVID-19 patients (27 of 200, 13.5%) was statistically significantly higher than in the control group ($p<0.05$). ANCA positivity was significantly higher in intensive care unit (ICU) patients (21 of 77, 27.3%) compared to non-ICU patients (6 of 123, 4.9%) ($p<0.05$).

Conclusion: ANCA presence in ICU patients supports the hypothesis that COVID-19 triggers ANCA synthesis and contributes to disease severity.

Keywords: COVID-19, anti-neutrophil cytoplasmic antibodies, vasculitis, indirect immunofluorescence assay

Introduction

In addition to specific antibodies in coronavirus disease-2019 (COVID-19) patients, researchers have investigated whether autoantibodies are produced that can increase the severity of the disease by attacking some cells and tissues. Although the exact reason for the formation of autoantibodies is not known, two different theories have been proposed. First, the development of a hypersensitivity reaction within the immune system due to the coronavirus infection, which can damage the patient's cells and tissues. Second, some of the virus-specific antigenic epitopes are similar to the patient's cell antigens (1,2).

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Autoantibodies formed in COVID-19 are recognized as one of the key factors influencing disease severity. It has been reported that antinuclear antibody, antiphospholipid antibody, anti-type 1 interferon antibody, and, rarely, anti-neutrophil cytoplasmic antibody (ANCA) are encountered frequently (40-50%) in COVID-19 cases. The number of original studies investigating ANCA levels in COVID-19 patients is very low. With these limited studies, research indicates that ANCA production is triggered in some cases. ANCA, whose production can be triggered in COVID-19, can cause serious organ damage, leading to vasculitis development in the respiratory tract, kidneys, and small arteries in the skin. In the COVID-19 pandemic, cases of immune glomerulonephritis have been reported as a result of vasculitis due to ANCA production (3-5). We hypothesized that COVID-19 is associated with vasculitis and that autoantibodies capable of causing vasculitis could be detected in patients with COVID-19.

The primary aim of this study is to investigate the presence of ANCA, which may be triggered in COVID-19 patients, and to highlight the risk of vasculitis that ANCA could induce. Thus, the detection of ANCA autoantibodies in COVID-19 patients in clinical practice will contribute to predicting disease progression, taking preventive measures, and developing treatment protocols. The data obtained from this study will serve as a resource for more comprehensive research to be conducted in the future.

Methods

Compliance with Ethical Standards

This study was approved by the decision dated 25.02.2021 and approval numbered 233 of the Dicle University Faculty of Medicine Ethics Committee for Non-Interventional Studies. Informed consent forms were obtained from the patients and control group members.

Study Design

The study was a cross-sectional analysis conducted between June 2021 and November 2022. A total of 200 patients, aged 18-90 years, who presented to the Dicle University Hospital COVID-19 outpatient clinic or were hospitalized in the COVID-19 clinic or intensive care unit (ICU) with a positive polymerase chain reaction (PCR) test and no prior history of autoimmune disease were included. The age, gender, and clinical information of the patients who were followed up/treated were recorded. Fifty healthy blood donors who did not have COVID-19, did not have a positive PCR test, and had no known autoimmune disease were selected as the control group.

Venous blood samples (5-6 mL) were collected from the patients and the control group under aseptic conditions and delivered to the indirect immunofluorescence assay (IFA) laboratory within 30 minutes. After the blood was centrifuged, the serum was separated and kept in a deep freezer at -80 °C until it was studied.

One of the methods used to investigate the ANCA profile is the IFA. In our study, the EUROPLUS Granulocyte Mosaic EUROPattern (EUROIMMUN, Germany) IFA test kit was used to investigate the ANCA profile. Positive and negative controls were included for each run.

The patient's diluted blood serum was dripped onto the slides in the commercial kit, and the preparation was allowed to sit in accordance with the procedure recommended by the manufacturer. After the first wash with the buffer solution, the anti-human antibody (conjugate) labeled with fluorescein isothiocyanate was added, and then the second wash was performed with the buffer solution, waiting for an appropriate time. Finally, the slides were covered with glycerol and mounted with a coverslip to be examined under a fluorescent microscope. Slides were examined under a fluorescent microscope as soon as possible.

The ethanol-fixed chamber was examined and cytoplasmic/perinuclear differentiation of ANCA was performed. Cytoplasmic ANCA (c-ANCA) positivity: a diffuse, granular green fluorescent uptake is observed in the cytoplasm into the neutrophil cytoplasm, while there is no fluorescent uptake in the cell nucleus. In perinuclear ANCA (p-ANCA) positivity, there is green fluorescent uptake surrounding the neutrophil nucleus (6).

The formalin-fixed chamber is then examined. In formalin-resistant ANCA types, only fluorescent staining is seen in the cytoplasm. However, fluorescent uptake is not seen in formalin-sensitive ANCA types. In formalin-resistant c-ANCA types, positive fluorescence is mostly observed in the proteinase 3 (PR3) compartment, whereas in formalin-resistant p-ANCA types, positive fluorescence is mostly observed in the myeloperoxidase (MPO) compartment.

Blood serum with non-fluorescent neutrophils was recorded as ANCA negative. In the formalin- and ethanol-fixed chamber, granular-looking fluorescent positivity was evenly distributed in the cytoplasm of neutrophils, and the samples showing green circular fluorescence in the PR3 area were recorded as c-ANCA, PR3 formalin-resistant positive. C-ANCA appeared in the ethanol-fixed chamber, but this fluorescence disappeared in the formalin-fixed chamber. Samples that did not fluoresce in PR3 were recorded as c-ANCA, formalin-sensitive PR3 negative.

Patients with perinuclear fluorescence surrounding the fragmented nuclei of neutrophils in the ethanol-fixed chamber, fluorescence scattered in the cytoplasm in the area with formalin, and circular green fluorescence in the MPO area were recorded as p-ANCA, formalin-resistant MPO positive. Samples that are formalin-sensitive but do not fluoresce in this area and MPO were recorded as p-ANCA, while formalin-sensitive MPO was recorded as negative.

Statistical Analysis

The obtained data were analyzed using SPSS version 20.0. Percentages were reported for categorical variables to reflect the distribution of the data. Chi-square tests were performed to assess relationships between categorical variables (gender, age, and unit of care). If the expected frequency was less than 20% in any cell, the p-value from Fisher's exact test was reported instead of that from the chi-square test. In statistical analysis, a 95% confidence interval was used, and a p-value of <0.05 was considered statistically significant.

Results

P-ANCA was positive in 12 (6.0%) patients and c-ANCA in 15 (7.5%) patients out of 200 in the patient group, while ANCA was not detected in the control group (n=50). Eleven patients who tested p-ANCA positive were formalin sensitive/MPO negative, and one patient was formalin resistant/MPO positive, while all c-ANCA positive patients were formalin sensitive/PR3 negative. The distribution of ANCA positivity according to the COVID-19 patient and control groups is presented in Table 1. The positivity rate in the patient group was high (13.5%), and the difference compared to the control group was statistically significant (χ^2=8.291, p=0.004).

Four (3.6%) out of 112 female patients and eight (10.0%) out of 88 male patients were found to be p-ANCA positive. Seven (6.3%) of 112 female patients and eight (10.0%) of 88 male patients were found to be c-ANCA positive. The difference in p-ANCA positivity and gender (χ^2=2.648, p=0.104) and c-ANCA positivity and gender (χ^2=0.605, p=0.437) in the patient group is not statistically significant. There is no difference between the two genders.

The distribution of p-ANCA positivity and c-ANCA positivity according to the clinic where the patients are followed/treated is presented in Table 2 and Table 3, respectively. The differences between p-ANCA positivity (χ^2=6.269, p<0.05) and c-ANCA positivity (χ^2=16.295, p<0.05) and the clinic where the patients were followed/treated were statistically significant. It is noteworthy that both p-ANCA and c-ANCA positivity are significantly higher in patients hospitalized in the COVID-19 intensive care unit than in patients hospitalized in the general or outpatient clinic.

The distribution of p-ANCA positivity by age group is presented in Table 4, while c-ANCA positivity is in Table 5. It was observed that both p-ANCA and c-ANCA positivity rates were higher in patients over 60 years of age. However, the difference between p-ANCA positivity and age was statistically significant (χ^2=5.404, p=0.020), while the difference between c-ANCA positivity and age was not significant (χ^2=2.698, p=0.100).

Table 1. Distribution of ANCA positivity by COVID-19 patient and control groups

Group name	ANCA		χ2	p-value
	Positive/n (%)	Negative/n (%)		
Patient group	27 (13.5)	173 (86.5)	8.291	0.004
Control group	0	50 (100.0)		

Fisher's exact test was performed
COVID-19: Coronavirus disease-2019, ANCA: Anti-neutrophil cytoplasmic antibody

Discussion

Autoantibodies are rarely encountered in COVID-19 patients. ANCA-related vasculitis is a condition that may develop in COVID-19 patients. It is an inflammatory process that damages small arteries in the body, including the respiratory system, kidneys, and skin (1,2,5).

Table 2. Distribution of p-ANCA positivity according to the clinic where the patients were followed/treated

The patient's	p-ANCA		χ2	p-value
	Positive/n (%)	Negative/n (%)		
Intensive care unit	8 (10.4)	69 (89.6)	6.269	0.044
Clinic	4 (6.1)	62 (93.9)		
Outpatient clinic	0	57 (100.0)		
Total	12 (6.0)	188 (94.0)		

Fisher's exact test was performed
p-ANCA: Perinuclear anti-neutrophil cytoplasmic antibody

Table 3. Distribution of c-ANCA positivity according to the clinic where the patients were followed/treated

The patient's	c-ANCA		χ2	p-value
	Positive/n (%)	Negative/n (%)		
Intensive care unit	13 (16.9)	64 (83.1)	16.295	0.00
Clinic	2 (3.0)	64 (97.0)		
Outpatient clinic	0	57 (100.0)		
Total	15 (7.5)	185 (92.5)		

Fisher's exact test was performed
c-ANCA: Cytoplasmic anti-neutrophil cytoplasmic antibody

Table 4. Distribution of p-ANCA positivity by age

Age	p-ANCA		χ2	p-value
	Positive/n (%)	Negative/n (%)		
≤60	1 (1.3)	77 (98.7)	5.404	0.020
>60	11 (9.0)	111 (91.0)		
Total	12 (6.0)	188 (94.0)		

Fisher's exact test was performed
p-ANCA: Perinuclear anti-neutrophil cytoplasmic antibody

Table 5. Distribution of c-ANCA positivity by age				
Age	c-ANCA		χ2	p-value
	Positive/n (%)	Negative/n (%)		
≤60	3 (3.9)	75 (96.1)	2.698	0.100
>60	12 (9.8)	110 (90.2)		
Total	15 (7.5)	185 (92.5)		
Fisher's exact test was performed c-ANCA: Cytoplasmic anti-neutrophil cytoplasmic antibody				

In many studies conducted during the pandemic and in the following years, rapidly progressive necrotizing glomerulonephritis cases have been reported due to ANCA positivity-related vasculitis in patients with COVID-19 (7-15). In addition, cases that were reported in this period of ANCA-associated pediatric vasculitis that developed after COVID-19 were noted (16,17).

The studies presented above show that there may be an association between ANCA production, triggered by severe acute respiratory syndrome-coronavirus-2 infection, and vasculitis, as well as organ damage, that may develop. It is also thought that autoantibodies increase the severity of the disease and prolong the recovery period. On the other hand, it has been determined that autoantibodies formed during the disease can remain in the body for a long time afterward (18-20). Recent studies have indicated that COVID-19 may trigger the production of ANCA, leading to the development or exacerbation of vasculitis. Therefore, assessing patients for autoantibody positivity during or after the acute phase of COVID-19 infection is crucial for evaluating disease progression and optimizing the treatment protocol. Similarly, some studies conducted recently have demonstrated the development of ANCA-associated vasculitis following COVID-19 vaccination, as well as after COVID-19 infection (21-23).

In the literature, there are two other studies, with 45 and 80 patients respectively, that have investigated the presence of ANCA autoantibodies in COVID-19 patients using a methodology similar to that of this study. However, the number of patients included in this study (200 patients) is significantly higher than that of the other studies (24,25).

Study Limitations

The limitations of this study include the limited number of patients, inability to obtain repeated samples, and the exclusion of specific ANCA antibodies other than MPO and PR3. Despite these limitations, the detection of ANCA positivity in COVID-19 patients, particularly those in the intensive care unit, clearly demonstrates the laboratory association between COVID-19 and vasculitis. The number of cases in this study is still higher than similar studies in the literature (e.g., 45 and 80 cases) (24,25).

Conclusion

We think that COVID-19 may trigger autoimmune diseases, including ANCA-related vasculitis. Thus, we demonstrated through laboratory data that COVID-19 infection triggers ANCA production, leading to vasculitis that exacerbates disease severity. This finding highlights the clinical significance of the study. In the literature, the number of original studies on the development of ANCA-related vasculitis and ANCA positivity in COVID-19 patients is very low. Therefore, more extensive research on the subject is needed. We believe that these study data will be a source for more comprehensive research.

Ethics

Ethics Committee Approval: This study was approved by the Non-Interventional Studies Ethics Committee of the Dicle University Faculty of Medicine (date: 25.02.2021, approval no.: 233).

Informed Consent: Informed consent forms were obtained from the patients and control group.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.A., N.O., A.C.T., Concept: Z.A., N.O., C.M., S.A., Design: Z.A., N.O., Data Collection or Processing: C.M., A.C.T., Analysis or Interpretation: A.C.T., Literature Search: Z.A., N.O., C.M., S.A., Writing: Z.A.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Comprehensive Survival Analysis of Reverse Shoulder Arthroplasty: Do Gender, Age, and Surgical Indication Influence Prosthesis Survivorship?

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Abstract

Aim: The parameters such as age, gender, and indication for surgery would have a significant influence on the survival of reverse shoulder arthroplasty (RSA). In this context, we aimed to determine how long patients survive after primary and revision RSA procedures and how factors like sex, age, and different reasons for surgery affect survival in a similar group of patients treated by the same surgeon.

Methods: This study presents a retrospective analysis of prospectively collected data from 376 patients who underwent RSA surgery between April 2014 and February 2023 in a tertiary university hospital that serves as a referral center for shoulder disorders. Complication and revision rates were assessed, and survivorship analysis was performed using Kaplan-Meier survival plots in different groups according to gender, age, and indication.

Results: Forty-six complications were observed in the study population, and 35 (76.1%) of them needed revision surgery. Ten-year revision-free survival was significantly lower in revision RSA compared to primary RSA cases (75.0% vs. 88.7%). Gender did not have a significant influence on complication rates, and survival probabilities were comparable between male and female patients. Younger patients (<60 years) had a higher complication rate and the lowest revision-free survival at 10 years (75.6%). According to the indication, revision RSA for failed arthroplasty and RSA for infection sequelae led to the worst 10-year revision-free survival rates (75.0% and 62.2%, respectively).

Conclusion: RSA showed satisfactory survivorship at 10 years, reaching up to almost 90% in the overall population. Age and indication showed significant influence on the survival of RSA, with lower survival probability and a higher complication rate in younger patients.

Keywords: Arthroplasty, replacement, shoulder, prosthesis failure, treatment outcome, survivorship, survival rate, shoulder joint/surgery

Introduction

Reverse shoulder arthroplasty (RSA) was first designed by Grammont et al. (1) with an effort to establish an effective treatment for cuff tear arthropathy (CTA). Due to promising early reports (2), it has become a popular treatment option with a significant increase in its usage over the years. In the following decades, indications for RSA have expanded, including proximal humeral fracture (PHF), fracture sequelae, glenohumeral osteoarthritis (OA), avascular necrosis of the humeral head, the revision of failed shoulder arthroplasty, and the development of other pathologies (3).

Despite favorable clinical outcomes, RSA is not devoid of complications, and instability, infection, and loosening have been reported to be among the most common complications associated with RSA (4,5). Some of these complications may lead to a revision surgery that yields variable and unpredictable results (6), which can be markedly debilitating. Therefore, determination of factors related to failure and prosthesis survival is of great

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importance to make proper risk assessments and patient counseling.

Previous studies indicated an overall survival rate around 90% for RSA in the short- to mid-term (6-10), but these data mostly rely on multicenter retrospective studies and registry studies combining a large number of different prosthesis designs, surgical techniques, surgeons, or follow-up protocols. This heterogeneity may reduce the accuracy of the study, especially if the cohort size is not large enough or the aforementioned parameters are not confined to overcome possible biases. We hypothesized that parameters such as age, gender, and indication for surgery would have a significant influence on the survival of RSA. In this study, we aimed to determine how long patients survive after primary and revision RSA procedures and how factors like sex, age, and different reasons for surgery affect survival in a similar group of patients treated by the same surgeon.

Methods

Study Design

This is a retrospective analysis of prospectively collected data from patients who underwent RSA surgery between April 2014 and February 2023 in a tertiary university hospital that serves as a referral center for shoulder disorders. Institutional Review Board approval was obtained from the relevant Bezmialem Vakif University board before the initiation of the study (approval no.: 6, date: 04.03.2024). Written informed consent regarding the use of their medical records data with the purpose of publication has been obtained from all patients before surgical interventions.

All patients were operated on by a single surgeon who is a fellowship-trained, experienced shoulder surgeon, and they were clinically and radiologically followed up on a regular basis. Clinical follow-up visits were performed by two authors at the 2nd, 4th, and 8th weeks postoperatively, the 3rd and 6th months, and each consecutive year with additional visits if required. Medical records of all patients were obtained from an institutional shoulder arthroplasty database. The dataset included information on patient demographics, date, diagnosis, and indication for RSA surgery complications, reoperations, and revisions (including date and cause for reoperation/revision). Reoperation was defined as any kind of surgical intervention, including revision surgery, following the index procedure, and overall survivorship was evaluated using patients' reoperation-free survival time. A revision surgery was defined as any surgical intervention following the index procedure, including the change, addition, or removal of any part of the prosthesis. The date of revision was used to assess revision-free survival of patients.

Patient Selection and Study Groups

Patients who underwent RSA surgery due to oncologic indications and patients who did not have complete follow-up data were excluded. Included patients were categorized into 8 groups according to indication as follows: cuff deficient shoulder (CDS), acute PHF, fracture sequelae (malunion or nonunion) of previous proximal humeral fracture, glenohumeral OA, avascular necrosis of humeral head, failed previous arthroscopic rotator cuff repair (FARCR), infection sequelae (previous history of osteomyelitis or septic arthritis), and the revision of failed shoulder arthroplasty (previous hemiarthroplasty, RSA, or total anatomical shoulder arthroplasty). The CDS group included patients with massive irreparable rotator cuff tears without imminent CTA [Hamada et al. (11) grade I-II and III] and patients with CTA (Hamada et al. (11) grade IV and V). The FARCR group consisted of patients who had a history of previous arthroscopic intervention (rotator cuff repair, latissimus dorsi tendon transfer, or superior capsular reconstruction) for rotator cuff tear and who underwent RSA surgery due to clinical and radiological failure of the index procedure.

Surgical Procedure and Rehabilitation

Surgical setup and skin preparation were standard, and the same protocol was applied for all patients. All patients were operated on under general anesthesia in the beach-chair position. Povidone-iodine paint solution combined with isopropyl alcohol was used for skin preparation, and the operative area was fully covered with Ioban 2 surgical drapes (3M, St. Paul, MN, USA). A standard deltopectoral approach was preferred in all procedures. Uncemented humeral stems were used for all primary cases, but cemented stems were occasionally preferred in revision surgeries, considering the bone stock and tissue quality of the humerus. Comprehensive Reverse Shoulder System (Zimmer Biomet, Warsaw, Indiana, USA), SMR Reverse (LimaCorporate, Udine, Italy), Delta Xtend (Depuy, Warsaw, Indiana, USA), and Next Shoulder Solutions (Next, Ankara, Turkey) were the implants used during the study period. Suction drains or medical prophylaxis for deep venous thrombosis was not routinely used.

All patients in the infection sequelae group underwent two-stage surgery. The first surgery included resection of the humeral head, debridement of avascular bone and soft tissue, and implantation of a spacer with antibiotic-loaded cement. Following an antibiotics regimen for a minimum of 6 weeks, second-stage surgeries (removal of spacer and implantation of prosthesis) were performed.

Depending on the indication and surgical status, patients were immobilized using an abduction sling, putting the shoulder in 30° of abduction and neutral rotation, for 4 weeks. Active elbow, wrist, and hand motions were

encouraged immediately after surgery. A physiotherapist visited all patients on the first postoperative day and gave instructions about immobilization and home exercises. At the 4th postoperative week, passive range of motion (ROM) exercises were initiated by a physiotherapist until full ROM was achieved. At the 6th to 8th postoperative weeks, active-assisted and active ROM exercises were gradually initiated, followed by deltoid strengthening exercises. Individually, considering the recovery level of each patient, return to full physical activity was allowed between the 3rd and 6th postoperative months.

Statistical Analysis

Descriptive statistical methods, including mean, standard deviation, range, percentage, and frequency, were used to analyze the data. During the follow-up period, patients were censored on the date of the event (reoperation or revision surgery) or on the date of the last follow-up visit or death if the event did not occur. Reoperation and revision rates were stratified by age, sex, and indication for RSA surgery and compared between strata using Fisher's exact test or chi-square test. Estimated survival probabilities and their pointwise 95% confidence intervals were then calculated and plotted using the Kaplan-Meier method. The log-rank (Mantel-Cox) test was then used to compare the survivorship distributions. The significance level was set at p=0.05, and all analyses were performed using GraphPad Prism software for Windows (version 9.3.0, San Diego, California, USA).

Results

During the study period, 394 primary and revision RSA procedures were performed for 379 patients (15 patients underwent a sequentially bilateral surgery). According to defined inclusion and exclusion criteria, 376 patients (356 primary and 20 revision RSA procedures) were included in the final analysis, which consisted of 82 (22.7%) male and 279 (77.3%) female patients (Figure 1). The mean age of patients was 69.7±10.6 (range: 29.0-95.0) years, and the mean follow-up duration was 61.4±25.3 (17.7-125.6) months. The most common indication for RSA was CDS, which constituted 40.7% of the study population. The distribution of the study population according to indication was summarized in Table 1.

46 complications were noted, of which some caused reoperation or revision surgery. The most common complications were infection (n=21, 45.7%), followed by instability (n=13, 28.3%). Among these 46 complications, 35 shoulders (76.1%) needed revision surgery. The mean delay for a complication to occur was 20.6±19.9 months. In one patient, evident neurological impairment was observed (musculocutaneous nerve dysfunction) immediately after surgery. The diagnosis was neuropraxia of the nerve due to overtensioning, and an exchange to a smaller-diameter glenosphere was performed the following day. Full recovery was observed immediately after the revision surgery. Data regarding complications were detailed in Table 2.

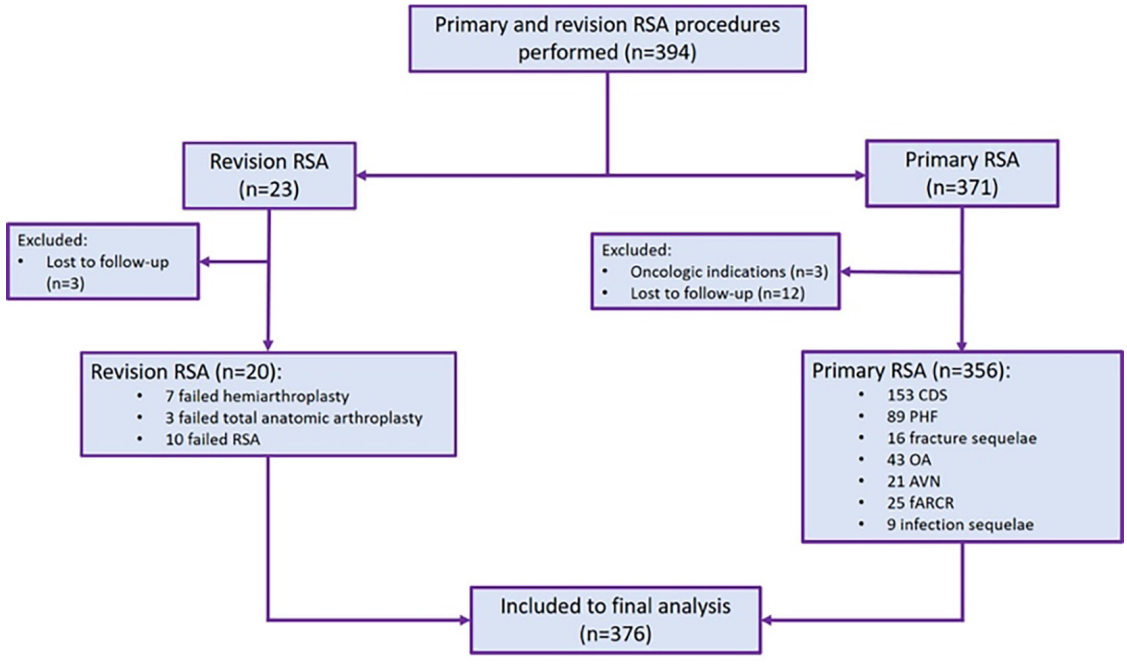

Figure 1. Patient selection flowchart
RSA: Reverse shoulder arthroplasty, CDS: Cuff deficient shoulder, PHF: Proximal humeral fracture, OA: Osteoarthritis, AVN: Avascular necrosis, FARCR: Failed arthroscopic rotator cuff repair

The estimated overall and revision-free survival probabilities of the study population, including both primary and revision RSAs, were 85.5% and 88.5%, respectively, at the 10th postoperative year (Figure 2). When stratified between primary and revision RSAs, both overall and revision-free survival rates were significantly inferior in the revision RSA group (p=0.0005 and 0.01, respectively). Assessment of survival curves showed that in the revision RSA group, almost all complications occurred within the first 24 months, with a mean delay of 8.6±7.8 months (Table 3, Figure 3).

Complication and revision rates were comparable for female and male patients (p>0.05) (Table 4). Even though the survival rates were similar at 10 years between sexes, survival curves showed that for male patients, an earlier complication/revision was more likely in the short term. Two-year overall survival rates were 94.5% for female patients and 88.5% for male patients. Distribution of survivorship for both overall and revision-free survival rates during the follow-up period did not show a significant difference by gender (p>0.05) (Table 5, Figure 4).

Younger patients had significantly higher complication and revision rates. Patients younger than 60 years of age at the time of surgery had the highest complication and revision rates (23.4% and 21.3%, respectively) (Table 6). Accordingly, at 10 years, younger patients (<60 years) had the lowest overall and revision-free survival rates, 73.4% and 75.6%, respectively, and the survival differences between age groups were statistically significant. (p=0.018 for overall survival and p=0.014 for revision-free survival) (Table 7, Figure 5).

Complication and revision rates varied significantly between indication groups (p=0.012 for complication rate and p=0.008 for revision rate), with the highest complication rates observed in the revision RSA group for failed arthroplasty (35.0%) and in the infection sequelae group (33.3%). Infection sequelae (33.3%) and failed arthroplasty (25.0%) groups were associated with the highest rates of revision (Table 8). All complications in the infection sequelae group were due to recurrence of infection, which needed two-stage revision surgery. Assessment of survival curves showed that the distribution of overall and revision-free survivorship varied significantly among indication groups (p=0.008 and p=0.01, respectively) (Figure 6) and that infection sequelae and

Table 1. Distribution of study population according to indication for RSA surgery

Indication	Frequency (%) (n=376)
CDS	153 (40.7)
• Massive irreparable rotator cuff tear (Hamada grade I-II-III)	• 58 (15.4)
• CTA (Hamada grade IV and V)	• 95 (25.3)
PHF	89 (23.7)
Fracture sequelae	16 (4.3)
Glenohumeral OA	43 (11.4)
AVN	21 (5.6)
fARCR	25 (6.6)
• Previous arthroscopic repair	• 18 (4.8)
• Previous latissimus dorsi transfer	• 4 (1.1)
• Previous superior capsular reconstruction	• 3 (0.8)
Infection sequelae	9 (2.4)
Revision for failed previous shoulder arthroplasty	20 (5.3)
• Revision of previous hemiarthroplasty	• 7 (1.9)
• Revision of previous total anatomic shoulder arthroplasty	• 3 (0.8)
• Revision of previous RSA	• 10 (2.7)

RSA: Reverse shoulder arthroplasty, CDS: Cuff deficient shoulder, CTA: Cuff tear arthropathy, PHF: Proximal humeral fracture, OA: Osteoarthritis, AVN: Avascular necrosis, FARCR: Failed arthroscopic rotator cuff repair

Table 2. Observed complications during follow-up period that needed a surgical treatment

Complication	Frequency (%) (n=46)	Mean delay (months)	Treatment
Infection	21 (45.7)	19.4±21.4	DAIR (n=4) One-stage revision (n=2) Two-stage revision (n=15)
Instability	13 (28.3)	15.6±13.8	Open reduction (n=3) Humeral component and insert revision (n=2) Glenosphere and insert revision (n=6) One-stage RSA revision (n=2)
Periprosthetic fracture	4 (8.7)	14.2±12.6	Osteosynthesis with plate fixation (n=4)
Humeral component loosening	3 (6.5)	43.0±14.2	Humeral component revision (n=2) One-stage RSA revision (n=1)
Glenoid component loosening	4 (8.7)	38.2±23.8	Glenoid component revision (n=3) Revision to BIO-RSA using femoral head allograft (n=1)
Neurological injury	1 (2.2)	0.03	Glenosphere revision

DAIR: Debridement, antibiotics and implant retention, RSA: Reverse shoulder arthroplasty, BIO-RSA: Bony increased-offset reverse shoulder arthroplasty

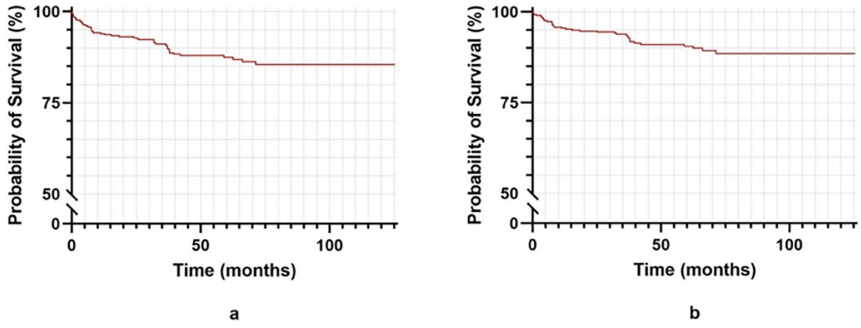

Figure 2. Kaplan-Meier curves of overall (a) and revision-free (b) survivals of RSA in study population
RSA: Reverse shoulder arthroplasty

Table 3. Overall and revision-free survival rates of primary and revision RSA			
	Primary RSA (n=356) (95% CI)	**Revision RSA (n=20) (95% CI)**	**p-value[a] (comparison of survivorship distribution)**
	Overall survival		
2-year	94.4% (91.4-96.4%)	70.0% (45.1-85.3%)	**0.0005**
10-year	86.7% (81.9-90.3)	65.0% (40.3-81.5%)	
	Revision-free survival		
2-year	95.8% (93.1-97.5%)	75.0% (50.0-88.7%)	**0.01**
10-year	89.3% (84.7-92.6%)	75.0% (50.0-88.7%)	
a: Log-rank test, bolded p-values indicate statistical significance RSA: Reverse shoulder arthroplasty, CI: Confidence interval			

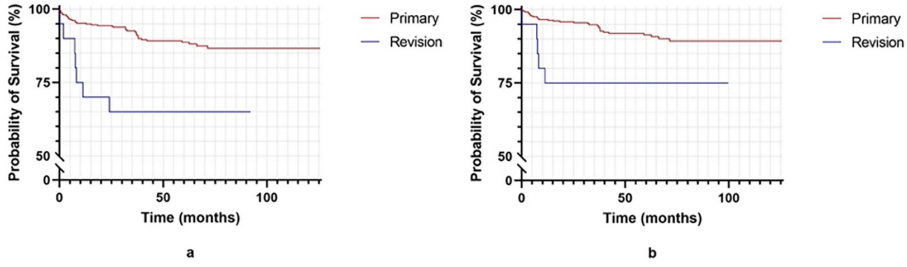

Figure 3. Kaplan-Meier curves of overall (a) and revision-free (b) survivals of primary and revision RSA
RSA: Reverse shoulder arthroplasty

Table 4. Complication and revision rates according to gender		
	Complication, frequency (%)	**Revision, frequency (%)**
Female (n=289)	34 (11.8)	25 (8.7)
Male (n=87)	12 (13.8)	10 (11.5)
p-value[a]	0.58	0.4
[a]: Fisher's Exact test		

revision RSA groups had the lowest survival rates. At 10 years, estimated revision-free survival rates were 62.2% in the infection sequelae group and 75.0% in the revision RSA group.

Discussion

This study has several important findings. First, primary RSA had a satisfactory survival rate in the long term, reaching up to almost 90% at 10 years. Secondly, revision RSA led to significantly lower survival rates compared to primary RSA, with all failures occurring within the first 24 months. Thirdly, in our series, gender did not have a significant impact on complication and revision rates. Even though survival rates were comparable in the long term, male patients had earlier complications, and survival rates were lower in the short term compared to female patients. This finding implies that failures tend to occur earlier in male patients; however, further evidence is required to

Table 5. Overall and revision-free survival rates of RSA according to gender			
	Female (n=289) (95% CI)	**Male (n=87) (95% CI)**	**p-value[a] (comparison of survivorship distribution)**
	Overall survival		
2-year	94.5% (91.2-96.6%)	88.5% (79.7-93.6%)	0.55
10-year	85.3% (79.6-89.5%)	86.1% (76.8-91.9%)	
	Revision-free survival		
2-year	95.8% (92.8-97.6%)	90.8% (82.4-95.3%)	0.39
10-year	88.6% (83.2-92.4%)	88.4% (79.5-93.6%)	
[a]: Log-rank test RSA: Reverse shoulder arthroplasty, CI: Confidence interval			

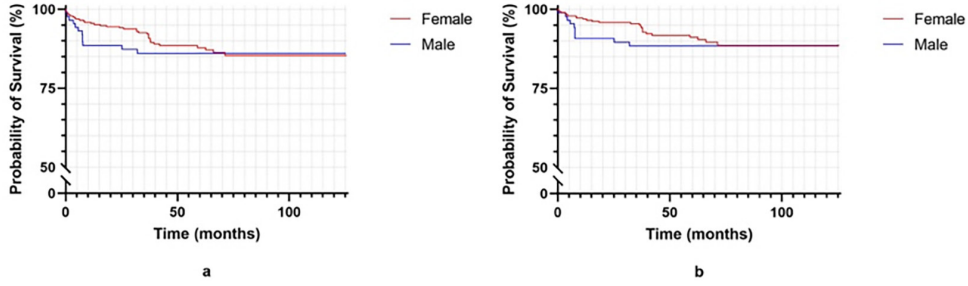

Figure 4. Kaplan-Meier curves of overall (a) and revision-free (b) survivals according to gender

Table 6. Complication and revision rates according to age at time of surgery		
	Complication, frequency (%)	**Revision, frequency (%)**
<60 years (n=47)	11 (23.4)	10 (21.3)
60-70 years (n=124)	13 (10.5)	11 (8.9)
70-80 years (n=150)	12 (8.0)	10 (6.7)
>80 years (n=55)	10 (18.2)	4 (7.3)
p-value[a]	**0.017**	**0.023**
[a]: Chi-square test, bolded p-values indicate statistical significance		

draw such a conclusion. Another finding that needs to be mentioned is that younger age at the time of surgery was associated with higher complication and revision rates and lower prosthesis survival.

In our series, 76.1% of complications required revision surgery, and the most common complications were infection and instability, which is consistent with previous literature (6,7,12,13). The mean delay time for a complication to occur was 20.6±19.9 months. Aseptic loosening (humeral or glenoid) tended to occur in the mid-term, with a mean delay time of 43.0±14.2 months for humeral loosening and 38.2±23.8 months for glenoid loosening. Other complications, such as infection, instability, or periprosthetic fracture, which constituted the majority of all complications, were most likely to occur in the short term. Especially in revision RSA cases, almost all failures occurred within the first two years, with a mean delay of 8.6±7.8 months. Similar findings have been reported in previous studies. In their registry-based observational study, Di Martino et al. (8) reported that 67% of all revisions occurred within the first year following index surgery. Another registry study evaluating 3828 RSA procedures indicated that the majority of revisions were performed in the short term, with 51% within the first 6 months (6).

In accordance with previous reports (7,14-16), revision RSA showed significantly inferior survival rates compared to primary RSA at every time point (70.0% vs. 94.4% at 2 years and 65.0% vs. 86.7% at 10 years) in our series. Zumstein et al. (12) reported that revision RSA had more than twice the complication rate compared to primary RSA (33% vs. 13%). The revision status (primary pathology and indication for revision) has been reported to be the most important predictor for intraoperative and postoperative complications (16). These findings imply that revision RSA is a challenging surgery with high rates of complication and low survival rates and that surgeons should make proper risk assessments for each patient requiring revision surgery.

Sex has been reported to have a significant impact on complication/revision rates, and male sex has been related to lower survival rates in previous reports. In their study, Chelli et al. (7) reported a higher complication rate (23.1% vs. 14.2%) and a lower 10-year revision-free survival rate (83.2% vs. 91.5%) in male patients. Similar findings have been reported in the Nordic registry, with higher revision

Table 7. Overall and revision-free survival rates of RSA according to age				
	Overall survival (95% CI)		**Revision-free survival (95% CI)**	
	2-year	**10-year**	**2-year**	**10-year**
<60 years (n=47)	87.2% (73.7-94.0%)	73.4% (56.6-84.5%)	87.2% (73.7-94.0%)	75.6% (58.9-86.2)
60-70 years (n=124)	92.7% (86.5-94.1%)	87.2% (78.0-92.7%)	94.4% (88.6-97.3%)	88.9% (79.9-94.0%)
70-80 years (n=150)	96.7% (92.2-98.6%)	91.0% (84.6-94.8%)	96.7% (92.2-98.6%)	92.4% (86.3-95.9)
>80 years (n=55)	89.1% (77.3-95.0%)	78.9% (63.5-88.4)	96.4 (86.3-99.1%)	90.0% (74.5-96.3%)
p-value[a]	**0.018**		**0.014**	
[a]: Log-rank test, bolded p-values indicate statistical significance RSA: Reverse shoulder arthroplasty, CI: Confidence interval				

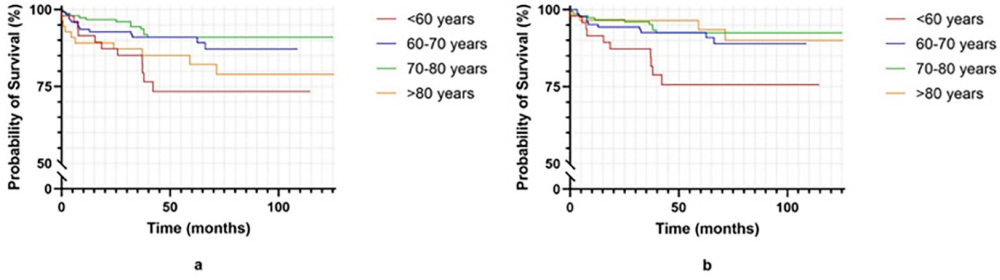

Figure 5. Kaplan-Meier curves of overall (a) and revision-free (b) survivals according to age

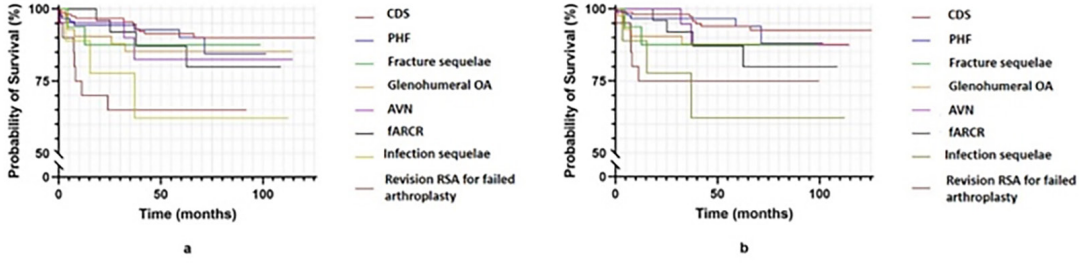

Figure 6. Kaplan-Meier curves of overall (a) and revision-free (b) survivals according to indication
RSA: Reverse shoulder arthroplasty, CDS: Cuff deficient shoulder, PHF: Proximal humeral fracture, OA: Osteoarthritis, AVN: Avascular necrosis, FARCR: Failed arthroscopic rotator cuff repair

Table 8. Complication and revision rates according to indication for RSA		
	Complication, frequency (%)	**Revision, frequency (%)**
CDS (n=153)	12 (7.8)	8 (5.2)
PHF (n=89)	8 (9.0)	5 (5.6)
Fracture sequelae (n=16)	2 (12.5)	2 (12.5)
Glenohumeral OA (n=43)	7 (16.3)	6 (14.0)
AVN (n=21)	3 (14.3)	2 (9.5)
FARCR (n=25)	4 (16.0)	4 (16.0)
Infection sequelae (n=9)	3 (33.3)	3 (33.3)
Revision RSA for failed arthroplasty (n=20)	7 (35.0)	5 (25.0)
p-value[a]	**0.012**	**0.008**
[a]: Chi-square test, bolded p-values indicate statistical significance RSA: Reverse shoulder arthroplasty, CDS: Cuff deficient shoulder, PHF: Proximal humeral fracture, OA: Osteoarthritis, AVN: Avascular necrosis, FARCR: Failed arthroscopic rotator cuff repair		

rates in male patients (6). Authors stated that this might be due to more prevalent Cutibacterium acnes colonization in male skin (17) or due to a higher level of activity in male patients, which might cause a higher stress level placed on the prosthesis. This finding was supported by the Norwegian registry showing higher revision rates in male patients due to infection (18). However, some reports suggested that male sex increases the risk of revision only in the short term and does not have a significant influence on survival rates in the long term. The Australian registry indicated a higher risk of revision for male patients only in the short term (first three months postoperatively) (19). In accordance with this finding, our results showed that complication and revision rates, as well as 10-year survival rates, were comparable between male and female patients. However, male patients had lower overall and revision-free survival at 2 years (88.5% vs. 94.5% and

90.8% vs. 95.8%).

Previous data has related younger age at the time of surgery to higher complication rates and lower survival rates. Chelli et al. (7) reported that patients younger than 60 years had a higher revision rate and a lower survival rate of 75.7% at 10 years compared to other age intervals. A registry-based study by Di Martino et al. (8) also suggested that the revision rate was higher in young patients undergoing RSA. This might be due to a higher level of activity in young patients and less favorable indications for RSA, which are possibly related to higher morbidity. Accordingly, our study showed that patients younger than 60 years had the highest complication and revision rates (23.4% and 21.3%, respectively). In our series, younger (<60 years) and older (>80 years) patients had lower overall survival rates at 10 years (73.4% and 78.9%, respectively) compared to other age intervals. However, 10-year revision-free survival was lower in younger patients (75.6%) compared to older patients (90.0%). This might be because a revision surgery could have been avoided in older patients due to the high risk of complications and morbidity, and those complications could have been managed conservatively. Despite these findings, recent data showed that there was a trend towards a younger population with the advancements in prosthetic designs and management of postoperative complications (20).

Indication for RSA, apart from age at the time of surgery, was another factor that had a significant influence on complication/revision rates and prosthesis survival. In our series, revision RSA for failed previous arthroplasty had the highest complication rate (35.0%), followed by the infection sequelae (33.3%). Among primary RSA procedures, CDS and PHF had the lowest rates of complications (7.8% and 9.0%, respectively) and revision (5.2% and 5.6%, respectively). In accordance with our results, Chelli et al. (7) stated that diagnosis of primary RSA was one of the main predictive factors for complications and revisions. The authors reported high survival rates of RSA in massive cuff tears at 10 years. In their series, RSA for tumors, fracture sequelae, and revision RSA were associated with inferior survival rates and with major complications. The authors related this to the high frequency of missing bone stock in these patients and possible impaired stability of the prosthesis (21).

Our findings provide clinical recommendations by highlighting the necessity for personalized decision-making in RSA. Surgeons must take into account patient age, indications, and surgical history while planning RSA, as these elements significantly influence outcomes. In younger patients or those receiving revision for previous unsuccessful arthroplasty, collaborative decision-making must consider the increased risk of early failure and the possibility of reoperation.

A further practical consideration is the time of follow-up. Considering that the majority of complications and failures occurred within the initial two years, particularly in revision cases or younger patients, more rigorous and frequent early postoperative monitoring may be warranted in these subgroups. Adjusting rehabilitation intensity or imposing activity modifications may be necessary for these higher-risk populations. Consequently, this study supplements the existing knowledge regarding RSA outcomes and survival and offers insights into patient and procedural characteristics that may inform prognosis and treatment approaches. This also emphasizes that a nuanced approach, rather than a uniform method, is crucial in RSA.

Study Limitations

We acknowledge that there are several limitations related to our study. The retrospective nature of the study is the first limitation that needs to be mentioned. Complication, revision, and survival rates are the only reported data. Clinical baseline and outcome data were not evaluated, which might be considered another drawback of this study. Another limitation is the relatively small patient population compared to registry studies. However, this study has one of the largest series in the literature from a single center, which constitutes its main strength. Most of the available data regarding the survival of RSA are derived from registry studies or multicenter studies with numerous surgeons, surgical techniques, implants, or follow-up protocols. This heterogeneity might cause some possible biases if these parameters are not controlled in these studies. Therefore, more accurate inferences can be made from our findings. Despite the use of a standardized surgical technique and an established follow-up protocol, four different prosthetic systems were used throughout the study period. Potential variations in prosthesis design, instrumentation, or component characteristics among prosthesis types may have introduced confounding effects on survivorship results and should be acknowledged as a limitation.

Conclusion

RSA showed a satisfactory mid- to long-term survival probability, reaching almost 90% in the overall population. Younger age at surgery led to a higher complication rate and worse survival probability. Even though male patients showed a tendency to fail in the short-term, survival probabilities were comparable between male and female patients in the long-term and gender did not have a significant impact on complications and revision rates. Revision RSA had a significantly lower survival probability and higher complication rates than primary RSA. Among

primary RSA indications, CDS showed the most successful results with the lowest complication and revision rates and the highest survival probabilities. These findings would make a valuable contribution to decision-making and risk assessment in clinical practice. However, further research is needed to make more precise conclusions.

Ethics

Ethics Committee Approval: Institutional Review Board approval was obtained from the relevant Bezmialem Vakif University board before the initiation of the study (approval no.: 6, date: 04.03.2024).

Informed Consent: Written informed consent regarding the use of their medical records data with the purpose of publication has been obtained from all patients before surgical interventions.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.Ş., M.K., K.B., Concept: K.Ş., H.B.K., M.K., K.B., Design: K.Ş., H.B.K., M.K., K.B., Data Collection or Processing: K.Ş., H.B.K., Analysis or Interpretation: K.Ş., H.B.K., Literature Search: K.Ş., H.B.K., Writing: K.Ş.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Evaluation of Venous Thromboembolism in Multiple Myeloma and Its Impact on Mortality

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Abstract

Aim: Thromboembolism in multiple myeloma (MM) is a common complication and its relationship with increased mortality is unclear. We aimed to reveal the incidence of venous thromboembolism (VTE) in the first year of treatment for newly diagnosed MM patients, its effects on mortality, and to evaluate predictive models of VTE in our patients.

Methods: This study was conducted as a retrospective cohort study. A total of 150 consecutive adult patients who were newly diagnosed with and treated for MM were included in the study, conducted at our university hospital from January 2013 to June 2022. The study gathered information on patients' age, gender, type of disease, history of blood clots, surgeries and fractures, body mass index, lab and genetic test results at diagnosis before starting treatment for MM, initial treatment given, use of central venous catheters, blood clot events in the first year of treatment, when these events happened, how they were managed, outcomes of the blood clot events, whether they received preventive treatment for blood clots related to MM or other reasons, their status regarding autologous hematopoietic stem cell transplantation, and their survival.

Results: The incidence of VTE was 8% in the first year of treatment. The median VTE occurrence was 60 days. The mortality rate in the entire patient group was 48%. Median survival was 72 months in patients with a VTE event, while it was 58 months in patients without a VTE event. This difference was not found to be statistically significant (p=0.357). Being in the high-risk group of the IMPEDE VTE score was a statistically significant predictor of a VTE event (p=0.027) in univariate logistic regression analysis.

Conclusion: We showed that VTE events in the first year of treatment did not increase mortality. Except for high risk, the IMPEDE VTE score and the PRISM score models did not predict the risk of VTE in our group of patients.

Keywords: Multiple myeloma, venous thromboembolism, risk assessment, mortality

Introduction

Thromboembolism (TE) is one of the most common complications in multiple myeloma (MM), with a risk of more than 10%, especially in the first year of the diagnosis (1-3). The risk of venous TE (VTE) in patients with MM is 20 times higher than that in the general population (4). Underlying factors for TE are defined as patient-related, disease-related, and treatment-related (5). In recent years, some risk assessment models for VTE have been developed. The SAVED score was introduced and validated in 2019 using the Surveillance, Epidemiology, and End Results-Medicare data, and the IMPEDE VTE score was validated using the Veterans Health Administration database, respectively (6-8). Lastly, in 2022, the PRISM score, which consists of abnormal metaphase cytogenetics as a variable, was announced by Cleveland Clinic (9).

Although it is generally accepted that morbidity and mortality due to deep vein thrombosis (DVT) and pulmonary embolism (PE) are increased in MM, the effect of VTE on mortality is controversial. In particular, the results of single-center studies in recent years have shown that VTE has no effect on mortality (1-3,10,11).

Therefore, our study aimed to analyze the incidence of VTE events in newly diagnosed MM patients during the first year of treatment and their impact on survival. Additionally, we aimed to identify predisposing risk factors

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for VTE and evaluate the role of the IMPEDE VTE and PRISM score models in predicting VTE risk.

Methods

Compliance with Ethical Standards

The study was approved by the Trakya University Faculty of Medicine Non-Interventional Scientific Research Ethics Committee (approval no.: 25/01 date: 26.12.2022) and was conducted in accordance with the Declaration of Helsinki.

Study Design

This study was conducted as a retrospective cohort study. A total of 150 consecutive adult patients who were newly diagnosed with and treated for MM were included in the study, conducted at our university hospital from January 2013 to June 2022. Patients with active synchronous malignancy, amyloid light-chain amyloidosis, known thrombotic disease, and thrombotic events before treatment initiation were excluded (Figure 1). All data were collected from the patients' medical files and electronic medical records. The data regarding patients' age, gender, subtype of the disease, history of VTE, surgery and fracture, body mass index (BMI), laboratory and genetic test results at diagnosis before starting MM treatment, initial induction treatment, use of central venous catheter, VTE event in the first year of treatment, timing of VTE, management and outcome of VTE event, receiving thromboprophylaxis related to MM or non-MM indications, the status of autologous hematopoietic stem cell transplantation (ASCT) and survival were collected. The diagnosis of MM was made according to International Myeloma Working Group (IMWG) criteria (12,13). Patients' laboratory tests included levels of total protein (g/dL), albumin (mg/L), lactate dehydrogenase (LDH) (U/L), urea (mg/dL), creatinine (mg/dL), beta 2 microglobulin (mg/L), D-dimer (mg/L), and C-reactive protein (mg/dL). For genetic tests, fluorescent in situ hybridization (FISH) and chromosomal cytogenetic analysis were used. Prognostic staging was made according to the International Staging System (ISS) and revised-ISS (R-ISS) based on the level of serum beta 2 microglobulin, albumin, LDH, and chromosomal abnormalities detected by FISH (14,15). Glomerular filtration rate was calculated with the Modification of Diet in Renal Disease formula (16). Treatment was chosen according to the reimbursement policy prevailing in the country during the study period. The dose of dexamethasone was adjusted according to the age and clinical condition of the patients. IMPEDE VTE and PRISM risk scores were calculated, and risk stratification was applied according to risk models (8,9). The diagnosis of deep venous thrombosis (DVT) was confirmed by the presence of an intraluminal thrombus detected via color Doppler ultrasonography. Pulmonary embolism was confirmed by identifying a total or partial intraluminal defect in a segmental, lobar, or main pulmonary artery via computed tomography angiography and/or a perfusion defect with normal ventilation via ventilation/perfusion scintigraphy in symptomatic patients. Patients were followed until the last follow-up date or death during the study period. All patients who received lenalidomide had thromboprophylaxis with acetylsalicylic acid (ASA) or low-molecular-weight heparin (LMWH) according to IMWG recommendations (6). Low molecular weight heparin was used in the treatment of VTE events and subsequently in thromboprophylaxis. However, due to heparin-induced thrombocytopenia, treatment and prophylaxis of VTE were provided with fondaparinux and rivaroxaban, respectively. Patient groups were compared based on the occurrence of VTE events in terms of demographic, clinical, laboratory, and mortality factors. Additionally, the predictors of VTE events were analyzed.

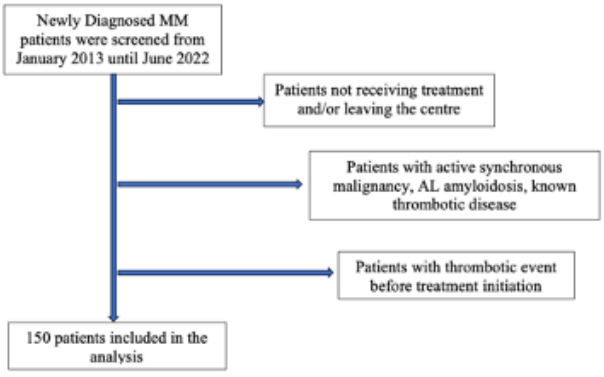

Figure 1. Flowchart of the study
MM: Multiple myeloma

Statistical Analysis

We used statistical package for the social sciences for all statistical analyses. For continuous variables, we determined the mean (±standard deviation) and median (with interquartile range 25-75) values. Categorical variables were shown as percentages. We used Mann-Whitney-Wilcoxon and t-tests for comparing continuous variables due to normal distribution, which is appropriate, and the χ^2 test or Fisher's exact test for comparing categorical variables, as appropriate. We used Kaplan-Meier analysis to determine the survival rates. We performed univariate and multivariate logistic regression analysis to identify predisposing factors for VTE. P-values less than 0.05 were regarded as statistically significant.

Results

One hundred and fifty patients were analyzed. The median age was 64 years, and 56% of patients were female. The most common heavy chain subtype of MM

was IgG (58.7%). Additionally, 18.6% of the patients had the light chain subtype of MM. 41.3% of the patients had ASCT during the study period. The most common initial induction treatment was the bortezomib, cyclophosphamide, and dexamethasone (VCD) protocol, accounting for 62.7%. The median BMI was 26.4 kg/m², and all patients were Caucasian. The median duration of follow-up was 36 months. The mortality rate was 48% during the follow-up.

The median IMPEDE VTE score was 3, and 76% of patients were categorized as low-risk. Revised-International Staging System and PRISM scores could not be determined in 22 patients due to the lack of genetic tests. The median PRISM score was 0, and 61.7% of the patients were categorized as low-risk. Pre-treatment D-dimer value was present in 76 patients, and the median level was 0.93 mg/L. Patients' demographic, epidemiological, and clinical characteristics are shown in Table 1.

Deep venous thrombosis and/or PE occurred in 12 patients (8%) in the first year of treatment. The median day of VTE occurrence was 60 days. DVT occurred in the first 6 patients, while PE developed with or without DVT in the other 6 patients. One of the thrombosis events occurred in the upper extremity, with cephalic venous thrombosis. The remainder of the DVT events were in the lower extremity. One patient experienced a VTE event after central venous catheter insertion for stem cell mobilization prior to autologous transplantation in the eighth month of treatment. Two patients were in remission, while the remaining 10 patients had active disease when the VTE event occurred.

Seventeen patients received thromboprophylaxis. Five of the 17 patients received ASA or LMWH when using IMiDs, while the remaining 12 patients received ASA, clopidogrel, LMWH, rivaroxaban (2/12) or apixaban (1/12), regardless of the indication for MM, mostly for cardiac disease. Two of the patients (2/17) had VTE events during thromboprophylaxis. Sixty five patients (43.3%) received LMWH as enoxaparin sodium, tinzaparin sodium, or bemiparin sodium at the prophylactic dose during hospitalization for initial induction chemotherapy. These patients were not classified as having received thromboprophylaxis because thromboprophylaxis was limited.

In Table 2, the distribution of VTE events according to scores for predicting thrombosis risk and thromboprophylaxis status is shown.

In the comparison of the patient groups according to the occurrence of VTE events in the 1st year of treatment, the difference in PRISM risk classification between groups was statistically significant (p-value 0.021). Detailed analysis is shown in Table 3.

In Kaplan-Meier analysis, the median survival was 62 months (±6.41) in all patient groups. The median survival

Table 1. Characteristics of 150 newly diagnosed multiple myeloma patients

Median age (IQR)	64 years
Gender	Female: 56%
	Male: 44 %
Initial induction treatment	VAD: 17.3%
	VCD: 62.7%
	VRD: 3.3%
	VTD-PACE: 4%
	VELDEX: 12%
	MP: 0.7%
Subtype of disease	IgG κ: 44%
	IgG λ: 14.7%
	IgA κ: 12%
	IgA λ: 10%
	κ: 11.3%
	λ: 7.3%
	Non-secretory: 0.7%
Median total protein (NR: 6.6-8.3) (IQR)	8.40 g/dL
Median D-dimer (NR: 0-0.55) (76 pts) (IQR)	0.93 mg/L
Median glomerular filtration rate (IQR)	65.7 mL/min/1.73 m^2
Median C-reactive protein (NR: 0-0.5) (IQR)	0.55 mg/dL
VTE event in the 1st year of treatment	8%
Receiving thromboprophylaxis	11.3%
Median BMI (IQR)	26.40 kg/m2
Median IMPEDE score (IQR)	3
IMPEDE VTE risk	Low: 76%
	Intermediate: 20.7%
	High: 3.3%
Median PRISM score (128 pts) (IQR)	0
PRISM risk (128 pts)	Low: 61.7%
	Intermediate: 35.9 %
	High: 2.3%
ISS	Stage 1: 44.7%
	Stage 2: 26%
	Stage 3: 29.3%
R-ISS (128 pts)	Stage 1: 46.1%
	Stage 2: 39.1%
	Stage 3: 14.8%
ASCT	41.3%
Mortality rate during follow-up	48%
Median follow-up time (months) (IQR)	36

κ: Kappa light chain, λ: Lambda light chain
IQR: Interquartile range, VAD: Vincristine-doxorubicin and dexamethasone, VCD: Bortezomib-cyclophosphamide and dexamethasone, VRD: Bortezomib-lenalidomide and dexamethasone, VTD-PACE: Bortezomib, cisplatin, cyclophosphamide, dexamethasone, doxorubicin, etoposide and thalidomide, VELDEX: Bortezomib and dexamethasone, MP: Melphalan and prednisone, BMI: Body mass index, IMPEDE: Interventions to prevent deep venous thrombosis and embolism, PRISM: Preserved ratio impaired spirometry, ISS: International Staging System, R-ISS: Revised-International Staging System, ASCT: Autologous hematopoietic cell transplantation, NR: Normal range

Table 2. VTE event and thromboprophylaxis status according to IMPEDE VTE and PRISM risk scores						
Risk score	**Low**		**Intermediate**		**High**	
	VTE event	**TP**	**VTE event**	**TP**	**VTE event**	**TP**
IMPEDE VTE	7%	11.4%	6.45%	9.68%	40%	20%
PRISM	8.8%	11.4%	-	10.9%	33.3%	66.6%

VTE: Venous thromboembolism, TP: Thromboprophylaxis (Percentages were calculated according to the number of patients in risk score categories), IMPEDE: Interventions to prevent deep venous thrombosis and embolism, PRISM: Preserved ratio impaired spirometry

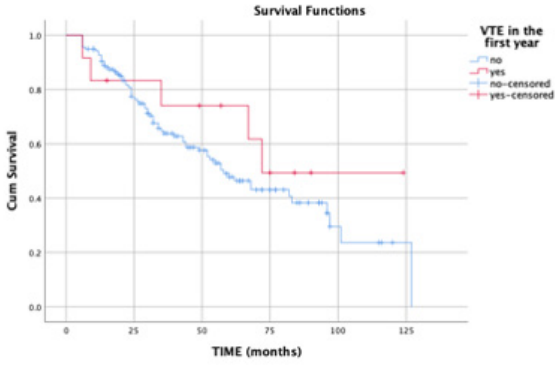

Figure 2. Kaplan-Meier analysis according to the status of VTE event at first year of treatment
VTE: Venous thromboembolism

Table 3. Comparison of the patient groups with VTE event and without VTE event in the 1st year of treatment			
Variables	**With VTE event (n=12 pts)**	**Without VTE event (n=138 pts)**	**p-value**
Age (years) (Mean)	65.08 (±11.10)	63.38 (±10.99)	0.655*
Gender	Male: 58.3%	Male: 42.8%	
	Female: 41.7%	Female: 57.25%	0.459[x]
Initial induction treatment	VAD: 25%	VAD: 16%	
	VCD: 66.7%	VCD: 62.3%	
	VRD: 0	VRD: 3.65%	
	VTD-PACE: 0	VTD-PACE: 0	
	VELDEX: 0	VELDEX: 13%	
	MP: 8.3%	MP: 4.35%	0.152[y]
Subtype of MM	IgG κ: 58.3%	IgG κ: 42.8%	
	IgG λ: 16.7%	IgG λ: 14.5%	
	IgA κ: 16.7%	IgA κ: 11.6%	
	IgA λ: 0	IgA λ: 10.9%	
	κ: 0	κ: 12.3%	
	λ: 8.3%	λ: 7.2%	
	Non-secretory: 0	Non-secretory: 0.7%	0.683[y]
Mean total protein (g/dL)	8.80 (±2.16)	8.35 (±1.52)	0.606*
Mean D-dimer (mg/L) (76 pts)	1.64 (±1.04)	1.71 (±2.04)	0.248*
Mean GFR (mL/min/1.73 m^2)	73.8 (±38.18)	66.56 (±34.18)	0.467*

Table 3. Continued			
Variables	**With VTE event (n=12 pts)**	**Without VTE event (n=138 pts)**	**p-value**
Mean C-reactive protein (mg/dL)	2.95 (±3.52)	1.61 (±2.73)	0.060*
Receiving thromboprophylaxis	16.7%	10.9%	0.628[x]
Mean BMI (kg/m^2)	28.49 (±3.78)	27.38 (±5.79)	0.284*
Mean IMPEDE score	4.17 (±2.20)	3.24 (±1.85)	0.154*
IMPEDE VTE risk	Low: 66.6%	Low: 76.8%	
	Intermediate: 16.7%	Intermediate: 21%	
	High: 16.7%	High: 2.2%	0.082[y]
Mean PRISM score	1 (±2.82)	1.02 (±1.59)	0.210*
PRISM risk (128 pts)	Low: 87.5%	Low: 60%	
	Intermediate: 0	Intermediate: 38.3%	
	High: 12.5%	High: 1.7%	0.021[y]
ISS	Stage 1: 44.2%	Stage 1: 44.2%	
	Stage 2: 33.3%	Stage 2: 25.4%	
	Satge 3: 16.7%	Stage 3: 30.4%	0.597[y]
R-ISS (128 pts)	Stage 1: 62.5%	Stage 1: 45%	
	Stage 2: 37.5%	Stage 2: 39.2%	
	Stage 3: 0	Stage 3: 15.8%	0.551[y]
ASCT	41.7%	41.3%	1.000[x]
Deaths during the follow-up	41.7%	48.6%	0.876[x]
Mean duration of follow-up (months)	56.92 (±35.89)	43.33 (±28.87)	0.207*

*Mann-Whitney U test, [x]: χ^2 test, y: Fisher's exact test, κ: Kappa light chain, λ: Lambda light chain
VTE: Venous thromboembolism, VAD: Vincristine-doxorubicin and dexamethasone, VCD: Bortezomib-cyclophosphamide and dexamethasone, VRD: Bortezomib-lenalidomide and dexamethasone, VTD-PACE: Bortezomib, cisplatin, cyclophosphamide, dexamethasone, doxorubicin, etoposide and thalidomide, VELDEX: Bortezomib and dexamethasone, MP: Melphalan and prednisone, GFR: Glomerular filtration rate, BMI: Body mass index, ISS: International Staging System, R-ISS: Revised International Staging System, ASCT: Autologous hematopoietic cell transplantation

was 72 months in patients with a VTE event in the first year of treatment and 58 months in patients without a VTE event. This difference was not found to be statistically significant (p-value 0.357) (Figure 2). Cumulative survival rate was 94% (±2%) at 12 months in the group without

a VTE event, while it was 83% (±8%) at 12 months in the group with a VTE event in the first year of treatment. None of the deaths were attributed to VTE.

Regarding predictors of VTE, univariate logistic regression analysis showed that being in the high-risk IMPEDE VTE categorization was a predictor of an 8.8-fold increased risk of VTE (p-value 0.027). None of the variables was found to be predictive of VTE risk in the multivariate logistic regression analysis.

Discussion

Multiple myeloma patients have an increased risk of VTE, especially in the first six months of diagnosis (4). VTE risk assessment should be carefully conducted at diagnosis to include patient, disease, and treatment factors, and the need for thromboprophylaxis should be revealed. In recent years, some risk assessment models have been developed and validated, although there is no recommendation for thromboprophylaxis (7-9,17).

The incidence of VTE was reported to be between 6.5% and over 10% within the first year in newly diagnosed MM (NDMM) patient groups in various studies, where the thromboprophylaxis ranged between 22% and 99% in patient groups (1-3,10,11,18). A recent retrospective study at Mayo Clinic reported an 11.7% incidence of VTE within the first year of diagnosis for NDMM patients using triplet or quadruplet lenalidomide-based induction regimens (19). In the studies from Asia and Mexico, where immunomodulatory drugs (IMIDs) were used in more than half of the patients' initial treatment, the incidence of VTE ranged between 10% and 15% (1-3). The median timing of VTE was reported to range from 66 days to 3.5 months, and the most common site of VTE was lower extremity DVT, with a rate of >50% in the studies (1,3,10,11). In our patient group, the median time of VTE occurrence and the site of VTE were compatible with the literature. However, the incidence of VTE was slightly lower than the literature at a rate of 8%, despite the low rate of thromboprophylaxis at 11.3% in the entire patient group. Although the use of doxorubicin, which is a risk factor for thrombosis in induction therapy, was common in our study group, the use of IMID was very limited. Besides that, more than 90% of the patients in our study were on VCD, vincristine-doxorubicin and dexamethasone (VAD), or bortezomib and dexamethasone (VELDEX) regimens, with over 60% receiving the VCD regimen for induction treatment. None of the patients with VTE received IMIDs-based induction therapy, while all patients who had IMIDs in induction therapy were in the non-VTE group. We could not show a statistically significant difference between groups with and without VTE when comparing groups based on induction treatments. This lower VTE rate may be related to our standard clinic practice of hospitalizating patients and administrating thromboprophylaxis with LMWH during the first cycle of induction chemotherapy, regardless of the clinical status and the high thromboprophylaxis compliance in the use of subsequent lenalidomide treatment.

In the studies, there was no difference between groups with and without TE regarding subtype of disease, ISS, R-ISS, M protein level, creatinine level, paraprotein type, and renal failure like ours (10,19).

Most patients in our study group were classified as low-risk according to IMPEDE VTE and PRISM score models, with no intermediate-risk patients in the VTE event group. The IMPEDE VTE and PRISM risk scores did not differentiate the VTE risk well enough. We think that this situation could be related to the decreased use of IMIDs in the induction treatment, while the use of doxorubicin was more common. The high-risk classification of the IMPEDE VTE risk score was found to be a VTE predictor in our patient group, probably because doxorubicin is a strong variable in this model. The PRISM risk score could not predict a VTE event, probably due to limited use of IMID in induction treatment, which is a very strong variable in this risk assessment model. In addition, all the patients except one who were treated with had dexamethasone. Dexamethasone dose, a variable in the IMPEDE VTE risk score, was "low" due to adjustments related to fragility and age in our clinical practice (8). Ethnicity is also a variable in both score models. In the study with a group of Chinese patients, IMPEDE VTE was found to be a predictor of VTE, while in our study, where all patients were of Caucasian race, it was not a predictor of VTE, except in cases classified as high-risk (20). In the study from Malaysia, IMPEDE VTE was not an independent factor for thrombosis in multivariate analysis, while the study from Mexico reported that the IMPEDE VTE score was efficient in discriminating between high- and intermediate-risk patients (1,2).

The impact of VTE on mortality has been unclear in previous studies. In a population-based study that was conducted between 1987 and 2005, the group with a VTE event had a higher mortality rate than the group without VTE at 1.5, and 10 years (hazard ratio 2.9, 1.6, and 1.6, respectively). However, the occurrence of VTE was not associated with inferior survival at 6-month mortality (21). In the other study, the median survival was 32.5 months, and the mortality rate was 27.2% within 1 year. VTE was found to be a factor that increases mortality with a 67% relative risk at 6 months (11). Barrett et al. (18) reported the mortality odds ratio as 3.3 in patients with a VTE event compared to the age-matched control group. The occurrence of VTE was found to be an independent risk factor for early death, although there were no VTE-related deaths in the study. In the study of lenalidomide-based

induction regimens in newly diagnosed MM patients, TE was reported as a predictive factor for mortality according to univariate and multivariate analysis (19). In contrast to these previous studies, occurring thrombosis was not found to impact survival (2,3). The 3-year overall survival was 60% and 63% in the groups with and without thrombosis, respectively, at a p-value of 0.6 (3). In our study, the median survival time was 62 months and the mortality rate was 48% in the cohort during the follow-up. Surprisingly, the median survival was longer (72 months) in patients with a VTE event than in patients without one (58 months), a difference that was not statistically significant. This difference might be due to better monitoring and treatment of VTE events, careful prevention measures, and different treatment choices based on the specific type of event in the VTE group.

Study Limitations

The study, retrospectively designed, has limitations due to the limited use of IMIDs in initial induction therapy and the small number of patients.

Conclusion

This study showed that VTE status does not affect survival. In addition, only the high-risk category of the IMPEDE VTE risk score predicted VTE events. We believe that the new VTE risk score models are evolving. However, the utility of the models in daily practice, the lack of thromboprophylaxis recommendations, and compliance with recommendations are currently unresolved issues.

Ethics

Ethics Committee Approval: This study was approved by the Trakya University Faculty of Medicine Non-Interventional Scientific Research Ethics Committee (date: 26.12.2022, approval no.: 25/01).

Informed Consent: All the patients or first-degree relatives have signed informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.A.K., H.O.K., E.U., A.M.D., Concept: T.A.K., H.O.K., Design: T.A.K., H.O.K., E.U., A.M.D., Data Collection or Processing: T.A.K., H.O.K., E.U., Analysis or Interpretation: T.A.K., H.O.K., E.U., Literature Search: T.A.K., H.O.K., A.M.D., Writing: T.A.K., H.O.K., E.U., A.M.D.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Clinical Characteristics of Patients with Cancer in Older Ages of 85 Years and Over

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Abstract

Aim: With the aging global population, cancer in very elderly individuals has become an increasingly relevant clinical concern. In this study, we aimed to analyze the clinical characteristics and management approaches of patients aged 85 years and older who were diagnosed with solid tumors.

Methods: This retrospective descriptive study included patients aged ≥85 years who were diagnosed with solid malignancies between January 2010 and December 2022 in a tertiary oncology center. Medical records were reviewed to collect data on demographics, presenting symptoms, comorbidities, cancer types, diagnostic methods, treatment decisions, and smoking status. Statistical analyses were performed using descriptive methods, with results expressed as means ± standard deviations. A p-value of <0.05 was considered statistically significant.

Results: The mean age of 150 patients was 89.53±2.68 years and 58% were male. The most common complaint was palpable mass/lesion (31%). Comorbidities were present in 75% of the patients. The most common cancer diagnoses were skin (30%), lung (13%) and bladder (11%) cancers. At the time of diagnosis, in the staging, positron emission tomography-computed tomography was used most frequently (43%). 27% of the patients were smokers. Surgical and hormonal treatments were primarily administered because of advancing age and co-morbidities, but the best supportive treatment was the first decision in 43% of the patients.

Conclusion: This study highlights the distribution of malignancy types, comorbidities, diagnostic trends, and treatment challenges in patients aged 85 and above, underlining the need for individualized approaches in this growing patient population.

Keywords: Geriatric oncology, very elderly patients, solid tumors, comorbidities, treatment decision, supportive care

Introduction

As the global population continues to age, the incidence of cancer in older adults is rising significantly (1). Age is one of the most important risk factors for developing cancer due to cumulative exposure to carcinogens and age-related decline in DNA repair mechanisms (2). Elderly individuals constitute a heterogeneous group not only physiologically, but also psychologically, socially, economically, and culturally (3). Consequently, cancer management in this age group presents complex challenges, including polypharmacy, comorbidities, and variability in functional status (4).

While there are numerous studies investigating cancer in elderly populations, the literature specifically focusing on patients aged 85 years and above is scarce (5). Individuals in this age bracket, often referred to as the "oldest old," are underrepresented in clinical trials, leading to gaps in evidence-based recommendations for their treatment (6). Moreover, diagnostic and therapeutic decisions for these patients are frequently influenced by clinical intuition, comorbidities, or perceived frailty, rather than standardized protocols (7-11).

We hypothesized that patients aged 85 years and older with solid tumors would present with distinct demographic, clinical, and diagnostic characteristics

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compared to younger cohorts of the elderly population and that treatment decisions would be heavily influenced by age-related factors such as comorbidity and functional limitations. The aim of this study was to analyze the demographic and clinical features, staging practices, and treatment decisions in patients aged 85 and above with solid tumors. This study will contribute to the limited literature in this area and may help guide individualized treatment strategies for this growing patient population.

Materials and Methods

Compliance with Ethical Standards

This study was approved by the Non-Interventional Clinical Research Ethics Committee of the Aydin Adnan Menderes University Faculty of Medicine (date: 22.02.2018, approval no.: 1342). The study was conducted in accordance with the principles of the Declaration of Helsinki. As the study was retrospective, informed consent was not required.

Study Design and Population

This retrospective descriptive study included patients aged ≥85 years who were diagnosed with solid malignancies and followed up at the oncology department of a tertiary care center between January 1, 2015, and December 31, 2020.

Patients aged 85 years and older with a histopathologically confirmed diagnosis of a solid tumor and complete medical records were included in the study. Patients were excluded if they had hematologic malignancies, lacked histopathological confirmation of their cancer diagnosis, or had incomplete or missing clinical data.

The variables assessed in this study included demographic characteristics such as age, sex, and socio-economic status; clinical characteristics such as the type and location of the primary tumor, histological subtype, disease stage at diagnosis, and presenting symptoms; and medical background variables, including comorbidities, smoking history, and family history of cancer. Additionally, data on diagnostic imaging methods used during staging [e.g., positron emission tomography-computed tomography (PET-CT), CT, magnetic resonance imaging], treatment modalities (e.g., surgery, chemotherapy, hormonal therapy, best supportive care), and the intended purpose of treatment (curative, palliative, or supportive) were collected and analyzed.

Statistical Analysis

The distribution of variables was assessed using the Kolmogorov-Smirnov test. Since most variables did not follow a normal distribution, data were expressed as median (minimum-maximum). Non-parametric tests were used accordingly. The Mann-Whitney U test was applied for comparisons between gender groups. Categorical variables were analyzed using the chi-square or Fisher's exact test as appropriate. Statistical analyses were conducted using SPSS version 22.0 (IBM Corp., Armonk, NY, USA), and a p-value of <0.05 was considered statistically significant.

Results

A total of 150 patients aged 85 years and older with histologically confirmed solid tumors were included in the study. While a full overview of clinical and demographic characteristics is presented in Tables 1 and 2, the results below focus on statistically significant findings.

Comorbidities and lifestyle factors demonstrated notable gender-based differences. Chronic obstructive pulmonary disease (COPD) was significantly more common among male patients (36%) than females (8%) (p=0.013). Similarly, smoking history was markedly higher in men, with 44% of males reporting a history of smoking versus only 3% of females (p=0.009). These patterns may partially explain the gender disparity observed in certain cancer types.

At the time of diagnosis, presenting symptoms also differed significantly between sexes (p=0.044). While palpable mass or lesion was the most common complaint among women (41%), urinary tract infection was the leading symptom in men (25%), suggesting possible sex-related diagnostic pathways (Table 1). Skin cancer was the

Table 1. Demographic and clinicopathological characteristics of the patients as well as comparison of these variables in terms of gender

Variables	All patients	Female	Male	p value[α]
n (%)	150	63 (42)	87 (58)	
Age (year); Median (minimum-maximum)	89 (85-99)	87 (85-96)	86 (85-99)	0.393
Comorbidities				
Hypertension	99 (66)	48 (76)	51 (59)	0.013
Heart failure	39 (26)	15 (24)	24 (28)	
COPD	36 (24)	5 (8)	31 (36)	
Diabetes mellitus	19 (13)	6 (10)	13 (9)	
Chronic renal failure	4 (3)	0	4 (15)	
Other comorbidities*	10 (7)	5 (8)	5 (6)	
Status of comorbidity				
Present	113 (75)	54 (86)	59 (68)	0.059
Absent	37 (25)	9 (14)	28 (32)	
Smoking habits				
Present	40 (27)	2 (3)	38 (44)	0.009
Absent	110 (73)	61 (97)	49 (56)	
Cancer history in family				
Present	32 (21)	12 (19)	20 (23)	0.561
Absent	118 (79)	51 (81)	67 (77)	

Table 1. Continued

Variables	All patients	Female	Male	p value[α]
Presentation				
Palpable mass/lesion	47 (31)	26 (41)	21 (24)	0.044
Urinary tract infection	26 (17)	4 (6)	22 (25)	
Pain	24 (16)	14 (22)	10 (12)	
Shortness of breath	19 (13)	5 (8)	14 (16)	
Fatigue	18 (12)	8 (13)	9 (10)	
Constipation	6 (4)	2 (3)	4 (5)	
Dysphagia	5 (3)	1 (2)	4 (5)	
Other symptoms**	9 (6)	5 (8)	4 (5)	
Primary tumor localization				
Skin	45 (30)	24 (38)	21 (24)	0.041
Lung	19 (13)	3 (5)	16 (18)	
Bladder	17 (11)	4 (6)	13 (15)	
Colorectum	14 (9)	9 (14)	5 (6)	
Prostate[β]	11 (7)	-	-	
Liver	9 (6)	1 (2)	8 (9)	
Head-and-neck	7 (5)	3 (4)	4 (4)	
Breast	4 (3)	4 (6)	0	
Others***	24 (16)	15 (24)	9 (10)	
Disease status at time of diagnosis				
Metastatic	76 (51)	26 (41)	50 (58)	0.294
Non-metastatic	74 (49)	37 (59)	37 (42)	
Treatment modalities				
BSC	65 (43)	26 (41)	39 (45)	0.112
Surgery	54 (36)	29 (46)	29 (33)	
RT	19 (13)	9 (14)	10 (12)	
Endocrine treatment	13 (7)	3 (5)	10 (12)	
TACE or RFA	4 (3)	1 (2)	3 (3)	
Targeted treatment	2 (1)	0	2 (2)	
Chemotherapy	2 (1)	0	2 (2)	
Purpose of the cancer treatment				
BSC	65 (43)	26 (41)	39 (45)	0.054
Palliative	45 (30)	11 (18)	34 (39)	
Curative	40 (27)	26 (41)	14 (16)	

[α]The distribution of the data was determined by the Kolmogorov-Smirnov test, and it was determined that the data were not equally distributed for all variables. Non-parametric Mann-Whitney U test was used to compare groups. The Kolmogorov-Smirnov test was used for group comparisons for data with <5 patients. A p-value less than 0.05 was considered statistically significant. It is indicated on the table in bold font.
[β]It was not included in the comparison analysis because it was gender specific
*Thyroid diseases, dementia, rheumatoid arthritis, chronic liver disease
**Palpitation (1), headache (1), balance disorder (1), abdominal discomfort (2), dry cough (2), hemoptysis (2)
***Stomach (3), pancreas (2), biliary tract (3), gallbladder (4), thyroid (7), glioblastoma multiforme (1), endometrium (2), cervix (2)
COPD: Chronic obstructive pulmonary disease, BSC: Best supportive care, RT: Radiation treatment, TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation

Table 2. Comparison of some characteristics in cancer types in terms of gender

Variables	All patients (n=150)	Female (n=63)	Male (n=58)	p-value[α]
Skin cancer				
n	45	24	21	
Histological type; n (%)				
SqCC	25 (56)	15 (63)	10 (48)	0.024
BCC	13 (29)	4 (17)	9 (43)	
MM	2 (4)	2 (7)	0	
Others*	5 (11)	3 (13)	2 (9)	
Lung cancer				
n	19	3	16	
Histological type; n (%)				
SCLC	3 (16)	0	3 (19)	0.019
Adeno	6 (32)	2 (67)	4 (25)	
SqCC	9 (47)	1 (33)	8 (50)	
LCLNE	1 (5)	0	1 (4)	
Presence of smoking; n (%)				
Present	14 (74)	1 (33)	13 (81)	0.006
Absent	5 (26)	2 (67)	3 (19)	
Colorectal cancer				
n	14	9	5	
Location of the primary tumor; n (%)				
Colon	10 (71)	8 (89)	2 (40)	0.099
Rectum	4 (29)	1 (11)	3 (60)	
Presence of smoking; n (%)				
Present	4 (29)	1 (22)	3 (60)	0.104
Absent	10 (71)	8 (89)	2 (40)	
Bladder cancer				
n	17	4	13	
Histological type; n (%)				
PUC	14 (82)	2 (50)	12 (92)	0.034
SCC	1 (6)	1 (25)	0	
Adeno	1 (6)	1 (25)	0	
MM	1 (6)	0	1 (8)	
Presence of smoking; n (%)				
Present	7 (41)	0	7 (54)	0.215
Absent	10 (59)	4 (100)	6 (46)	

*Baso-squamous cell carcinoma (2), Meckel cell carcinoma (1), Lentigo maligna melanoma (1), undifferentiated carcinoma (1)
[α]The distribution of the data was determined by the Kolmogorov-Smirnov test, and it was determined that the data were not equally distributed for all variables. Nonparametric Mann-Whitney U test was used to compare groups. The Kolmogorov-Smirnov test was used for group comparisons for data with <5 patients. A p-value less than 0.05 was considered statistically significant. It is indicated on the table in bold font
SqCC: Squamous cell carcinoma, BCC: Basal cell carcinoma, MM: Malignant melanoma, SCLC: Small-cell lung cancer, Adeno: Adenocarcinoma, LCLNE: Large-cell lung neuroendocrine tumor, SCC: Small cell carcinoma, PUC: Papillary high-grade urothelial carcinoma

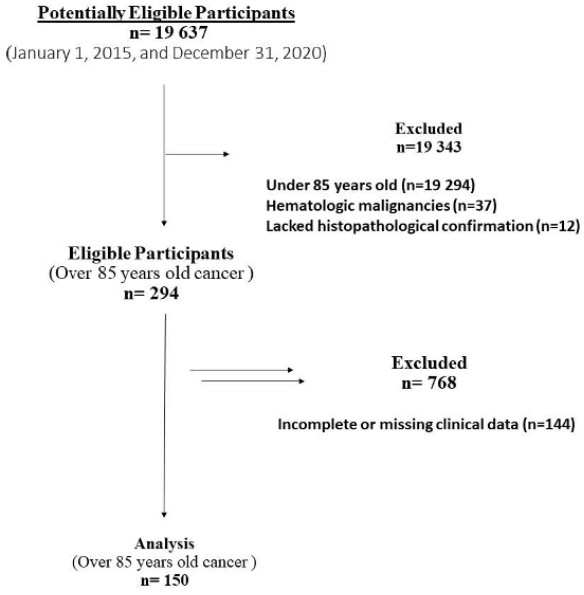

Figure 1. Flowchart of the study

most frequent solid malignancy overall, and its histological subtypes varied significantly between sexes (p=0.024). Squamous cell carcinoma was more common in women (63%), whereas basal cell carcinoma predominated in men (43%) (Table 2). This disparity may reflect differences in lifetime sun exposure or occupational risk factors.

Lung cancer was significantly more common in male patients (18% vs. 5%, p=0.013) and was strongly associated with smoking history. Among lung cancer cases, 81% of men had a history of smoking compared to 33% of women (p=0.006). Non-small cell lung cancer was the predominant subtype.

In addition, bladder cancer was diagnosed more frequently in men than in women (15% vs. 6%, p=0.034). Urothelial carcinoma was the most common histological type observed in these cases (Table 2).

Other findings, including age distribution, family history of cancer, and overall treatment patterns, did not demonstrate statistically significant differences and are provided for reference in Tables 1 and 2.

Discussion

This study provides one of the few detailed overviews of clinical characteristics, gender-related patterns, and treatment approaches in patients aged 85 years and older with solid tumors. Given the increasing proportion of this "oldest old" group in the population, a more profound understanding of their cancer profiles is of growing clinical importance.

Our findings revealed significant gender-based differences in comorbidities and cancer risk factors. The notably higher prevalence of COPD and smoking history in men aligns with global epidemiologic trends but also underscores the importance of obtaining detailed behavioral and environmental exposure histories even in advanced age (12,13). These factors appear to directly influence cancer distribution, particularly the increased rates of lung and bladder cancers among men in our cohort (14,15).

One of the more novel findings in our study was the significant gender difference in initial presenting symptoms. The predominance of palpable masses in women and urinary tract infections in men may reflect both anatomical differences and diagnostic pathways shaped by prior comorbidities or healthcare access. This observation suggests that clinicians should maintain a high index of suspicion when evaluating non-specific symptoms in elderly patients, as classical "red flag" signs may be absent (16).

The histological variation in skin cancers between genders-squamous cell carcinoma being more common in women and basal cell carcinoma in men-could be related to differing patterns of sun exposure, occupational background, or immune senescence. The relatively high prevalence of skin cancer overall may also be linked to geographic and climatic factors, as the majority of patients in our study resided in the Aegean region, which has high year-round UV exposure (17,18).

An unexpected finding was the widespread use of PET-CT for staging, even among patients for whom no active treatment was eventually administered. While this might suggest an overuse of imaging in certain settings, it may also reflect defensive medical practice or institutional policy (19,20). This raises important questions about the appropriateness and cost-effectiveness of advanced imaging in this age group, particularly when treatment is unlikely to be pursued. Future studies should explore how oncologists make diagnostic decisions in very elderly populations and whether clinical tools or geriatric assessments might improve decision-making (20-24).

The low rate of chemotherapy use in our sample was not surprising, as many patients were managed with either surgical or hormonal or best supportive care approaches (25-30). This reflects both patient-related factors (e.g., frailty, comorbidities) and physician-related considerations (e.g., hesitancy to use cytotoxic treatments in elderly patients) (25-27). Importantly, our study emphasizes that treatment decisions in this age group are often not based solely on cancer stage or histology but rather on broader geriatric and ethical considerations.

From a clinical standpoint, our findings suggest that cancer care in patients aged 85 and over must go beyond disease-specific algorithms and incorporate individualized assessments that balance benefit, harm, and patient preference. In particular, the presence of comorbidities

and the nature of presenting symptoms should inform not just treatment but also the extent of diagnostic workup.

Study Limitations

This study has several limitations. First, its retrospective design may have led to incomplete or biased data collection. Second, the heterogeneity of cancer types and the relatively small sample size limited the ability to perform subgroup or survival analyses. Furthermore, data on performance status, frailty scores, or geriatric assessment tools were not available, which might have provided more profound insight into treatment decisions. Despite these limitations, this study provides valuable real-world evidence on cancer characteristics, gender-specific differences, and treatment patterns in patients aged 85 years and older. It contributes to the limited data available on this unique and vulnerable population and may help guide more personalized and age-sensitive oncological care strategies.

Conclusion

This study highlights the clinical complexity of managing patients aged 85 years and older with solid tumors. Significant gender-based differences were observed in comorbidities, cancer types, and lifestyle factors such as smoking. The high prevalence of skin and lung cancers, as well as the reliance on supportive care, underscores the importance of individualized treatment planning. Additionally, the frequent use of advanced imaging even in patients who are not receiving active treatment points to evolving diagnostic trends in geriatric oncology.

As the proportion of very elderly patients continues to grow, our findings emphasize the need for more inclusive research and the development of tailored guidelines that go beyond chronological age and consider biological age, comorbid conditions, and patient preferences.

In conclusion, this study adds important real-world evidence about the diversity and complexity of cancer presentation and management in the oldest age. By highlighting gender-specific differences, imaging trends, and treatment patterns, it underscores the need for geriatric-specific oncology frameworks. As the elderly population continues to expand, so too does the urgency to develop nuanced, evidence-based strategies tailored to their unique needs.

Ethics

Ethics Committee Approval: This study was approved by the Non-Interventional Clinical Research Ethics Committee of the Aydin Adnan Menderes University Faculty of Medicine (date: 10.07.2018, approval no.: 1342).

Informed Consent: As the study was retrospective, informed consent was not required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.K., O.T., S.B., Concept: O.T., S.B., Design: O.T., S.B., Data Collection or Processing: E.K., O.T., Analysis or Interpretation: E.K., O.T., S.B., Literature Search: E.K., O.T., Writing: M.F.D.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Case Report

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A Rare Complication of Perforated Appendicitis in an Adult: Septic Thrombophlebitis of the Portal Vein

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Abstract

Septic thrombophlebitis of the portal vein (STPV) is an extremely rare but potentially fatal complication of acute appendicitis. Patients often present with fever and abdominal pain. In patients presenting with these symptoms, deterioration in liver function tests and right upper quadrant pain should be taken into consideration when evaluating thrombophlebitis. It is thought that the infective process originating from the areas drained by the portal vein plays a role in the etiology of STPV. In this case, we aimed to present the imaging findings of STPV, a rare complication of perforated appendicitis, and to raise awareness of the diagnostic approach.

Keywords: Portal vein, thrombophlebitis, appendicitis, phlebitis

Introduction

Septic thrombophlebitis, first described by Osler (1) in 1882, is a condition that may develop due to intra-abdominal suppurative foci and can cause high mortality and morbidity. Studies have reported annual incidence rates between 2 and 4/100,000 (2). Although diverticulitis most commonly contributes to the etiology, appendicitis also plays a significant role. The presence of a single pathogen in pathogen isolation is more common than the occurrence of polymicrobial infections. In addition, coagulation factor deficiency, malignancy, or HIV infection, which can cause hypercoagulation, may contribute to the development of septic thrombophlebitis of the portal vein (STPV) (3).

Case Report

A 46-year-old male patient with no additional disease presented with a complaint of chronic abdominal pain. On physical examination, there was guarding and rebound in the right lower quadrant of the abdomen. The patient's laboratory findings showed deterioration in liver function tests (LFT) and an increase in acute phase reactants. The ultrasound (US) examination revealed increased echogenicity and a heterogeneous appearance in the fatty planes in the right lower quadrant. The appendix could not be evaluated due to its retrocecal location. A Doppler US examination revealed a thrombosed appearance in the lumens of the superior mesenteric vein (SMV), portal vein, and left portal branch. On the computed tomography (CT) examination, a heterogeneous area with peripheral contrast enhancement was observed in the right lower quadrant of the abdomen, in the appendiceal area, which was evaluated as an abscess (Figure 1). Additionally, a contrast material-filling defect compatible with thrombosis was observed, extending from the SMV to the portal vein and the left portal branch (Figures 2, 3). The findings were consistent with STPV secondary to abscess formation caused by perforated appendicitis. The patient was started on broad-spectrum antibiotic treatment and surgery was planned. After the appendectomy, the patient received antibiotic therapy. *Streptococcus* was detected in the blood culture. The patient was discharged after clinical and laboratory findings improved. After discharge, the patient did not attend any follow-up visits. The materials for this case report were obtained in May 2021, and informed consent was obtained from the patient.

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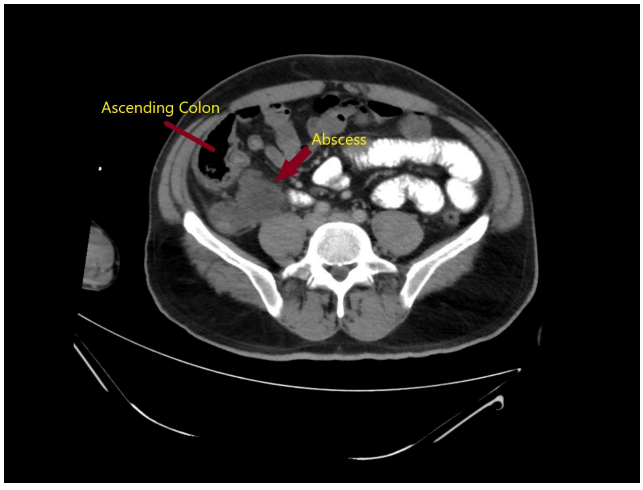

Figure 1. In the axial plane CT image with oral-IV contrast, an appendiceal abscess is observed, showing peripheral contrast enhancement and accompanied by heterogeneous fatty tissues (red arrow)
CT: Computed tomography

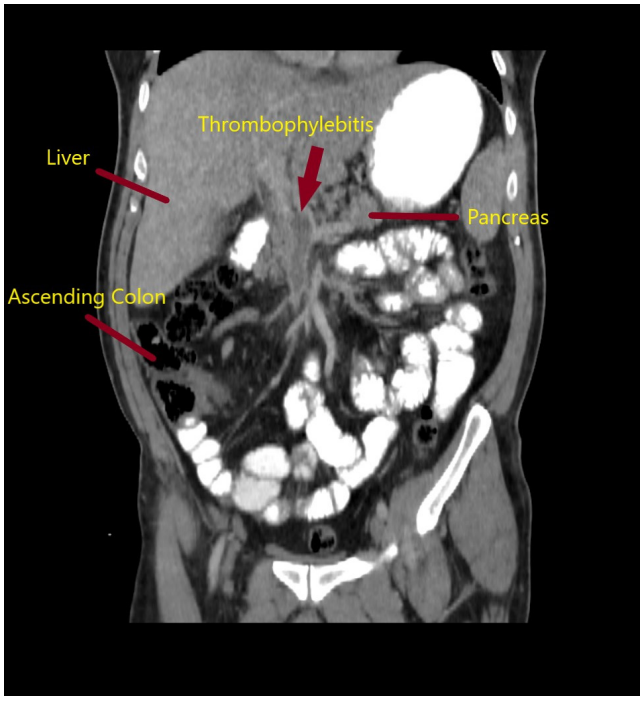

Figure 2. In the coronal plane CT image with oral-IV contrast, a hypoattenuating thrombus extending from the SMV to the portal vein is observed (red arrow)
CT: Computed tomography, SMV: Superior mesenteric vein

Discussion

Septic thrombophlebitis of the portal vein, also known as septic thrombophlebitis or pylephlebitis, is a complication in which diagnosis is crucial because it can be asymptomatic and cause life-threatening consequences.

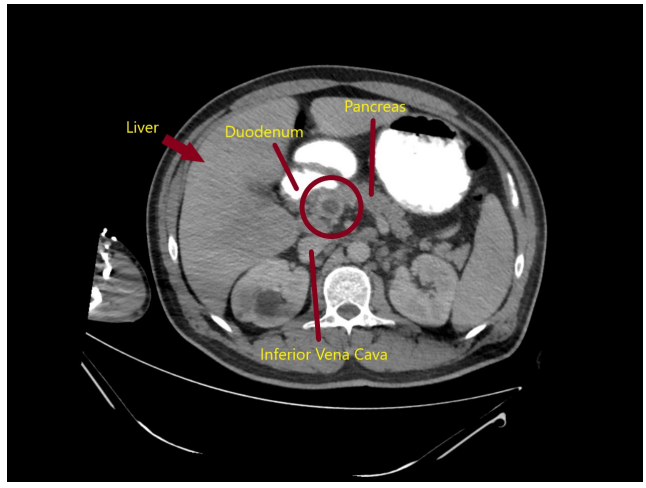

Figure 3. In the axial plane CT image with oral-IV contrast, a central luminally located, hypoattenuating thrombus causing a filling defect in the portal vein is observed (red circle)
CT: Computed tomography

It often develops following an intra-abdominal infection that is drained by the portal vein and its branches. Clinical findings and symptoms vary depending on the location and severity of involvement. It may be asymptomatic or present with symptoms such as fever, nausea, vomiting, and right upper quadrant pain. In addition, leukocytosis, deterioration in LFTs, and an increase in acute phase reactants are prominent findings in laboratory tests (3,4). In our case, similar to the literature, right upper quadrant pain, an increase in acute-phase reactants, and leukocytosis were present. The most common focus of infection has been reported as diverticulitis. Appendicitis is more common in patients with an earlier average age of involvement, and diverticulitis is more common in older patients (3). The most frequently isolated pathogens are *Escherichia coli, Proteus mirabilis*, *Bacteroides fragilis,* and *aerobic streptococci* (3,5). In our case, the response to antibiotic therapy was favorable, and pathogen isolation was not deemed necessary.

Different diagnostic modalities can be used in the radiological evaluation of STPV. Filling defects in the portal vein and its branches can be seen on Doppler US examination. Computed tomography examination is preferred because of its high resolution, ability to determine the primary source of infection, and capacity to evaluate portal venous anatomy. On CT examination, the primary source of infection may appear as heterogeneity in fatty tissues and enlarged lymph nodes. if an abscess is suspected, air-fluid levels, fluid-fluid levels, and peripheral heterogeneous contrast enhancement are noteworthy findings (2,3). Gas and filling defects may be seen in the portal vein and its branches. The presence of gas in the

portal vein may be the first radiological finding (6). To evaluate the portal system under optimal conditions on CT examination, the images must be obtained using the appropriate protocol and in the portal venous phase (3).

Mortality rates of up to 19% have been reported in the literature, but they are decreasing due to modern diagnostic techniques and early and effective initiation of broad-spectrum antibiotics. Treatment focuses on broad-spectrum antibiotics and eliminating the source of infection (3,5).

In conclusion, STPV is an important complication due to its rarity, severe course, and potential for fatality. As observed in this study, when clinical findings and patient complaints are present, imaging of regions distant from the source of infection should be prioritized. Since it is a rare complication and requires imaging of distant areas, it can be easily overlooked. With radiologists' familiarity with the diagnostic findings, early diagnosis can be made, and effective and rapid treatment can be initiated.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case and any accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.T., Concept: M.I.I., M.T., Design: M.I.I., M.T., Data Collection or Processing: M.I.I., M.T., Analysis or Interpretation: M.I.I., F.C., M.T., Literature Search: M.I.I., F.C., Writing: M.I.I., F.C.

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Case Report

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A Different Result of Minor Head Trauma; Aggressive Periosteal Reaction

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Abstract

While the literature reports cases of calvarial lytic lesion, the association with aggressive periosteal reaction is rare. There are various opinions about the mechanics and treatment of these lesions. This article discusses a case of periosteal reaction, which caused a calvarial lytic lesion after minor head trauma, within the framework of existing literature.

Keywords: Skull fracture, lytic lesion, periosteum, tumor-like imaging, skull bone tumor

Introduction

Skull fractures are common lesions whose outcomes are well known. Uncomplicated fractures can generally heal without any problems. In all head traumas, the severity of the trauma, the ratio of the surface area exposed to trauma, and the physical properties of the skull area are of importance (1). In post-traumatic skull fractures, the scalp on top is also exposed to the trauma. On the scalp, lacerations and closed injuries, such as cephalic hematoma, at various sizes may impair tissue integrity. In the healing process, lesions on the scalp may develop an infection at the wound site, which may extend to the parietal bone. Furthermore, complications such as the calcification of a cephalic hematoma may also occur (2). Complications are not expected, especially in childhood linear and simple displaced skull fractures. However, "growing skull fracture" (also known as post-traumatic porencephaly, bone absorption, leptomeningeal cyst, post-traumatic aseptic necrosis of the skull, or traumatic ventricular cyst) was identified in children under the age of 3 (3). Calvarial lytic lesions that developed after head trauma have been reported in the literature. These articles, which include case reports or case series, discuss pathogenesis and treatments. This article presents a calvarial lytic lesion, a result of an aggressive periosteal reaction that emerged several years after minor head trauma.

Case Presentation

Consent was obtained from the patient and his relative. A 15-year-old male patient presented to our clinic with the complaint of painful swelling in his head. In the examination, painful swelling in the parietal region on the right side of the back was present, and no neurologic deficit was seen. He has stated that in the anamnesis, he experienced a swelling after hitting his head six years ago, but then the swelling decreased and became hollow. Later, it started swelling again. The patient who did not apply to any medical institution after the trauma has expressed that this swelling has gradually increased recently, and pain has developed as a result. Cranial computed tomography and magnetic resonance imaging revealed a lytic destructive lesion with a heterogeneous contrast involvement in a sporadic punctate pattern affecting the tabula externa in the right posterior parietal (Figure 1a-c). The lesion was first interpreted as significant, suggestive of eosinophilic granuloma. In the differential diagnosis, arachnoid granulation, multiple myeloma, plasmacytoma, and lytic bone metastases were observed. In the patient who

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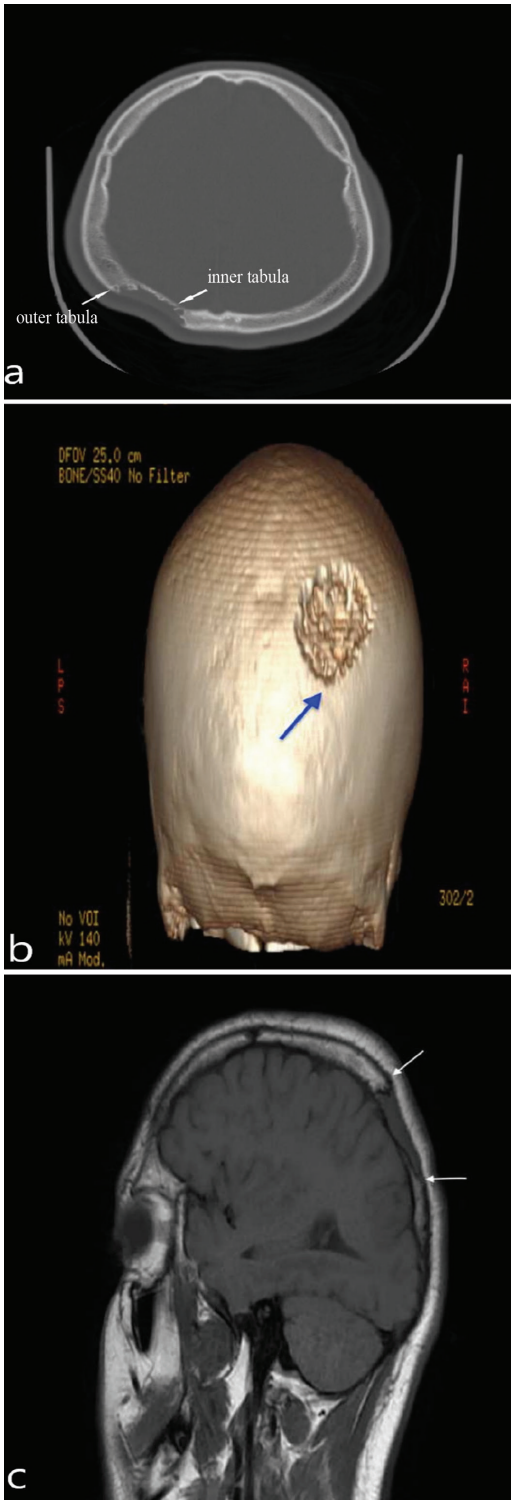

Figure 1. Fifteen-year-old male patient: from a section taken at the a-transverse computed tomography (CT) bone window, a lytic lesion of about 4 cm in diameter destructing the outer tabula in the right parietal bone posterior was found **(a)**; The inner tabula was kept 3D CT inspection **(b)**; Sagittal T1-weighted magnetic resonance imaging shows no intracranial extension of the destructive lytic lesion (between the arrows) **(c)**

underwent surgery after preoperative preparations, the lytic mass was totally removed with 1 cm of solid surrounding tissue. The lesion had no attachment to the dura, and the cranioplasty was performed with titanium mesh. The patient was discharged at the end of the third day without any complications. In the histopathological examination, loss and decrease of bone trabecular volume at the diploe margin, ineffective/intramembranous ossification filling in the margin, and intense fibrous/mesenchymal tissue enlargement showing severe periosteal reaction, bone trabecular fragments of old bone fraction in fibrous tissue, normal diploe in the periphery and calvarial bone with bone marrow were present (Figure 2a, b).

Discussion

The presented case is the development of a tumor-like calvarial lytic lesion, a rare result of the external table fracture, caused by minor closed-head trauma. Since the patient did not seek care from any healthcare facilities after the trauma, the fracture at that time could not be documented. The skull fracture was identified through the detection of bone trabeculae of the old fracture from the pathology report and through the patient's anamnesis. Aggressive periosteal reactions can be seen not only with malignant tumors but also with more benign processes such as infection, eosinophilic granuloma (Langerhans cell histiocytosis), aneurysmal bone cyst, osteoid osteoma, hemophilia, and trauma (4,5). However, aggressive periosteal reaction after trauma is rarely observed. The histopathological findings of calvarial osteolytic lesions reported in the literature have shown differences and have suggested the availability of different mechanisms. In 2011, 2 cases reported by Hermann et al. (6) and pathological examinations of 3 cases from the literature review revealed organized hemorrhage with papillary endothelial hyperplasia, a nonspecific inflammatory reaction with intertrabecular fibroblast proliferation, and reactive fibrous tissue without dural infiltration (7,8). In the mechanism underlying all these cases, it is understood that the nonspecific inflammatory reaction of the periosteum plays a significant role. The triggering factor for this inflammatory process may be intradiploic or subgaleal hematomas resulting from trauma. In the pathological examination of the presented case, the trabecular fragments of the outer tabula indicate the presence of cephalic hematoma and hematoma in the diploe, whereas intense fibrous and mesenchymal tissue enhancement is a sign of severe periosteal reaction. These findings strongly support the information in the literature. While the aggressive periosteal reaction generally affects only the diploe and the external tabula of the skull, there are cases in the literature involving both the internal and the external tabula (7). Although surgical resection can

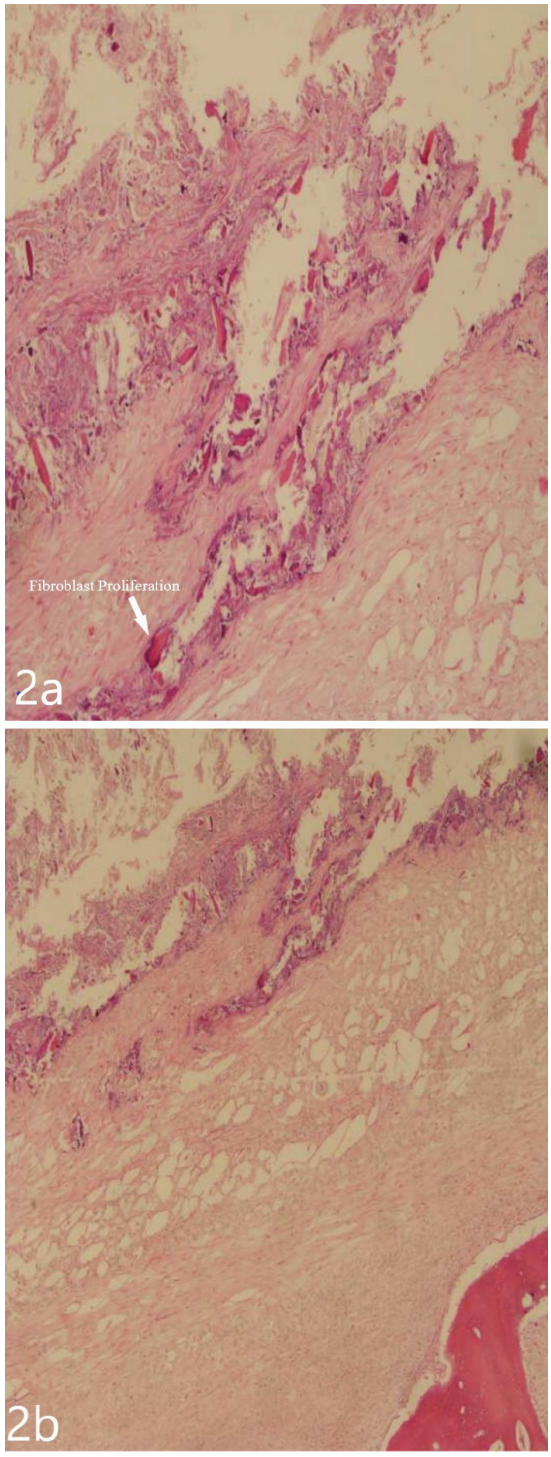

Figure 2. Fibrin, ossification around the fragmented old bone trabeculae in the bone fracture site and fibroblast proliferation surrounding them (H&Ex100) **(a)**; Fragmented bone in the fracture site in the upper left corner; fibroblastic proliferation in between; narrowing at the diploe margin; and Haversian bone in the lower right corner (H&Ex40) **(b)**

H&Ex: Hematoxylin and eosin

be considered for histopathologic diagnosis and other diagnoses, literature information is found stating that spontaneous reossification is also possible (6-8). On the other hand, the fact that the presented case has lasted for about 6 years and the pathologic findings showing ineffective ossification within the range of the diploe and a decrease in the bone trabecular volume indicate that reossification is not always possible. The periosteal reaction contributes to the healing of the bone structure. However, an aggressive periosteal inflammatory reaction may result in focal osteolysis, as in our case, through invasion of the diploe margin on the fracture surface. In the cases presented in the literature, the time between the trauma and admission is between 1 and 7 months (6-8). Due to our presented case being diagnosed about 6 years after the trauma, having radiological features of the lesion and eosinophilic granuloma as pre-diagnosis, and being a painful lesion, craniotomy and cranioplasty were performed.

In conlcusion, the aggressive periosteum reaction should be kept in mind and prior head trauma should be examined in the differential diagnosis of the calvarial lytic lesions. Options such as surgery and monitoring should be considered in the treatment of these types of lesions. The decision should be made according to the characteristics of the patient and the lesion.

Ethics

Informed Consent: Consent was obtained from the patient and his relative.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.E.A., Concept: E.E.E., Design: M.E.A., Data Collection or Processing: E.E.E., Analysis or Interpretation: E.K., Literature Search: E.E., Writing: M.E.A., E.K.

Conflict of Interest: No conflicts of interest were declared by the authors.

Financial Disclosure: This study received no financial support.

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Letter to the Editor

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Smartphone Pinky: Myth or Reality

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Dear Editor,

The rapid integration of smartphones into daily life has undoubtedly reshaped modern behavior; however, it has also given rise to concerns about potential health consequences. A notable concern, popularized under the term "smartphone pinky", suggests that prolonged use of smartphones may result in deformities or functional impairments in the little finger (1).

The concept of the "smartphone pinky" emerged from observations of individuals who noted indentations or deviations in their fifth fingers after prolonged use of their smartphones. These reported changes typically involve lateral indentations on the proximal phalanx or altered finger alignment (2). However, scientific literature on the subject remains limited, leaving room for speculation and misinformation.

Anatomically, the fifth digit plays a vital role in maintaining grip stability and hand function. The fifth digit contributes significantly to power grips by coordinating with the ring finger and the hypothenar muscle group. The proximal phalanx of the fifth digit is particularly vulnerable to pressure-induced marks, especially when smartphones are held in a cradled position for extended periods (1-4). However, it is essential to differentiate between temporary, reversible pressure marks and pathological deformities.

Recent studies have indicated a potential link between excessive smartphone use and an increased incidence of musculoskeletal discomfort, particularly in the hands and wrists. Prolonged usage of these devices has been demonstrated to have a negative impact on hand functionality, grip strength, and pinch strength (2,4). This discomfort may stem from inflammation of the tendon sheath in muscles such as the extensor pollicis brevis and abductor pollicis longus. Furthermore, the pressure exerted on the phalanx of the hand can result in localized pain, a condition known as "smartphone pinky", which may affect the middle phalanx of the fifth finger, leading to discomfort or impaired dexterity (2).

It is noteworthy that well-established conditions such as De Quervain's tenosynovitis and carpal tunnel syndrome have stronger evidence linking them to excessive smartphone use compared to any structural deformity, including the "smartphone pinky". The adaptability of the human hand is such that minor pressure marks or indentations caused by gripping objects are generally transient and not indicative of permanent anatomical changes. Furthermore, factors such as device size, weight, grip strength, and duration of use can significantly influence pressure distribution and the likelihood of discomfort (2,4).

From an ergonomic standpoint, the minimization of repetitive strain and the maintenance of neutral hand positions are foundational principles in the prevention of musculoskeletal injuries. Appropriate device manipulation, uniform distribution of pressure across the hand, and regular rest periods are pivotal in ensuring hand health. Despite its remarkable adaptability, the human hand is susceptible to prolonged exposure to awkward postures, which can lead to the development of musculoskeletal concerns over time (5).

It is recommended that healthcare providers educate patients on the significance of hand ergonomics and the potential risks associated with extended smartphone usage. Encouraging patients to take breaks, adjust their

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grip, and utilize hands-free options can help mitigate the risk of developing recognized musculoskeletal conditions. In treatment, it is imperative to first address the underlying cause. Additionally, the use of braces or splints can be effective in correcting misalignment (2,3,5).

In conclusion, while the concept of "smartphone pinky" reflects a growing concern about the impact of technology on physical health, it appears to be more myth than reality in the current scientific context. Healthcare professionals must prioritize addressing the proven risks of smartphone overuse while advocating for healthy device usage habits. By concentrating on evidence-based ergonomic strategies, we can more effectively preserve hand health in the digital era.

Footnotes

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