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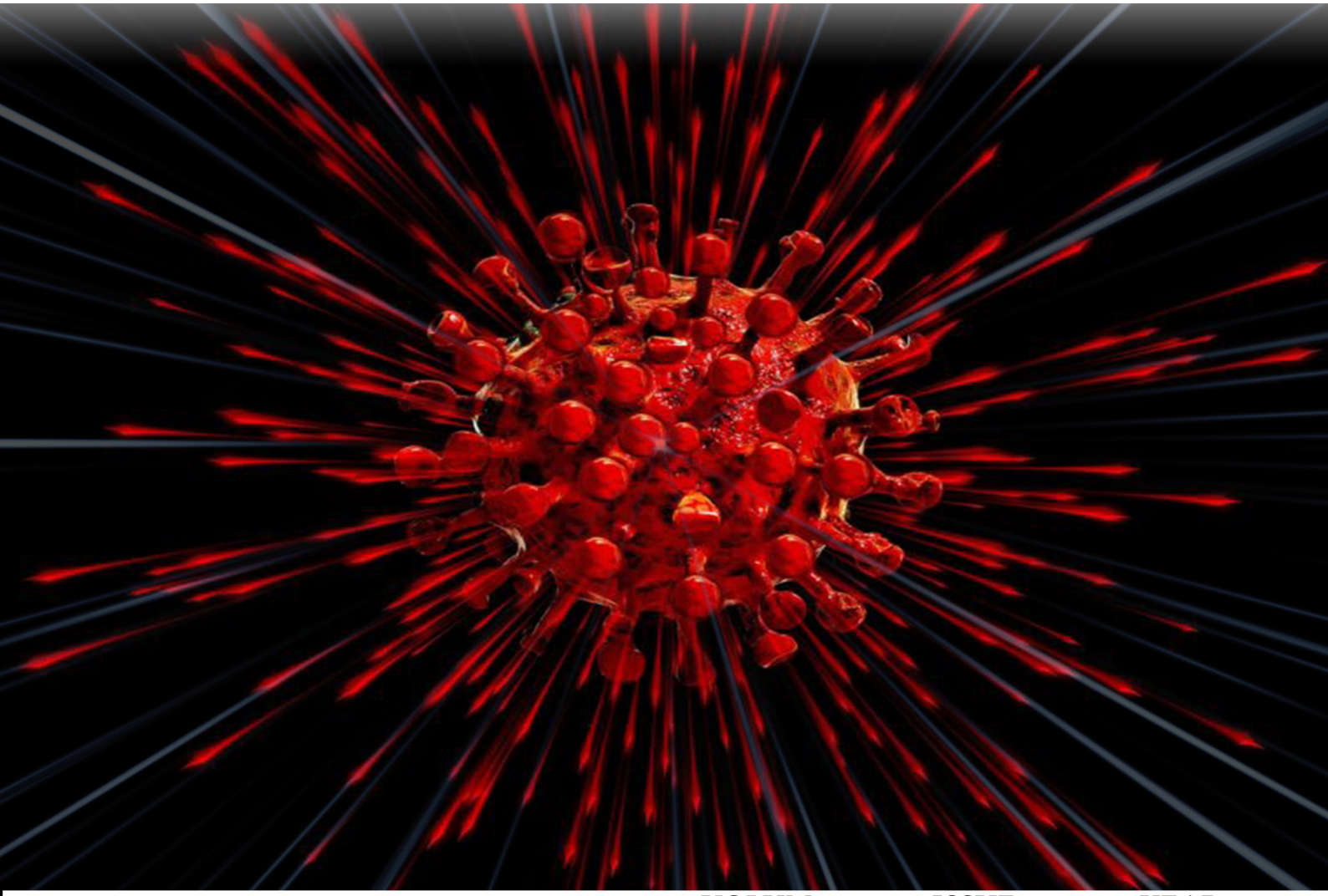

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Our dear readers,

We are proud to publish the second issue of our journal for 2022 with 16 original articles that we think that we think will attract your attention. We increase the scientific quality of our journal day by day.Our goal is to improve our publication quality day by day with the support of all our writers and readers and to appeal to a wider readership. Principally, we want to contribute to international literature at an increasing level and to increase the success bar of our journal by entering indexes such as PubMed, SCI and SCI-Expanded. I would like to thank all authors for submitting articles contributing to both domestic and international literature with their comprehensive scientific content for publication in our journal. I would also like to thank our referees and editors who gave us their precious time. We hope that this issue will be useful to our readers. All the best, see you again in our next issue.

Best regards,

Assoc. Prof. Kenan ÇADIRCI, MD
Editor

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ANATOLIAN CURRENT MEDICAL

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Structured practices increasing patient compliance to noninvasive mechanical ventilation therapy: example of best practice

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ABSTRACT

Aim: The initiation of non-invasive mechanical ventilation (NIV) therapy, mask choice, device settings, and patient follow-up are carried out jointly by physicians and nurses. The physician and the nurses should have knowledge and experience. A checklist for the patient follow-up may increase identifying and preventing problems that may occur. Our study aims to share our data and experiences by documenting the NIV implementation success of our pulmonary intensive care unit (PICU) as an example of best practice.

Material and Method: Patients with respiratory failure who had an indication for NIV therapy between 01.01.2021 and 15.09.2021 were included in the study. Patient data were obtained retrospectively. With the NIV therapy application checklist, what should be done in the preparations, initiation, and follow-up steps of the therapy are standardized. All checkpoints and the outcome of the checklist were recorded routinely.

Results: One hundred one patients with the diagnosis of hypercapnic respiratory failure treated by NIV therapy in PICU were included in the study. There was a significant difference between NIV compliant and NIV noncompliant patients in terms of $PaCO_2$ in arterial blood gas analysis ($p=0.009$). $PaCO_2$ was significantly lower in patients who were noncompliant to treatment than those who were compliant with treatment ($p<0.05$). In all of the patients who were noncompliant with NIV treatment, the problem was detected, the training and the motivation were repeated, and the noncompliance was resolved in 52.6%. For the non-compliant patients who were not resolved, the need for restriction (21.1%) and/or the need for sedation (21.1%) were observed.

Conclusion: Structured checklist is useful in common problems in the implementation and follow-up of the NIV therapy. Increased compliance with NIV therapy reduces the length of stay in the hospital and intensive care unit and decreases the rates of mortality and morbidity.

Keywords: Noninvasive mechanical ventilation, pulmonary intensive care, respiratory failure

INTRODUCTION

Noninvasive mechanical ventilation (NIV) is a therapy that provides positive pressure support through a mask without the use of an endotracheal tube (1). The NIV has been accepted as the first-line therapy in patients with acute respiratory failure and acute exacerbation of chronic obstructive respiratory disease (COPD) (2). Compared with invasive mechanical ventilation (IMV), NIV reduces the length of stay in hospital and intensive care units, mortality, and morbidity of patients with acute and chronic respiratory failure (3).

The most appropriate management of NIV can be achieved if all team members are experienced and trained. NIV practices are successfully implemented by trained intensive care nurses under the management and control of physicians. In many countries, respiratory therapists are responsible for selecting the appropriate mask, optimal mask placement on the face, adjusting ventilator settings, and initiating NIV (4). In our country, nurses in intensive care units often replace the mask, start or pause the ventilator for

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inhalation treatments, nutritional support, removal of secretions, and monitoring the vital values of the patient. Also, nurses are responsible for the compliance, and management of mask complications together with physicians. For this reason, nurses and physicians should be knowledgeable and experienced in the follow-up of the patient, identifying and preventing problems that may occur while NIV therapy.

Many factors affect the success of NIV such as choosing the right mask and connecting it correctly to the patient, ensuring the compatibility of the patient and the ventilator, and the training status and experience levels of the practitioners.

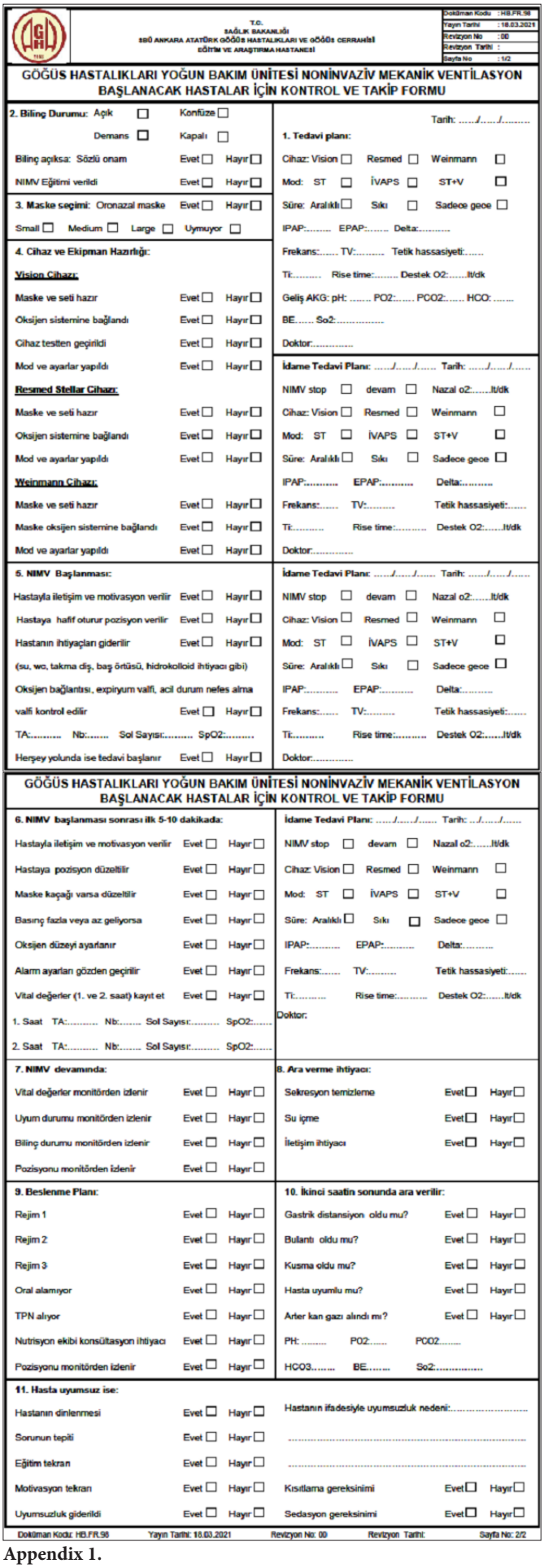
In the studies about the success of NIV in COPD acute exacerbation and acute respiratory failure, the results were shifting between 5% and 60% (5). In an NIV knowledge level survey study conducted by Raurell-Torredà et al. on 407 physicians and nurses in 3 university hospitals, they showed that the rate of correct answers to the questions measuring the level of knowledge was 50%, with no difference between units and hospitals. The level of knowledge of the physicians was significantly higher than the nurses (6).

Our hospital's pulmonary intensive care unit (PICU) has a team of experienced physicians and nurses who specializes in the implementation of NIV. In our PICU, the rate of the NIV failure (due to all causes) was 11.2% in 2019 (n=720) and 9.26% in 2020 (n=745). This study aims to share the experience and the data about the NIV implementation success as an example of best practice.

MATERIAL AND METHOD

This study was approved by the Health Sciences University Keçiören Education and Training Hospital Clinical Studies Ethics Board (Date: 12/10/2021, Decision No: 2012-KAEK-15/2394). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was carried out in a tertiary pulmonary diseases training and research hospital. Our study included 101 patients with respiratory failure who were needed NIV therapy and hospitalized in the PICU between 01.01.2021 and 15.09.2021, and their data were obtained retrospectively. The NIV implementation checklist, which was created by the education officer and physicians of PICU and approved by the hospital's internal quality control unit and the administration of the hospital, was used (**Appendix 1**). This checklist standardized what should be done to the patient before, during, and immediately after NIV therapy.



T.C.
SAĞLIK BAKANLIĞI
SBÜ ANKARA ATATÜRK GÖĞÜS HASTALIKLARI VE GÖĞÜS CERRAHİSİ
EĞİTİM VE ARAŞTIRMA HASTANESİ

Doküman Kodu : HB.FR.96
Yayın Tarihi : 16.03.2021
Revizyon No : 00
Revizyon Tarihi :
Sayfa No : 1/2

GÖĞÜS HASTALIKLARI YOĞUN BAKIM ÜNİTESİ NONİNVAZİV MEKANİK VENTİLASYON BAŞLANACAK HASTALAR İÇİN KONTROL VE TAKİP FORMU

2. Bilinç Durumu: Açık ☐ Konfüze ☐ Derin ☐ Kapalı ☐
Bilinç açıksa: Sözlü onam Evet ☐ Hayır ☐
NIMV Eğitimi verildi Evet ☐ Hayır ☐

3. Maske seçimi: Oronazal maske Evet ☐ Hayır ☐
Small ☐ Medium ☐ Large ☐ Uymuyor ☐

4. Cihaz ve Ekipman Hazırlığı:
Vision Cihazı:
Maske ve seti hazır Evet ☐ Hayır ☐
Oksijen sistemine bağlandı Evet ☐ Hayır ☐
Cihaz testten geçirildi Evet ☐ Hayır ☐
Mod ve ayarlar yapıldı Evet ☐ Hayır ☐
Resmed Stellar Cihazı:
Maske ve seti hazır Evet ☐ Hayır ☐
Oksijen sistemine bağlandı Evet ☐ Hayır ☐
Mod ve ayarlar yapıldı Evet ☐ Hayır ☐
Weinmann Cihazı:
Maske ve seti hazır Evet ☐ Hayır ☐
Maske oksijen sistemine bağlandı Evet ☐ Hayır ☐
Mod ve ayarlar yapıldı Evet ☐ Hayır ☐

5. NIMV Başlanması:
Hastayla iletişim ve motivasyon verilir Evet ☐ Hayır ☐
Hastaya hafif oturur pozisyon verilir Evet ☐ Hayır ☐
Hastanın ihtiyaçları giderilir Evet ☐ Hayır ☐
(su, wc, takma diş, baş örtüsü, hidrokolloid ihtiyacı gibi)
Oksijen bağlantısı, expiryum valfi, acil durum nefes alma valfi kontrol edilir Evet ☐ Hayır ☐
TA:..... Nb:..... Sol Sayısı:..... SpO2:.....
Herşey yolunda ise tedavi başlanır Evet ☐ Hayır ☐

Tarih: ...../...../.....

1. Tedavi planı:
Cihaz: Vision ☐ Resmed ☐ Weinmann ☐
Mod: ST ☐ İVAPS ☐ ST+V ☐
Süre: Aralıklı ☐ Sıkı ☐ Sadece gece ☐
IPAP:..... EPAP:..... Delta:.....
Frekans:..... TV:..... Tetik hassasiyeti:.....
Ti:..... Rise time:..... Destek O2:.....lt/dk
Geliş AKG: pH: ..... PO2:..... PCO2:..... HCO: .....
BE..... So2:.....
Doktor:.....

İdame Tedavi Planı: ...../...../..... Tarih: ...../...../.....
NIMV stop ☐ devam ☐ Nazal o2:.....lt/dk
Cihaz: Vision ☐ Resmed ☐ Weinmann ☐
Mod: ST ☐ İVAPS ☐ ST+V ☐
Süre: Aralıklı ☐ Sıkı ☐ Sadece gece ☐
IPAP:..... EPAP:..... Delta:.....
Frekans:..... TV:..... Tetik hassasiyeti:.....
Ti:..... Rise time:..... Destek O2:.....lt/dk
Doktor:.....

İdame Tedavi Planı: ...../...../..... Tarih: ...../...../.....
NIMV stop ☐ devam ☐ Nazal o2:.....lt/dk
Cihaz: Vision ☐ Resmed ☐ Weinmann ☐
Mod: ST ☐ İVAPS ☐ ST+V ☐
Süre: Aralıklı ☐ Sıkı ☐ Sadece gece ☐
IPAP:..... EPAP:..... Delta:.....
Frekans:..... TV:..... Tetik hassasiyeti:.....
Ti:..... Rise time:..... Destek O2:.....lt/dk
Doktor:.....

GÖĞÜS HASTALIKLARI YOĞUN BAKIM ÜNİTESİ NONİNVAZİV MEKANİK VENTİLASYON BAŞLANACAK HASTALAR İÇİN KONTROL VE TAKİP FORMU

6. NIMV başlanması sonrası ilk 5-10 dakikada:
Hastayla iletişim ve motivasyon verilir Evet ☐ Hayır ☐
Hastaya pozisyon düzeltilir Evet ☐ Hayır ☐
Maske kaçağı varsa düzeltilir Evet ☐ Hayır ☐
Basınç fazla veya az geliyorsa Evet ☐ Hayır ☐
Oksijen düzeyi ayarlanır Evet ☐ Hayır ☐
Alarm ayarları gözden geçirilir Evet ☐ Hayır ☐
Vital değerler (1. ve 2. saat) kayıt et Evet ☐ Hayır ☐
1. Saat TA:..... Nb:..... Sol Sayısı:..... SpO2:.....
2. Saat TA:..... Nb:..... Sol Sayısı:..... SpO2:.....

İdame Tedavi Planı: ...../...../..... Tarih: .../...../.....
NIMV stop ☐ devam ☐ Nazal o2:.....lt/dk
Cihaz: Vision ☐ Resmed ☐ Weinmann ☐
Mod: ST ☐ İVAPS ☐ ST+V ☐
Süre: Aralıklı ☐ Sıkı ☐ Sadece gece ☐
IPAP:..... EPAP:..... Delta:.....
Frekans:..... TV:..... Tetik hassasiyeti:.....
Ti:..... Rise time:..... Destek O2:.....lt/dk
Doktor:

7. NIMV devamında:
Vital değerler monitörden izlenir Evet ☐ Hayır ☐
Uyum durumu monitörden izlenir Evet ☐ Hayır ☐
Bilinç durumu monitörden izlenir Evet ☐ Hayır ☐
Pozisyonu monitörden izlenir Evet ☐ Hayır ☐

8. Ara verme ihtiyacı:
Sekresyon temizleme Evet ☐ Hayır ☐
Su içme Evet ☐ Hayır ☐
İletişim ihtiyacı Evet ☐ Hayır ☐

9. Beslenme Planı:
Rejim 1 Evet ☐ Hayır ☐
Rejim 2 Evet ☐ Hayır ☐
Rejim 3 Evet ☐ Hayır ☐
Oral alamıyor Evet ☐ Hayır ☐
TPN alıyor Evet ☐ Hayır ☐
Nutrisyon ekibi konsültasyon ihtiyacı Evet ☐ Hayır ☐
Pozisyonu monitörden izlenir Evet ☐ Hayır ☐

10. İkinci saatin sonunda ara verilir:
Gastrik distansiyon oldu mu? Evet ☐ Hayır ☐
Bulantı oldu mu? Evet ☐ Hayır ☐
Kusma oldu mu? Evet ☐ Hayır ☐
Hasta uyumlu mu? Evet ☐ Hayır ☐
Arter kan gazı alındı mı? Evet ☐ Hayır ☐
PH: ..... PO2:..... PCO2:.....
HCO3:..... BE:..... So2:.....

11. Hasta uyumsuz ise:
Hastanın dinlenmesi Evet ☐ Hayır ☐
Sorunun tespiti Evet ☐ Hayır ☐
Eğitim tekrarı Evet ☐ Hayır ☐
Motivasyon tekrarı Evet ☐ Hayır ☐
Uyumsuzluk giderildi Evet ☐ Hayır ☐
Hastanın ifadesiyle uyumsuzluk nedeni:.....
.....
.....
Kısıtlama gereksinimi Evet ☐ Hayır ☐
Sedasyon gereksinimi Evet ☐ Hayır ☐

Doküman Kodu: HB.FR.96 Yayın Tarihi: 16.03.2021 Revizyon No: 00 Revizyon Tarihi: Sayfa No: 2/2

Appendix 1.

Statistical Analysis

Data analyzes were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by the Kolmogorov Smirnov test. Levene's test was used to evaluate the homogeneity of variances. Unless otherwise stated, continuous data were defined as mean±SD for normal distributions and median (interquartile range: third quartile - first quartile) for skewed distributions. Categorical data were defined as the number of cases (n, %). Statistical analysis differences in normally distributed variables between two independent groups were compared with Student's t-test. The Mann-Whitney U test was used to compare data that did not show normal distribution. Categorical variables were compared using the Pearson Chi-square test or the Fisher exact test. A p-value of <0.05 was considered significant in all statistical analyses.

RESULTS

The study comprised 101 patients with the diagnosis of hypercapnic respiratory failure who were needed NIV therapy in PICU between 01.01.2021 and 15.09.2021. Patients were classified into two groups as compliant with NIV therapy or not. The NIV mode selection and adjusting parameters were personalized for each patient by the chest physician. S/T mode was the most common choice (93.1%) and the second was intelligent volume assured pressure support (iVAPS (6.9%). The initiation inspiratory positive airway pressure (IPAP) varied between 16-26 cmH2O and, the expiratory positive airway pressure (EPAP) varied between 6-8 cmH2O, and backup respiratory rates (RR) were adjusted to be 14 or 16 or 18. The NIV therapy periods were analyzed and 88.1% of the patients were given NIV therapy 10-12 hours/day, 7.9% were given 18-20 hours/day, and 4% were given only for nighttime (**Table 1**). There was no significant difference in terms of any variable affecting compliance with the NIV therapy (p>0.05).

The analyzes of arterial blood gas (ABG) parameters between the compliant and non-compliant groups are shown in **Table 2.** These results were based on the results of baseline ABGs. There was no significant difference between the two groups in the ABG parameters other than $PaCO_2$ (p>0.05). The $PaCO_2$ levels were significantly lower in patients who were in the non-compliant group (p<0.009). In addition, if the patients' consciousness was acceptable, NIV training was given to all. The adherence to NIV therapy was not significantly affected by the patients' state of consciousness, the status of training, and the status of verbal consent given before NIV therapy (p>0.05). The blood pressure, pulse per minute, and respiratory rates before NIV therapy were compared between the two groups. There was no significant difference in terms of any variable that affected the compliance of NIV therapy (p>0.05). The median systolic blood pressure was lower in noncompliant patients but this difference was not statistically and clinically significant.

There was no significant difference in terms of any variable affecting the NIV compliance (p>0.05) (**Table 3**). However, it was observed that mask leakage was more common (10.5%) in those who were non-compliant but the difference was not statistically significant (p=0.236).

Table 1. Comparison of the parameters between the compliant and non-compliant groups

NIV parameters	NIV compliant		NIV noncompliant		Total		p value
	n	(%)	n	(%)	n	(%)	
Equipment							0.569
Vision™	7	8.5%	1	5.3%	8	7.9%	
Resmed™	68	82.9%	18	94.7%	86	85.1%	
Weinmann™	7	8.5%	0	0%	7	6.9%	
Mode							0.342
ST	75	91.5%	19	100%	94	93.1%	
iVAPS	7	8.5%	0	0%	7	6.9%	
Period (hours/day)							0.194
10-12 h	73	89%	16	84.2%	89	88.1%	
18-20 h	7	8.5%	1	5.3%	8	7.9%	
Full night	2	2.4%	2	10.5%	4	4.0%	
IPAP (cmH2O)							0.634
16	1	1.2%	0	0%	1	1.0%	
18	3	3.7%	2	10.5%	5	5.0%	
20	3	3.7%	1	5.3%	4	4.0%	
22	23	28%	6	31.6%	29	28.7%	
24	48	58.5%	9	47.4%	57	56.4%	
26	4	4.9%	1	5.3%	5	5.0%	
EPAP (cmH2O)							0.315
6	4	4.9%	2	10.5%	6	5.9%	
8	78	95.1%	17	89.5%	95	94.1%	
Delta for Weinmann™							0.999
4	2	28.6%	0	0%	2	25.0%	
6	4	57.1%	1	100%	5	62.5%	
8	1	14.3%	0	0%	1	12.5%	
RR (per min.)							0.287
14	29	35.8%	5	26.3%	34	34%	
16	51	63%	13	68.4%	64	64%	
18	1	1.2%	1	5.3%	2	2%	
Tidal Volume (mL)							-
400	1	14.3%	0	0%	1	14.3%	
500	5	71.4%	0	0%	5	71.4%	
550	1	14.3%	0	0%	1	14.3%	
Inspiration time (second)							0.724
1	7	8.6%	0	0%	7	7%	
1.1	21	25.9%	6	31.6%	27	27%	
1.2	40	49.4%	10	52.6%	50	50%	
1.3	13	16%	3	15.8%	16	16%	
Rise time (second)							-
0.1	81	100%	19	100%	100	100%	

Categorical variables were expressed as frequency (percentage). Variables were compared using Pearson's Chi-square test or Fisher exact test. Significant p-values were shown in bold.

Table 2. Baseline arterial blood gas parameters and baseline blood pressure, pulse per minute, and respiratory rates before the NIV therapy were compared between the two groups

Baseline parameters	NIV compliant		NIV noncompliant		Total		p-value
pH	7.38	±0.07	7.40	±0.09	7.39	±0.07	0.308
PaO_2	59	23.4	70	26.6	61	26.8	0.050
$PaCO_2$	68.9	16.6	56.8	20	65.5	18	0.009
HCO3	38.61	±7.76	36.92	±8.54	38.27	±7.90	0.421
BE	11.8	8.2	12.1	9	11.8	8.1	0.539
SaO_2	90.45	12.7	94	6.6	91.2	11.5	0.119
Systolic Blood Pressure	126.5	15	124	27	125	15	0.375
Diastolic Blood Pressure	67	11	64	10	65	10	0.153
Pulse per minute	81.5	12	80	9	81	9	0.698
Respiration Rate	20	2	20	2	20	2	0.856
SpO_2	93	4	93	3	93	4	0.662

Continuous variables were expressed as either the mean ± standard deviation (SD) or median (IQR). Continuous variables were compared with the Student t-test or Mann-Whitney u test. Statistically significant p-values were in bold.

Table 3. After initiation of the NIV therapy, the monitored parameters which may cause premature discontinuation, compared between the two groups

Interventions to provide sustainable NIV therapy		NIV compliant		NIV noncompliant		Total		p value
		n	(%)	n	(%)	n	(%)	
Communication and motivation	Yes	82	100%	19	100%	101	100%	-
Patient position	Yes	82	100%	19	100%	101	100%	-
Mask leakage								0.236
	No	79	96.3%	17	89.5%	96	95%	
	Yes	3	3.7%	2	10.5%	5	5%	
Pressure adjustments								0.282
	Yes	45	54.9%	13	68.4%	58	57.4%	
	No	37	45.1%	6	31.6%	43	42.6%	
Oxygen level adjustments	Yes	82	100%	19	100%	101	100%	-
Alarm settings	Yes	82	100%	19	100%	101	100%	-

Categorical variables were expressed as either frequency (percentage). Variables were compared using Pearson's chi-square test or Fisher exact test. Statistically significant p-values were in bold.

The analyzes of vital parameters between the compliant and non-compliant groups are shown in **Table 4**. There was no significant difference in terms of any variable affecting the NIV compliance (p>0.05).

Patients who needed a break from the NIV therapy were classified for their reasons. These reasons were secretion cleaning, the need for drinking water, and the need for communication. These parameters were compared between the two groups (**Table 5**). The need for communication reasons was significantly frequent in the non-compliant group (p<0.001). There was no significant difference in terms of other parameters (p>0.05).

After the second hour of the NIV therapy, ABG analysis was performed and early complications of the NIV therapy were questioned. Due to the success of agile interventions, nurses and practitioners must be aware of the early complications. Earl complications were compared between the two groups in **Table 6**. There was no significant difference in terms of early complications between the groups (p>0.05). However, gastric distension was common (10.5%) in non-compliant patients but the difference was not significant.

The analyzes of arterial blood gas (ABG) parameters compared between the compliant and non-compliant groups are shown in **Table 7**. These results were based on the results of the ABGs at end of the second hour. There was no significant difference between the two groups in terms of the ABG parameters (p>0.05).

The interventions for the patients who were non-compliant with NIV were shown in **Table 8**. Allowing the patient to talk freely, identifying the underlying reason for non-compliance, repeating the training, and repeating the motivation resolved the non-compliance status in 52.6% of the patients. If non-compliance status was continued, restriction of the patient (21.1%) and/or sedation was performed (21.1%).

Table 4. Monitored blood pressure, pulse per minute, respiratory rates, and pulse oximeter values while the recently started NIV therapy were compared between the two groups

Vital parameters	NIV compliant		NIV noncompliant		Total		p-value
1st hour							
Systolic Blood Pressure (mmHg)	123.77	±14.83	121.05	±21.08	123.26	±16.10	0.510
Diastolic Blood Pressure (mmHg)	67	11	65	11	66	11	0.121
Pulse per minute	84	9	86	10	84	8	0.311
Respiratory rate (min.)	20	0	20	2	20	0	0.050
SpO2 (%)	93	3	93	1	93	2	0.197
2nd hour							
Systolic Blood Pressure (mmHg)	122.43	±14.49	120.63	±14.81	122.09	±14.50	0.629
Diastolic Blood Pressure (mmHg)	69.71	±8.89	67.11	±8.43	69.22	±8.82	0.249
Pulse per minute	84.5	8	85	9	85	8	0.708
Respiratory rate (min.)	20	2	22	2	20	2	0.096
SpO2 (%)	92	4	90	4	92	4	0.532

Continuous variables were expressed as either the mean ± standard deviation (SD) or median (IQR). Continuous variables were compared with the Student t-test or Mann-Whitney u test. Statistically significant p-values were in bold.

Table 5. Comparisons of the reasons for a break from the NIV therapy were compared between the two groups

Monitoring parameters	NIV compliant		NIV noncompliant		Total		p value
	n	(%)	n	(%)	n	(%)	
Secretion cleaning							0.342
Yes	1	1.2%	1	5.3%	2	2%	
No	81	98.8%	18	94.7%	99	98%	
Need for drinking water							0.999
Yes	8	9.8%	1	5.3%	9	8.9%	
No	74	90.2%	18	94.7%	92	91.1%	
Need for communication							<0.001
Yes	13	15.9%	11	57.9%	24	23.8%	
No	69	84.1%	8	42.1%	77	76.2%	

Categorical variables were expressed as either frequency (percentage). Variables were compared using Pearson's chi-square test or Fisher exact test. Statistically significant p-values were in bold.

Table 6. Early complications after the second hour of the NIV therapy were compared between the two groups

Monitoring parameters	NIV compliant		NIV noncompliant		Total		p value
	n	(%)	n	(%)	n	(%)	
Gastric distension							0.236
Yes	3	3.7%	2	10.5%	5	5%	
No	79	96.3%	17	89.5%	96	95%	
Nausea							0.188
Yes	0	0%	1	5.3%	1	1%	
No	82	100%	18	94.7%	100	99%	
Vomiting							0.188
Yes	0	0%	1	5.3%	1	1%	
No	82	100%	18	94.7%	100	99%	
ABG analyze at the end of the 2nd Hour							-
Yes	82	100%	19	100%	101	100%	

Categorical variables were expressed as either frequency (percentage). Variables were compared using Pearson's chi-square test or Fisher exact test. Statistically significant p-values were in bold.

Table 7. The arterial blood gas parameters end of the second hour of the NIV therapy were compared between the two groups

ABG parameters	NIV compliant		NIV noncompliant		Total		p value
pH	7.42	±0.07	7.43	±0.08	7.42	±0.07	0.496
PaO_2	62.1	25.6	79	38.9	63	28.2	0.117
$PaCO_2$	61	13.3	57	13	60.6	13.6	0.194
HCO_3	38.41	±6.98	34.07	±10.81	37.61	±7.94	0.119
BE	11.5	8.7	9.9	10.6	11.4	9.1	0.683
SaO_2	92.2	8.9	96	11	92.7	9.9	0.157

Continuous variables were expressed as either the mean ± standard deviation (SD) or median (IQR). Continuous variables were compared with the Student t-test or Mann-Whitney U test. Statistically significant p-values were in bold.

Table 8. The interventions for the patients who were non-compliant with NIV therapy

Interventions for the patients who were non-compliant with NIV	n	(%)
Allowing the patient to talk freely		
Succesful	19	100%
Identifying the underlying reason of non-compliance		
Succesful	19	100%
Re-education		
Succesful	19	100%
Re-motivation		
Succesful	19	100%
Resolving the non-compliance status		
Yes	10	2.6%
No	9	47.4%
Need of restriction of the patient		
Yes	4	1.1%
No	15	8.9%
Need of sedation		
Yes	4	1.1%
No	15	8.9%

Categorical variables were expressed as either frequency (percentage).

DISCUSSION

The NIV therapy is frequently initiated and followed by physicians and nurses in the hospitals of Turkey and there is a similar situation in Europe (7). Some of the studies emphasize that there is a lack of knowledge and education. This is a fact that especially for the skills which generally nurses are responsible for such as choosing the appropriate NIV mask size and fitting it correctly. This is probably due to the low level of participation in the training sessions led by training nurses and practices on low-quality simulators, insufficient observation of real-life practices (6,8). Montravers et al. (9) surveyed 32 intensive care units all over France and found that only 39% of the nurses received NIV training and this training was provided by physicians in 87% of them. The hospital was provided practical NIV training only for a few hours. The theoretical training will not substitute real practical experience in fitting on the NIV mask to the patients or monitoring the patient's response to therapy. Nurses must have trainers who are knowledgeable about choosing the appropriate mask size, fitting the mask to the patient, and trying to keep the mask in place throughout the therapy (10). This potential issue has gained prominence with the widespread use of NIV in general wards besides intensive care units and intermediate intensive care units. As a result, we've taken steps in our unit to ensure that NIV is implemented correctly and that NIV failure is minimized.

Sorensen et al. (11) conducted a study in 2012 and they showed that experienced intensive care unit nurses are successful in ensuring patient adaptation to NIV, providing effective ventilation, and approaching carefully patients' perceptions of NIV. The healthcare professional who manages NIV therapy must be experienced, skilled, and high level of knowledge of the NIV therapy; this is the key component of success in practice (8). NIV training programs should include the sub-headings of the indications of NIV therapy, correct and effective mask choosing and fitting, correct use of ventilator equipment, adjusting ventilator settings, general maintenance of the ventilator, and solving problems in critical situations (12). Physicians should make decisions on how much oxygen to give and how to modify ventilator settings, and nurses should help set up the equipment. This setup includes installing a bacterial filter on the outlet port to reduce bacterial contamination, adjusting ventilator parameters, and adding oxygen to the circuit if needed. The nurses may consider using humidification as it can increase patient comfort and compliance. When installing the NIV therapy, the ventilator must be connected to the oxygen source and the amount of oxygen delivered (FiO_2) must be monitored carefully. The nurses have to be aware of the equipment being used, because some NIV delivery systems have a built-in escape valve, and other systems may require these valves to be fitted.

NIV therapy is provided via a face mask; however, patients generally reported that they felt uncomfortable and claustrophobic (13). Alternative forms of application such as nasal mask, mouthpiece, and helmet mask can be used. However, it is a fact that mask selection is limited by the equipment available in the intensive care units or wards. Mask compliance should be considered regardless of the mask type chosen because mask compliance enhances patient comfort and reduces complications such as skin necrosis and pressure injuries (14). It was found that 9-22% of patients could not tolerate NIV due to pain, discomfort, claustrophobia, or agitation, and there was a lack of awareness of this situation in chest wards other than ICUs (15). This complication can also lead to disruption of NIV therapy because the agitated patient removes the mask or ties and increased leakage causes non-compliance. Sedation is not routinely administered during NIV because, as is well known, poor consciousness at the start of NIV therapy is a relative contraindication. Despite this, patients may not be able to tolerate the discomfort caused by the mask, claustrophobia, and anxiety, and sedation may be required (16).

In our PICU, the patient's agitation and discomfort are frequent due to advanced age and/or numerous comorbidities. With the checklist, from the preparation period until the end of the second hour, the implementation of proper practices guaranteed and possible pitfalls that may occur during NIV therapy detected earlier and timely interventions were ensured. The non-compliant patients, which constitute the largest group in NIV failure, were identified and the communication with patients was assured, the problem was determined and tried to solve, the NIV therapy training and the motivation were repeated. With these interventions, 53.3% of the non-compliant patients' (n=10) situations were resolved and NIV therapy was performed successfully. If non-compliance was still continued, restriction of the patient (n=4, 21.1%) and/or sedation was performed (n=4, 21.1%). Although it may be difficult for a patient with shortness of breath to voice their concerns before NIV therapy begins, the nurse and the physician should fully explain the therapy and address the patient's concerns.

Tully et al. (17) suggest that preparation of the NIV therapy should include addressing face masks and mask-related communication problems. In this study, the rate of the patients who needed a break from the NIV therapy was significantly higher in those who were non-compliant with NIV therapy ($p<0.05$). In addition, this checklist increased the efficiency and awareness of the nurse team, which has a critical role in the initiation, implementation, and follow-up of NIV therapy. Thus, the harmony of physicians and nurses who implements NIV therapy has increased and individual differences in practice have been minimized.

CONCLUSION

In suitable conditions, it is a fact that morbidity and mortality are significantly reduced by NIV therapy instead of invasive mechanical ventilation. Identifying frequent problems and taking measures will increase the success in NIV therapy and will minimize the need for an invasive mechanical ventilator. For this reason, we conclude that the NIV team should provide the best care to the patients by the selection of the right ventilators and mode, choosing and fitting the right mask, and also have to manage frequent complications, and monitoring patients. For all these interventions to increase patient compliance to NIV therapy, implementing a checklist will provide reliable support to the NIV team and increase NIV therapy success.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Health Sciences University Keçiören Education and Training Hospital Clinical Studies Ethics Board (Date: 12/10/2021, Decision No: 2012-KAEK-15/2394).

Informed Consent: Since the study was designed retrospectively, informed consent was not obtained from the patients.

Conflict of Interest Status: The authors declared that there was no conflict of interest in this study.

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Author Contributions: All authors; declared that they participated in the design, execution, and analysis of the article and approved the final version.

REFERENCES

1. Saltürk C, Kargın F, Berk Takır H, et al. Yoğun bakım ünitesinde gece noninvaziv mekanik ventilasyon maske uygulama sıklığı. Göztepe Tıp Dergisi 2012; 27: 90-3
2. Rochwerg B, Brochard L, Elliott MW, et al. Members of the Steering Committee, Antonelli M, Brozek J, Conti G, et al., Members of the Task Force. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 2017; 50: 1602426.
3. Carron M, Freo U, BaHammam AS, et al. Complications of non-invasive ventilation techniques: a comprehensive qualitative review of randomized trials. Br J Anaesth 2013; 110: 896-914.
4. Hill NS. Where should noninvasive ventilation be delivered?. Respir Care. 2009;54(1):62-70.
5. Mas A, Masip J. Noninvasive ventilation in acute respiratory failure. Int J Chron Obstruct Pulmon Dis 2014; 9: 837-52.
6. Raurell-Torredà M, Argilaga-Molero E, Colomer-Plana M, Ródenas-Francisco A, Garcia-Olm M. Nurses' and physicians' knowledge and skills in non-invasive ventilation: Equipment and contextual influences. Conocimiento y habilidades de enfermeras y médicos en ventilación mecánica no invasiva: equipamiento e influencias contextuales. Enfermeria Intensiva 2019; 30: 21–32.
7. Scala R, Windisch W, Köhnlein T, Cuvelier A, Navalesi P, Pelosi P. European Respiratory Society Respiratory Intensive Care Assembly Targeting European Respiratory Society Group activities: a survey of the Noninvasive Ventilatory Support Group. Eur Respir Rev 2014; 23: 258-60.
8. Tarhan M, Hançer H, Polat F, Akbaş Gökduman S, Dalar L. Noninvasive mechanical ventilation knowledge level of the nurses: a questionnaire survey in a tertiary care training and research hospital. Eurasian J Pulmonol 2015; 17: 163-70.
9. Montravers P, Le Comité réanimation de la Sfar, Ichai C, et al. Organization of mechanical ventilation in French Intensive care units. Ann Fr Anesth Reanim 2013; 32: 736-41.
10. Chandra D, Stamm JA, Taylor B, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008. Am J Respir Crit Care Med 2012; 185: 152-9.
11. Sørensen D, Frederiksen K, Grøfte T, Lomborg K. Practical wisdom: a qualitative study of the care and management of non-invasive ventilation patients by experienced intensive care nurses. Intensive Crit Care Nurs 2013; 29: 174-81.
12. Elliott MW, Confalonieri M, Nava S. Where to perform noninvasive ventilation? Eur Respir J 2002; 19: 1159-66
13. Shee CD, Green M. Non-invasive ventilation and palliation: experience in a district general hospital and a review. Palliative Medicine 2003; 17: 21–6.
14. Hill NS. Noninvasive ventilation for chronic obstructive pulmonary disease. Respiratory Care 2004; 49: 72–89.
15. Masip J, Páez J, Merino M, et al. Risk factors for intubation as a guide for noninvasive ventilation in patients with severe acute cardiogenic pulmonary edema. Intensive Care Med 2003; 29: 1921-8.
16. Burk RS, Grap MJ, Munro CL, Schubert CM, Sessler CN. Predictors of agitation in critically ill adults. Am J Crit Care 2014; 23: 414-23
17. Tully V. Non-invasive ventilation: a guide for nursing staff. Nursing in Critical Care 2002; 7: 296-9.

Original Article

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Orbital MRI in thyroid-associated orbitopathy

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ABSTRACT

Aim: Thyroid-associated orbitopathy (TAO) is the most common cause of proptosis in adults and the clinical picture is mostly associated with thyroid dysfunction. MRI is frequently used because of its advantages, such as high soft tissue resolution, multiple plane evaluation, and no risk of ionizing radiation exposure to the lens. The research aim was to present cases of thyroid orbitopathy with MRI findings and to compare the findings with existing literature.

Material and Method: Patients who visited our radiology clinic with a preliminary diagnosis of TAO between April 2015 and February 2021 and underwent orbital MRIs were included in the study. We evaluated parameters such as age, sex, presence of proptosis, orbital muscle involvement, increase in orbital fatty tissue, and lacrimal gland involvement.

Results:A total of 35 patients were included in our study. The mean age was 40.6 (18-60) years, 19 (54%) patients were female, and 16 (46%) were male. All patients were diagnosed with Graves' disease, whereas no patient was diagnosed with Hashimoto's thyroiditis. The most common findings were proptosis in 33 (94%) patients, inferior rectus involvement in 27 (77%) patients, and medial rectus muscle involvement in 25 (71%) patients. No significant correlation was found between the presence of uni/bilateral involvement and TSH values ($p = 0.008$).

Conclusion: In conclusion, since the presence of orbital involvement is crucial for treating thyroid diseases, all orbital structures involved should be reported by imaging. Orbital MRI is an effective imaging modality in the detection and differential diagnosis of TAO.

Keywords: Thyroid, orbita, proptozis, magnetic resonance imaging

Our research's data was presented as a poster presentation at the 42nd National Radiology Congress (TURKRAD-2021, Antalya, 26-31 October 2021).

INTRODUCTION

Thyroid-associated orbitopathy (TAO) is the most common cause of proptosis in adults and the clinical picture is mostly associated with thyroid dysfunction (1-3). Besides proptosis, TAO is characterized by the involvement of extraocular muscles and an increase in orbital fat volume. While TAO is more common in women, the prevalence of severe orbitopathy is higher in men. The onset of TAO usually begins between the ages of 30-50 years and is more severe in older ages. It is the most common extrathyroidal involvement of Graves' disease. Orbitopathy develops in 25%-50% of patients with Graves' disease and a few (2%) with Hashimoto's thyroiditis. TAO may precede, occur simultaneously, or follow the onset of abnormal thyroid function (4-7).

Ultrasonography (US), magnetic resonance imaging (MRI) and computed tomography (CT), can be used as imaging modalities. Although US does not involve radiation exposure and provides a quick evaluation, not all orbital structures are examined using US and it is operator dependent. Whole orbital structures can be visualized using CT and MRI. CT has high sensitivity in revealing extraocular muscle enlargement; however, ionizing radiation exposure is a major disadvantage while performing CT. MRI is frequently used because of its advantages, such as high soft tissue resolution, multiple plane evaluation, and no risk of ionizing radiation exposure to the lens (8-11). Proptosis, muscle thickening, and increase in orbital fatty tissue can be easily visualized via MRI. Additionally, MRI is an essential imaging modality for the differential diagnosis of diseases that can be confused with thyroid orbitopathy (5-9). The research aim was to present cases of thyroid orbitopathy with MRI findings and to compare the findings with existing literature.

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MATERIAL AND METHOD

This research was designed as a retrospective study. Patients who visited our radiology clinic with a preliminary diagnosis of TAO between April 2015 and February 2021 and underwent orbital MRIs were included in the study. The study was initiated with the approval of Dicle University, Faculty of Medicine, Non-Interventional Clinical Researches Ethics Committee, (Date: 13.10.2021; Decision No: 423). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

We evaluated parameters such as age, sex, TSh, ft3 and Ft4 values at diagnosis presence of proptosis, orbital muscle involvement, increase in orbital fatty tissue, and lacrimal gland involvement. In cases with involvement, localization of involvement, presence of uni/bilateral involvement, and their relationship with thyroid-stimulating hormone (TSH) levels were also evaluated.

Patients with a preliminary diagnosis of TAO but without a pathological appearance on MRI, patients whose imaging was not performed at our center, and patients with an unconfirmed diagnosis of TAO were excluded from the study.

MRI Protocol

Orbital MRI was performed with 1.5-T and 3.0-T (Achieva; Philips Medical Systems, Best, Netherlands) MRI devices using an 8-channel cranial coil, which is the most suitable setup for evaluating orbitals. Images parallel to the optic nerve (oblique axial) were taken covering the entire orbital cavity. Coronal STIR, axial T2, axial T1-SPIR, sagittal T1, and diffusion-weighted images were obtained before contrast agent administration. During the procedure, 0.1 mmol/kg intravenous paramagnetic contrast agent was administered at a rate of 2 ml/sec through the antecubital vein. After administering the contrast agent, T1 fat-suppressed axial and coronal images were obtained in the 3D turbo field echo (TFE) sequence.

MRI Findings

Orbital MRIs were examined by two radiologists with at least 5 years of experience. The examinations were performed on Philips Extended Brilliance Workspace (Philips Medical systems, Best, Netherlands) workstations. The interzygomatic line was accepted as the reference line for measuring proptosis. The interzygomatic line is a line joining the anterior margins of the zygomatic bones. The distance between this line and the posterior sclera is normally 9.9±1.7 mm, and the decrease in this distance supports the diagnosis of proptosis. Additionally, the distance from the interzygomatic line to the anterior of the eyeball should be <23 mm, and a greater distance indicates proptosis (12,13) (**Figure 1**).

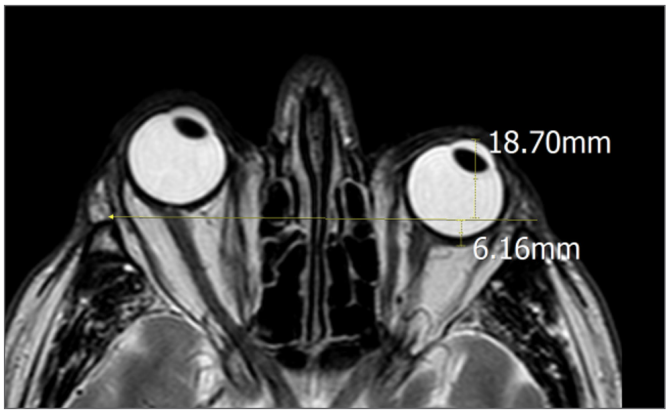

Figure 1. Evaluation of proptosis (proptosis on the right, normal appearance on the left)

While measuring orbital muscle thickness, muscle structures were observed on axial and coronal images and their average values were taken. The criteria for orbital muscle thickening were determined based on relevant literature (13-15). The criteria for normal muscle thicknesses were accepted as follows: 4.8 mm for the inferior rectus (3.2-6.5 mm), 4.2 mm for the medial rectus (3.3-5 mm), 4.6 mm for the superior rectus (3.2-6.1 mm), and 3.3 mm for the lateral rectus muscles (1.7-4.8 mm) (**Figure 2**) (**Table 1**).

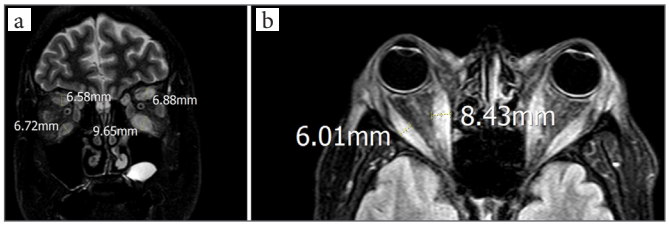

Figure 2. Orbital muscle thickness measurements (**a:** superior and inferior rectus muscle thickness measurements using coronal T2 image, **b:** lateral and medial rectus muscle thickness measurements using axial T1 image)

Table 1. Orbital muscle thickness normal reference values and orbital muscle thicknesses measured in cases with thyroid-associated orbitopathy

	Orbital muscle thicknesses in cases with involvement		Normal reference values of orbital muscle thickness	
	Muscle thicknesses (mm)	Average (mm)	Muscle thicknesses (mm)	Average (mm)
Inferior rectus	6.6-9	7.3	3.2-6.5	4.8
Medial rectus	5.3-8.5	6.2	3.3-5	4.2
Superior rectus	6.2-8.2	6.7	3.2-6	4.6
Lateral rectus	5-7.8	6.3	1.7-4.8	3.3

Increased orbital fatty tissue intensity, increased lacrimal gland size, and lacrimal gland herniation were also accepted as positive findings (**Figure 3**).

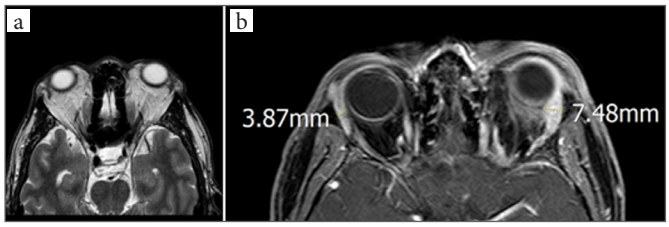

Figure 3. Increase in orbital fatty tissue **(a)** and left lacrimal gland involvement **(b)**

The SPSS package program was used for the statistical analysis of data. Standard deviation and mean values were calculated for age, sex, TSH, Ft3, Ft4 values; the presence of proptosis; orbital muscle, orbital fatty tissue, and lacrimal gland involvement. The chi-square test was used to investigate the relationship between TSH values and the presence of uni/bilateral involvement. Independent sample t-test was used for pairwise comparisons of normally distributed data, and Mann-Whitney U test was used for comparisons of non-normally distributed data.

RESULTS

Thirty five patients were included in our study. The mean age was 40.6 (18-60) years, 19 (54%) patients were female, and 16 (46%) were male. All patients were diagnosed with Graves' disease, whereas no patient was diagnosed with Hashimoto's thyroiditis. Contrast-enhanced orbital MRI was performed in all patients. The most common findings were proptosis in 33 (94%) patients (bilateral in 30 patients, unilateral in 3 patients), inferior rectus involvement in 27 (77%) patients (23 bilateral, 4 unilateral), and medial rectus muscle involvement in 25 (71%) patients (21 bilateral, 4 unilateral). Involvement of the superior rectus, lateral rectus, and superior oblique muscles was detected in 8 (23%), 4 (12%), and 2 (6%) patients, respectively. The findings showed unilateral involvement in 3 (9%) patients (right in 2 patients [**Figure 4**] and left in 1 [**Figure 5**)], whereas the involvement was bilateral in 32 (91%) patients (**Figure 6**) (**Table 2**).

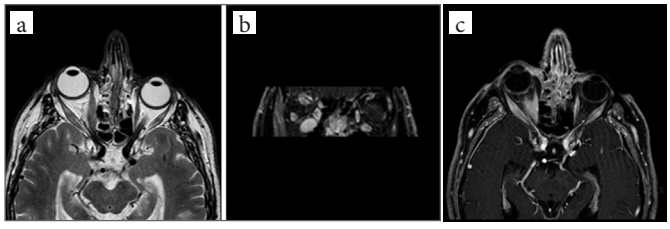

Figure 4. 60-year-old female patient (a: axial T2, b: coronal T1 fat suppression with contrast, c: axial T1 fat-suppressed sequence with contrast) with right proptosis and asymmetrical orbital muscle thickness with increased enhancement in the lateral and medial rectus muscles.

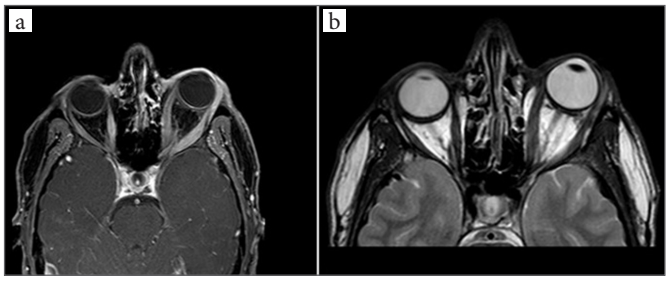

Figure 5. 28-year-old male patient (a: axial T1, b: axial T2 sequence fat suppression with contrast) with left proptosis, asymmetrical thickness and increased enhancement in the lateral and medial rectus muscles.

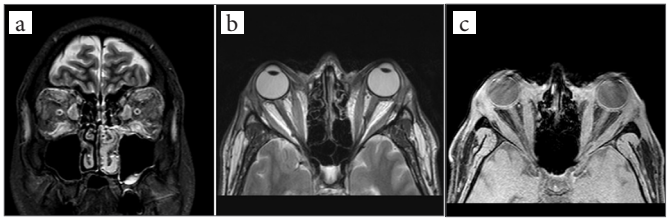

Figure 6. 35-year-old male patient, (a: coronal T2, b: axial T2, c: axial T1 sequence with fat-suppressed contrast) with bilateral proptosis, bilateral symmetric orbital muscle involvement and increase in periorbital fatty tissue and heterogeneity.

Isolated superior, lateral, and oblique muscle involvement was not observed in any patients, and all patients had proptosis, accompanied by inferior and medial muscle involvement. While isolated proptosis was detected in 6 (17%) patients, orbital muscle involvement without accompanying proptosis was observed in only 2 (6%) patients.

An increase in orbital fat tissue was observed in 12 (34%) patients (bilateral in 9 patients, unilateral in 3 patients). Lacrimal gland involvement was detected in 5 (14%) patients (bilateral in 3, unilateral in 2) (**Table 2**).

Table 2. Demographic data and magnetic resonance imaging findings

Age	40.6±6.4	
TSH	4.1± 0.8	
Ft3	2.2± 0.4	
Ft4	3.4± 0.6	
	n (number)	**% (percentage)**
Sex		
Female	19	54
Male	16	46
MRI FINDINGS		
Proptosis	33	94
Inferior rectus involvement	27	77
Medial rectus involvement	25	71
Superior rectus involvement	8	23
Lateral rectus involvement	4	12
Superior oblique involvement	2	6
Orbital fatty tissue involvement	12	34
Lacrimal gland involvement	5	14
Bilateral involvement	32	91
Unilateral involvement	3	9

In patients with TAO, the mean orbital muscle thickness measured at the levels of the inferior, medial, superior, and lateral rectus muscles was 7.3 mm (6.6-9 mm), 6.2 mm (5.3-8.5 mm), 6.7 mm (6.2-8.2 mm), and 6.3 mm (5-7.8 mm) respectively (**Table 1**).

All patients with TAO received medical treatment. Since post-treatment images of patients could not be accessed, the findings before and after treatment were not compared. TAO was detected in the first 5 years of disease onset in 14 (40%) patients, from 5-10 years in 12 (34%) patients, from 10-15 years in 7 (20%) patients, and at the time of initial diagnosis in two patients (6%).

DISCUSSION

In this research, orbital MRI examinations of patients with TAO were evaluated and the most common finding was proptosis (94%). Proptosis is a spontaneous decompression resulting from the enlargement of the extraocular muscles and connective tissue, as well as the orbital tissue infiltration by orbital fat deposits, glycosaminoglycans (GAG), and leukocytes. Proptosis is bilateral in 90% of cases(6,14-16). Our findings were consistent with the literature, where bilateral proptosis was detected in 90% of cases and unilateral proptosis in 10% of cases examined.

Muscle enlargement occurs because of the separation of muscle fibers by fluid and fat deposits, fibrosis, scar formation, and leukocyte infiltration. Despite the enlargement of the extraocular muscles, muscle fibers are normal in TAO. Trunk involvement of muscles and frequent preservation of insertions are key findings for differential diagnosis and based on these characteristics, TAO is differentiated from other diseases, such as orbital pseudotumor, orbital arteriovenous malformation, orbital sarcoidosis, lymphoma, and metastasis (6,7).

The inferior rectus muscle is the most frequently involved extraocular muscle in patients with orbitopathy followed by the medial and superior rectus muscles (16-18). In our study, extraocular muscle involvement was detected in 83% of cases, and consistent with the literature, the inferior rectus was most frequently involved. It was followed by the medial, superior, lateral rectus, and superior oblique muscles. None of the patients exhibited isolated superior, lateral, and oblique muscle involvement. Orbital muscle involvement without accompanying proptosis was observed in only 2 (6%) patients.

TAO is 2.5-6 times more common in women and severe orbitopathy is more common in men. The onset is generally between the ages of 30 and 50 and is more severe after the age of 50. Orbitopathy develops in 25%-50% of patients with Graves' disease and rarely (2%) in patients with Hashimoto's thyroiditis. Severe orbitopathy is seen in 3%-5% of these cases (5,6). In our study, 55% of the patients were female and the mean age was 40, which is consistent with the literature. All patients were diagnosed with Graves' disease, whereas none were diagnosed with Hashimoto's thyroiditis.

In most patients, orbitopathy develops within the first 18 months of diagnosis with Graves' disease. Consequently, TAO can develop anytime between 10 years before and up to 20 years after the diagnosis of Graves' disease (3). Orbitopathy findings are mostly bilateral, but unilateral or asymmetric findings have also been observed (11). In the current study, TAO was most frequently detected in the first 5 years of diagnosis with Graves' disease. We observed bilateral involvement in 92% of patients, whereas only 8% of patients exhibited a unilateral involvement. In patients with TAO, lacrimal gland involvement has been recognized as a potential cause of ophthalmopathy symptoms, and different studies have shown significant involvement of the lacrimal gland in patients with TAO compared to healthy controls. In these patients, decreased tear secretion and dry eyes can be observed due to lacrimal gland involvement. Active and inactive patients in terms of lacrimal gland involvement require different treatment strategies. Therefore, the lacrimal gland should be examined in imaging and its status should be reported. Lacrimal gland involvement can be observed as an increase in gland size or heterogeneity, or as herniation in the lacrimal gland. A high degree of proptosis, enlargement of retro-orbital structures, and accumulation of TSH-receptors in the lacrimal glands can be listed among the causes of lacrimal gland involvement (17,18). Lacrimal gland involvement was detected in 14% of patients in our study, and involvement was bilateral in 60% of these patients.

The relatively small number of patients and the lack of patients with Hashimoto's thyroiditis are the most important limitations of the current study. Moreover, patient findings before and after treatment could not be compared due to the lack of post-treatment imaging.

CONCLUSION

Since the presence of orbital involvement is crucial for treating thyroid diseases, all orbital structures involved should be reported by imaging. Orbital MRI is an effective imaging modality in the detection and differential diagnosis of TAO.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of Dicle University, Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee, (Date: 13.10.2021; Decision No: 423).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Ginsberg J. Diagnosis and management of Graves' disease. CMAJ 2003; 168: 575-585.
2. Chan LL, Tan HE, Teo F.T-H, L-H Lim, Seah L. Graves ophthalmopathy: the bony orbit in optic neuropathy, its apical angular capacity, and impact on prediction of risk. AJNR Am J Neuroradiol 2009; 30: 597-602.
3. North VS, Freitag SK. A review of imaging modalities in thyroid-associated orbitopathy. Int Ophthalmol Clin 2019; 59: 81-93.
4. Mishra S, Maurya VK, Kumar SA, Kaur A, Saxena SK. Clinical management and therapeutic strategies for the thyroid-associated ophthalmopathy: current and future perspectives. Curr Eye Res 2020; 45: 1325-41.
5. Bartalena L, Marcocci C, Pinchera A. Graves' ophthalmopathy: a preventable disease? Eur J Endocrinol 2002; 146: 457.
6. Şanlı E. Gündüz K. Tiroid Oftalmopati. Turk J Ophthalmol 2017; 47: 94-105
7. Davies MJ, Dolman PJ. Levator muscle enlargement in thyroid eye disease-related upper eyelid retraction. Ophthalmic Plast Reconstr Surg 2017: 33: 35-9.
8. Parmar H, Ibrahim M. Extrathyroidal manifestations of thyroid disease: thyroid ophthalmopathy. Neuroimaging Clin N Am 2008; 18: 527-36.
9. Ahn ES, Subramanian PS. Treatment modalities of thyroid related orbitopathy. Indian J Ophthalmol 2014; 62: 999-1002.
10. Hodgson NM, Rajaii F. Current understanding of the progression and management thyroid associated orbitopathy: a systematic review. Ophthalmol Ther 2020; 9: 21-33
11. Hennein L, Robbins SL. Thyroid-associated orbitopathy: management and treatment. J Binocul Vis Ocul Motil 2021: 1-15.
12. Haaga JR, Boll D. CT and MRI of the whole body. Mosby 2009; 2: 56-65
13. Ozgen A, Aydingoz U. Normative measurements of orbital structures using MRI. J Comput Assist Tomogr 2000; 24: 493-6.
14. Ozgen A, Ariyurek M. Normative measurements of orbital structures using CT. AJR. 1998; 170: 1093-6.
15. Monteiro ML, Gonçalves AC, Silva CT, Moura JP, Ribeiro CS, Gebrim EM. Diagnostic ability of Barrett's index to detect dysthyroid optic neuropathy using multidetector computed tomography. Clinics 2008; 63: 301-6.
16. Bahn RS. Graves' ophthalmopathy. N Engl J Med 2010; 362: 726-38.
17. Eckstein AK, Finkenrath A, Heiligenhaus A. et al. Dry eye syndrome in thyroid-associated ophthalmo- pathy: lacrimal expression of TSH receptor suggests involvement of TSHR-specific autoantibodies. Acta Ophthalmol Scand 2004; 82: 291-7.
18. Gagliardo C, Radellini S, Bubella RM, et al. Lacrimal gland herniation in Graves ophthalmopathy: a simple and useful MRI biomarker of disease activity. Eur Radiol 2020; 30: 2138-41

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COVID-19 and COVID-19 vaccines-related subacute thyroiditis: analysis of a case series

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ABSTRACT

Aim: It has been indicated that COVID-19 is related to many endocrinological abnormalities. The aim of this study is to demonstrate whether there is an impact of COVID-19 and COVID-19 vaccines on development of subacute thyroiditis (SAT).

Material and Method: This retrospective single-center study includes individuals with SAT who were diagnosed between March 2020 and August 2021. Patients were evaluated for a recent Covid-19 history and SARS-CoV-2 vaccination. SAT was diagnosed based on the clinical presentation and laboratory tests; including thyroid function tests, sedimentation rate, C-reactive protein, and thyroid ultrasound. SARS-CoV-2 PCR results of patients with past COVID-19 were obtained from the Ministry of Health electronic patient data system. Type, number, and dates of vaccine doses were recorded for each participant.

Results: A total of 31 patients were included in the study. Six patients (19.4%) were diagnosed with SAT following a COVID-19 vaccination schedule. Four patients with SAT had received two inactive (CoronaVac) + one dose of mRNA vaccines (Pfizer-BioNTech). The other 2 patients had received either two doses of inactive vaccine or two doses of mRNA vaccine. Five patients were diagnosed with SAT after the second dose of the vaccine. The median interval between last vaccination dose and diagnosis of SAT was 25.8 days. In one patient, SAT developed 28 days after the mRNA vaccine. Seven patients (22.6%) were diagnosed with SAT after COVID-19 disease. The median interval from the diagnosis of COVID-19 disease to SAT was 27.3 days. All cases of post-COVID-19 and post-vaccination SAT patients exhibited similar clinical presentation and findings to idiopathic SAT.

Conclusion: Covid-19 itself and Covid-19 vaccines might let a tendency to development of subacute thyroiditis. This study has to be supported by further studies.

Keywords: COVID-19, SARS-CoV-2, subacute thyroiditis, vaccination

INTRODUCTION

Since the report of the first case in China in December 2019, the SARS-CoV-2 pandemic has resulted in above 5 million loss of lives globally, as of January 2022. Although death rates significantly decreased after the introduction of the COVID-19 vaccines, the burden of the disease and the disease related effects have remained to be a crucial matter on human life. Although COVID-19 disease is substantially diagnosed after respiratory system symptoms and many deaths are associated with lung involvement, the disease has the potential to indicate a multisystemic involvement. The clinical dimension of extrapulmonary involvement is better understood day by day. The heart, kidney, gastrointestinal system, liver, eye, skin, and central nervous system can be involved at the course of the disease (1). From a point of endocrinology, diabetes mellitus has a dual role in COVID-19; it acts as a risk factor for more severe COVID-19, and also occurs de novo after or at the course of the COVID-19 disease. However, thyroid manifestations of COVID-19 have less frequent been described compared with diabetes mellitus (1).

SARS-CoV-2 damages thyroid tissue via angiotensin converting enzyme 2 (ACE2) and transmembrane protein serin 2 (TMPRSS2) receptors which are abundant in thyroid follicular cells (2). It has also been speculated that the thyroid gland involvement by COVID-19 might be due to its anatomical proximity to the entry sites of the virus to the body. Whatever the mechanism, three different thyroid manifestations were proposed to be

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related to COVID-19: destructive (inflammatory) thyroiditis, subacute thyroiditis, and chronic lymphocytic thyroiditis (3).

Subacute thyroiditis (SAT) is a self-limiting acute inflammatory and granulomatous disorder of the thyroid gland. Influenza virus, coxsackievirus, adenovirus, HIV, mumps, measles, rubella, and cytomegalovirus have been blamed for causing SAT via direct cytopathic and/or indirect autoimmunity-triggering activity (4). Furthermore, some case reports indicates development of SAT after some kind of vaccines (5-8).

In regard of COVID-19, several SAT cases concomitantly with COVID-19 or occurred shortly after COVID-19 were reported in the recent literature (9-12). SAT and COVID-19 share many common symptoms and signs, additionally, some other factors might impact the patients' admissions to hospital for health care during pandemic and all those lead to underestimate diagnosing COVID-19 related SAT rate. Self-limiting nature of the SAT also causes in the missed cases.

Different types of vaccination have been approved by the Food and Drug Administration of the United States (FDA) and the European Medicines Agency (EMA) for COVID-19. In Turkey, an inactive vaccine (CoronaVac, Sinovac Biotech, China) and an mRNA-based vaccine BNT162b2 (Pfizer-BioNTech, Pfizer, Inc., and BioNTech) were authorized. Approximately 54% of the people have been fully vaccinated in Turkey as of 10 October 2021 (12). There are limited number of report on SAT cases occurred following COVID-19 vaccines (14-16).

Considering a large number of vaccinations throughout the world (6.46 million doses in total as of 10 October 2021) is being performed, we think vaccine-related SAT cases might have been underreported (17).

In this study, we aimed to reveal the association of COVID-19 disease and COVID-19 vaccines with the SAT development.

MATERIAL AND METHOD

Subjects and Study Design

In this retrospective single-center case-control study all adult patients who were referred to our hospital between March 2020 and August 2021 on suspicion of SAT from primary care were evaluated. The study was carried out with the permission of Medicana International Ankara Hospital Ethics Committee (Date: 06.09.2021; Decision No: BŞH-28). The study was carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. No informed consent form was obtained for since this is a retrospective study. The hospital database system and endocrinology charts were screened for detection of SAT cases. Exclusion criteria comprised patients with a known thyroid disorder and patients receiving thyroid drugs. We also excluded SAT patients if they had missing data.

Data Collection

All patients with suspicion of SAT were evaluated regarding prior thyroid disease, presence of neck pain and thyrotoxicosis symptoms. Physical examination signs; thyroid tenderness, volume, and texture, data about lymph nodes in anterior and posterior cervical areas were noted. Laboratory evaluation included complete blood count, erythrocyte sedimentation rate, C-reactive protein level, thyroid-stimulating hormone (TSH), free thyroxine (T4), and free triiodothyronine (T3) concentrations. All patients had underwent thyroid and neck ultrasound (US) imaging. Thenafter they were evaluated regarding their COVID-19 vaccination status and whether they had past or ongoing COVID. The vaccinated individuals were investigated for the type of the vaccine, the number of vaccine applications, and the last vaccination date were recorded. If the patient had COVID-19 disease, we obtained information regarding of the date of infection, need for hospital or intensive care unit admission, method of how COVID-19 diagnosis was made, and treatments received.

Diagnosis of SAT

Subacute thyroiditis was diagnosed based on the typical clinical presentation of the disease and laboratory evaluation of thyroid hormone status. In a patient, the diagnosis was established on his complains including pain in the anterior neck that radiates to the jaw and/or ear, along with fatigue, malaise, fever, thyrotoxicosis symptoms, and on laboratory test result which indicated an overt thyrotoxicosis status. A tender and enlarged thyroid without any accompanying cervical adenopathy also supported the diagnosis of SAT. All patients underwent thyroid US. A heterogeneous hypoechoic pattern along with decreased vascularization is the expected US finding in patients with SAT as seen in our cases. Thyroid autoantibodies were investigated in a few patients. We did not perform thyroid scintigraphy or radioactive iodine uptake test in patients who had a typical clinical presentation for SAT. None of the included patients underwent percutaneous fine-needle aspiration of the thyroid gland.

Statistical Analysis

The Kolmogorov Smirnow test and a histogram evaluation test was used to confirm the normality of the continuous variables. Continuous variables were expressed as mean±standard deviation or median (interquartile range) depending on the distribution of the variable. Categorical variables were reported as numbers

and percentages. Based on the results of the normality test, the Mann-Whitney U test or independent samples t-test was used for the comparison of numeric variables. Analysis of categorical variables was performed with the Chi-squared test and Fisher's Exact Test. Statistical analyses were performed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). p<0.05 was accepted statistically significant with a 95% CI.

RESULTS

A total of 31 patients were evaluated in the study. The mean age was 42.6±8.9 years (min max: 26-61 years), and the majority (87.1%) of the participants were female. Mean age, sex distribution, laboratory findings, treatments and vaccination status of the patients were given in **Tables 1-3**. 13 of 31 cases of SAT (~%42) diagnosed in our hospital were related to COVID-19 disease or COVID-19 vaccination.

Table 2. Post-COVID-19 and post-vaccination SAT and administered treatments.

	Patients (n= 31)
Post-vaccination subacute thyroiditis n(%)	6 (19.4%)
Post-COVID-19 subacute thyroiditis n(%)	7 (22.6%)
Recurrent subacute thyroiditis n(%)	6 (19.4%)
Treatments for subacute thyroiditis	
None	4 (12.9%)
NSAID	11 (35.5%)
Glucocorticoids	15 (48.4%)
NSAID + Glucocorticoids	1 (3.2%)

NSAID: Nonsteroidal anti-inflammatory drug

Table 3. COVID-19 vaccination status of all SAT patients

	Vaccines (n=31)		
	1st dose	2nd dose	3rd dose
Inactivated SARS-CoV-2 vaccine	8 (25.8%)	7 (22.6%)	-
mRNA SARS-CoV-2 vaccine	19 (61.3%)	17 (54.8%)	5 (16.1%)
None	4 (12.9%)	7 (22.6%)	26 (83.9%)

Table 1. Mean age, sex distribution, and laboratory findings of the subacute thyroiditis (SAT) patients.

Parameters	Patients			p-value
	Total (n=31)	Post-COVID-19 and post-vaccination SAT (n=13)	Idiopathic SAT (n=18)	
Age (years)	42.6±8.9	45.0±11.0	40.8±6.8	0.196†
Sex (N)				
Female	27 (87.1%)	11 (84.6%)	16 (88.9%)	>0.999f
Male	4 (12.9%)	2 (15.4%)	2 (11.1%)	
TSH (μIU/mL)	0.72 (0.002-5.17)	1.39 (0.002-5.17)	0.55 (0.002-5.03)	0.303m
Free T4 (ng/dL)	1.05 (0.95-1.62)	1.05 (0.97-1.2)	1.04 (0.93-1.74)	0.814m
Free T3 (pg/mL)	3.74±1.12	3.39±0.73	3.9±1.24	0.294†
CRP (mg/dL) (normal range; 0-0.5 mg/dl)	1.64 (0.02-14.62)	1.21 (0.17-14,29)	2.05 (0.07-5.7)	0.968m
CRP in male	3.43 (0.02-14.29)	7.97 (1.64-14.29)	2.62 (0.02-5.22)	
CRP in female	1.53 (0.2-12.54)	0.97 (0.17-9.41)	2.05 (0.02-12.54)	
Sedimentation rate (mm/hour)	31.67±21.7	23.5±14.10	37.9±24.70	0.072†
Sedimentation in male (0-22)	23.25±15.84	25.5 (9.19)	21 (3-39)	
Sedimentation in female (0-29)	32.96±22.42	23.18 (15.13)	40.13±24.58	
Positive Anti-TPO (n, %)	3 (9.7%)	0	3 (16.7%)	0.245f
Positive Anti-TG (n, %)	6 (19.4%)	1 (7.7%)	5 (27.8%)	0.359f
Thyroglobulin (ng/mL)	51.6 (29.2-288.7)	79.9 (27.2-79.9)	51.6 (31.2-445)	0.844m
25(OH) Vitamin D (ng/mL)	27.9 (15.8-47.5)	32.5 (19.3-52.5)	24.9 (14.5-42.8)	0.413m
Red blood cells (million/mm³)	4.57 (4.35-4.72)	4.59 (4.51-4.66)	4.54 (4.21-4.72)	0.429m
Hemoglobin (g/dL)	13±1.2	13.1±1.3	12.9±1.2	0.672†
Hematocrit (%)	39±3.4	39.5±3.11	38.6±3.7	0.513†
MCV (fL)	85.5±5.2	85.5±4.97	85.6±5.54	0.972†
MCH (pg)	28.5±2.2	28.3±2.21	28.6±2.29	0.759†
MCHC (g/dL)	33.2±1.1	32.9±1.36	33.4±0.78	0.224†
Red cell distribution (%)	13.0±1.5	12.8±1.49	13.2±1.52	0.488†
White blood cell count (×10³/mm³)	8.57 (7.71-9.83)	8.85 (8.41-10.5)	8.18 (7.68-9.42)	0.170m
Neutrophil count (×10³/mm³)	5.28 (4.7-5.99)	5.4 (4.03-6.28)	5.28 (4.85-5.68)	0.877m
Lymphocyte count (×10³/mm³)	2.62 (1.96-3.26)	2.88 (2.06-3.54)	2.3 (1.95-3.14)	0.241m
Monocyte count (×10³/mm³)	0.63±0.23	0.71±0.27	0.58±1.86	0.118†
Eosinophil count (×10³/mm³)	0.17±0.13	0.17±0.97	0.16±0.14	0.903†
Basophil count (×10³/mm³)	0.08 (0.05-0.09)	0.08 (0.06-0.09)	0.07 (0.05-0.09)	0.309m
Platelet count (×10³/mm³)	276 (257-304)	268 (235-302)	280 (265-304)	0.564m
PDW (%)	17.6 (16.9-18.2)	16.8 (16.4-16.8)	17.6 (16.9-18.5)	0.131m
PCT %	0.21 (0.17-0.24)	0.2 (0.16-0.22)	0.21 (0.2-0.24)	0.182m

fFisher's Exact Test. mMann-Whitney U test, †Independent Samples t-test, P-values belong to comparison of variables between post-COVID-19 and post-vaccination. Not-normally distributed variables were presented as median (minimum-maximum) and normally distributed variables were presented as mean±standard deviation and n (%). Anti-TPO: Anti-thyroid peroxidase, Anti-TG: Anti-thyroglobulin, MCH: Mean Corpuscular Hemoglobin, MCHC: mean corpuscular hemoglobin concentration, MCV: Mean corpuscular volume, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, PCT: Plateletcrit, SAT: subacute thyroiditis TSH: Thyroid-stimulating hormone.

COVID-19 Characteristics

COVID-19 diagnosis was established on positive naso-oropharyngeal swab test for SARS-CoV2 polymerase chain reaction. None of the patients required intensive care unit hospitalization for COVID-19. All of the patients with COVID-19 had been diagnosed before the initiation of COVID-19 vaccination programs. Six patients (19.4%) were exhibited the symptoms suggestive of subacute thyroiditis after the COVID-19 vaccination. Clinical and laborotary features of SAT cases regarding their vaccination and thyroid hormone status are given in **Table 4**. The median duration of the presentation with symptoms of SAT since vaccination was 25.8 days (min. 16 days, max. 35 days). In only one patient, SAT was diagnosed 28 days after the first dose of the mRNA vaccine. In patients with post-vaccination SAT, 2 patients experienced a recurrent bout of SAT. Both episodes occurred after the third dose of the vaccination (after the mRNA vaccine dose).

Sedimentation rates and C-reactive protein levels were above normal laboratory ranges as expected in SAT patients. In idiopathic SAT cases sedimentation rates was tend to be higher compared to the COVID-19 disease or vaccine-related cases (the difference was at the limit of statistical significance), p=0.055.

Seven patients (22.6%) were diagnosed with SAT following COVID-19 disease (**Table 5**). The median duration from COVID-19 to subacute thyroiditis symptoms was 27.3 days (minimum 7 days and maximum 45 days). All patients except one had two doses of mRNA vaccine. However, in patients with post-COVID-19 SAT, 2 patients experienced a recurrent SAT episode before vaccination. Individuals with number 4, 2, and 1 were treated with glucocorticoids, NSAID, and a combination of glucocorticoids and NSAID, respectively (**Table 5**).

Table 4. Patients with post-vaccination SAT

	Age	Sex	Signs and symptoms at SAT onset	Thyroid function tests	COVID-19 Vaccinations	Duration to presentation following vaccination	Subacute thyroiditis treatments	Recurrence
Patient 1	27	F	Anterior neck pain, fever	TSH: 2.13, FT4: 1.05	C+C+PB	16 days after 2nd dose, 7 days after 3rd dose	Steroid	Once
Patient 2	35	F	Anterior neck pain, tender thyroid enlargement	TSH: 1.39, FT4: 0.96	C+C+PB	30 days after 2nd dose, 7 days after 3rd dose	NSAID	Once
Patient 3	61	M	Anterior neck pain, palpitation	TSH < 0.01, FT4: 3.03	C+C+PB	28 days after 2nd dose	Steroid	None
Patient 4	61	F	Anterior neck pain, fatigue	TSH: 3.47, FT4: 0.92	C+C+PB	35 days after 2nd dose	Steroid	None
Patient 5	27	F	Anterior neck pain, pain with movement	TSH: 5.17, FT4: 1.19	C+C	20 days after 2nd dose	Steroid	None
Patient 6	45	F	Anterior neck pain, tender thyroid enlargement	TSH: 2.23, FT4: 1.03	PB+PB	28 days after 1st dose	NSAID	None

F: female, M: male, NSAID: Nonsteroidal anti-inflammatory drugs, SAT: subcute thyroiditis. Laboratory reference ranges for thyroid function tests; TSH: 0.27-4.2 µIU/mL, fT4: 0.7-1.5 ng/dL. C: CoronaVac (inactivated SARS-CoV-2 vaccine), PB: Pfizer-BioNTech (mRNA SARS-CoV-2 vaccine)

Table 5. Patients with post-COVID-19 SAT

	Age	Sex	Signs and symptoms at SAT onset	Thyroid function tests	COVID-19 Vaccinations	Time to presentation since COVID-19	Subacute thyroiditis treatments	Recurrence
Patient 1	50	F	Anterior neck pain, tender thyroid enlargement	TSH: 2.69, FT4: 0.9	PB + PB	28 days	Steroids	1
Patient 2	41	F	Anterior neck pain, tachicardy	TSH: 0.2, FT4: 1.20	---	30 days	NSAID + Steroids	2
Patient 3	50	F	Anterior neck pain, fever palpitation	TSH: 0.08, FT4: 1.04	PB + PB	7 days	Steroids	None
Patient 4	52	M	Anterior neck pain, tender thyroid enlargement, fatigue	TSH: 0.18, FT4: 0.97	PB + PB	22 days	NSAID	None
Patient 5	44	F	Anterior neck pain, fatigue	TSH: 0.72, FT4: 1.0	PB + PB	26 days	Steroids	None
Patient 6	40	F	Anterior neck pain, tender thyroid enlargement	TSH: 0.02, FT4: 1.70	PB + PB	33 days	NSAID	None
Patient 7	52	F	Anterior neck pain, pain with neck movement	TSH: 1.87, fT4: 1.16	C	45 days	Steroids	None

F: female, M: male, NSAID: Nonsteroidal anti-inflammatory drugs, SAT: subcute thyroiditis. Laboratory reference ranges for thyroid function tests; TSH: 0.27-4.2 µIU/mL, fT4: 0.7-1.5 ng/dL. C: CoronaVac (inactivated SARS-CoV-2 vaccine), PB: Pfizer-BioNTech (mRNA SARS-CoV-2 vaccine)

Thyroid Evaluation

All referred patients had a typical clinical view of SAT. Neck pain, thyroid tenderness, and painful enlargement in the thyroid gland were present in all SAT patients. The clinical presentation of SAT in patients following COVID-19 disease or COVID-19 vaccination was not different from those of idiopathic SAT patients. Thyroid US combined with Doppler US demonstrated an enlarged thyroid gland with heterogeneous parenchyma along with hypoechoic areas and diminished vascularization in the gland in cases with SAT. In post-vaccination SAT groups, one patient (patient no 3) had suppressed serum TSH value. One patient (patient no 5) had subclinical hypothyroidism while other patients were euthyroid. Four patient with post-vaccination SAT were treated with glucocorticoids, while in 2 patients, NSAID sufficed.

In patients with SAT following COVID-19 disease, only one patient (patient no 6) had overt biochemical thyrotoxicosis, whereas the other 3 patients (patient no 2, 3, and 4) had subclinical hyperthyroidism. The remaining three patients were biochemically euthyroid.

Comparison of Post-COVID-19 and Post-Vaccination SAT with Idiopathic SAT

Mean age and gender distribution were comparable in COVID-19 and vaccine related SAT patients and idiopathic ones. In the similar vein, thyroid function tests, inflammatory markers and blood counts were not different, either. **Table 1** depicts the laboratory features of the both groups.

DISCUSSION

This is one of the largest study conducted to date reporting post COVID-19 disease, and COVID-19 vaccination-related SAT cases. SAT is probably a common, and missdiagnosed endocrinological abnormality during COVID-19 management (due to shared symptoms of COVID-19 disease). SAT incidence might be higher than usual during COVID-19 pandemic since its natural etiology substantially lies on virutic origin. Here, we demonstrate that the probability of as high as a %42 incidence of SAT following a COVID-19 disease or COVID-19 vaccination.

Early reports indicating a link between COVID-19 disease and endocrinological abnormalities were emphasizing to the hyperglycemia and diabetes mellitus and their adverse outcome in COVID-19 disease (18). Kumar et al. (19) reported endocrine abnormalities COVID-19 in patients with a focus on thyroid and adrenal function. After the report of the first case of SAT related to COVID-19 by Brancatella et al. (20), several similar reports further appeared in the literature (21). Most of these reports involved single case reports with a few case series not exceeding 6 patients at most (22-24). Muller et al. (25) than announced that incidence of atypical thyroiditis in a high dependency unit went up from 0.5% in 2019 to 10% in 2020 when admission ratio to hospital was raised due to COVID-19.

It should be taken into account that these case reports might have suffered from the positive case selection bias. In addition, it was not still clear whether COVID-19 actually increased the frequency of COVID-19 cases in a given population. The attempt to answer this question came with two studies; Trimboli and colleagues (26) retrospectively evaluated SAT cases who were diagnosed during a 10-month period in an Italian-speaking region of Switzerland. The authors determined 10 SAT cases during the specified time period. Interestingly none of the cases were deemed to be related to COVID-19. However, not all patients with SAT were evaluated by PCR or serologic tests for the presence of COVID-19. In four patients, PCR tests from nasopharyngeal swabs were found to be negative. In another study, Pirola et al. (27) evaluated SAT cases retrospectively in a region that was heavily affected by COVID-19 in Italy. The researchers detected 10 cases of SAT. Of these, only one patient had a recent history of COVID-19. The authors, moreover, reported that the frequency of SAT cases did not show a significant increase after the advent of COVID-19 in their region compared with records of the previous years. However, once again, the study was retrospective in nature, and COVID-19 PCR and/or immunologic status of the patients were not reported. In contrast to the aforementioned studies, all of the SAT patients whom we deemed related to COVID-19 had PCR proof of the SARS-CoV-2 infection.

Another issue complicating the association between COVID-19 and subacute thyroiditis is the lack of direct evidence, i.e., demonstration viral tissue PCR or other infection markers in thyroid epithelial cells. Evidence regarding the direct involvement of SARS-CoV-2 in extrapulmonary tissues has been shown in human gut enterocytes (28), myocardial cells (29), and kidneys (30), among others. Poma and colleagues (31), in their autopsy study, evaluated thyroid tissues of 25 patients who were died of COVID-19. The authors could demonstrate the SARS-CoV-2 genome and antigens in 36% of the studied thyroid specimens. These patients were not specifically selected because of a clinical thyroid dysfunction related to COVID-19. The latter observation is pathophysiologically plausible considering the increased expression of ACE2 receptors, which is the main way of entry of SARS-CoV-2 into thyroid follicular epithelial cells (32,33). Though we did not evaluate tissue biopsies indicating viral genome in thyroid tissue, as far as we know, none of the reported

cases in the literature reported direct evidence of SARS-CoV-2 invasion of thyroid tissue.

In our case series, as was in the literature, there was a clear-cut latent period between the COVID-19 related symptoms and the onset of SAT-related symptoms. Anterior neck pain was the invariable symptom of the SAT patients in our series. Thus, this distinctive symptom, along with a thyroid that was tender to palpation, makes it easier to discern the onset of SAT. Thus, it is reasonable to think that autoimmune phenomena triggered by SARS-CoV-2 rather than direct viral cytopathic effect might be chiefly responsible for the development of SAT after COVID-19. Interestingly, in 2 of our SAT patients, SAT symptoms recurred after complete resolution with appropriate treatment. Repeated SARS-CoV-2 PCR tests proved to be negative in these patients, and both patients responded favorably to the repeat of their previous treatments.

In Turkey, at the beginning of the pandemic, initially, an inactive SARS-CoV-2 vaccine was available. Soon, an mRNA-based SARS-CoV-2 vaccine was also available for use. As of the time of the preparation of this manuscript, 54% of the Turkish population has been fully vaccinated (13). Vaccination (influenza and H1N1) related SAT had been previously reported (34,35). As expected from a global mass vaccination program against a respiratory pathogen, cases of SAT coincided after SARS-CoV-2 vaccination have been reported. The SAT cases were described for mRNA-based, adenovirus-vectored, and inactive SARS-CoV-2 vaccines (15, 36). However, we should emphasize the fact that the number of reported SAT cases due to SARS-CoV-2 vaccination is much fewer compared to COVID-19 related cases. Here, we report the largest-to-date case series of patients who developed SAT after vaccination for COVID-19. All but one of our patients developed SAT after the administration of an inactive SARS-CoV-2 vaccine. The median latent period between the vaccination and onset of SAT symptoms was 25.8 days. In mRNA and adenovirus-vector-based vaccine administrations, this latent period was reported to be between 2-3 weeks. However, in a report from Turkey, SAT symptoms developed 2 and 4 days after the administration of an inactive SARS-CoV-2 vaccine (14). Both in the cases reported in the literature and our own cases, the presentation, and findings of the cases with SAT were not different from those of idiopathic cases. All of the cases responded favorably to the standard treatment regiment for SAT. It has been speculated that the vaccine-related SAT cases may be a product of ASIA syndrome in which adjuvants used to enhance the immunogenicity of the vaccines may lead to unintentional activation of the immune syndrome resulting in thyroid inflammation (37).

Inflamation related markers such as sedimentation and C-reactive protein (CRP) is a nonspecific indicator of the SAT. In our cohort CRP and sedimentation levels were above references ranges as expected. However, in postCOVID-19 or COVID-19 vaccine-related groups CRP levels was similar. On the other hand sedimentation rate was highet at a border of statistical significance. This is maybe due to etiological and pathogenetic variations; such as faster recovery from COVID related disease or low activity of COVID vaccines. SAT is perhaps clinically more silent, in COVID-19-related conditions compared to idiopathic or the disease originated other than COVID-19-related conditions.

Several limitations of the current work deserve mentioned further. Although the largest of its kind, this was a single-center study with a limited number of patients. As mentioned earlier, we did not have direct tissue evidence of thyroid invasion of the virus. However, if this association were a result of the autoimmune phenomenon, as was the case in (autoimmune/inflammatory syndrome induced by adjuvants) ASIA syndrome, looking for the viral genome would be a futile effort at the local level. Since patients first presented their general practitioners and then referred when it was suspected the patients might have SAT, not all patients presented us at the same stage of their disease. This fact was also reflected by the various test results of the thyroid function and inflammatory markers. In addition, we did not have thyroid autoantibodies in all patients.

Limitations of the study: Viral causes like mumps virus, coxsackie virus, adenovirus, Ebstein-Barr virus, influenzae and cytomegalovirus are accounted for common environmental factors of subacute thyroiditis (38). In our study we did not do the assays for the mentioned viral infections since the main infectious cause in the pandemic was COVID-19.

CONCLUSION

Our present study is one of the largest study in similar studies conducted to date. We also reported both COVID-19 related, and the SARS-CoV-2 vaccination-related SAT cases together in addition to the data of idiopathic SAT cases. Our results, although lacking direct tissue evidence thereof, showed a possible association of COVID-19 and SAT development. We also reported 6 cases who developed SAT after inactive and mRNA-based SARS-CoV-2 vaccines. In our study, all COVID-19 patients had PCR evidence of the infection. In this regard, caring physicians should be aware of the possibility of the interaction between SARS-CoV-2 and the thyroid gland in the form of SAT. We still do not have enough data if SAT occurs concurrently and among the

cloud of symptoms of COVID-19 infection. At least the presence of anterior neck pain and an enlarged tender thyroid gland should direct the physician to investigate the possibility of SAT in a COVID-19 patient.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medicana International Ankara Hospital Ethics Committee (Date: 06.09.2021; Decision No: BŞH-28).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020; 26: 1017-32.
2. Dong M, Zhang J, Ma X, et al. ACE2, TMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19. Biomed Pharmacother 2020; 131: 110678.
3. Caron P. Thyroiditis and SARS-CoV-2 pandemic: a review. Endocrine 2021; 72: 326-31.
4. Desailloud R, Hober D. Viruses and thyroiditis: an update. Virol J 2009; 6: 5.
5. Bostan H, Unsal IO, Kizilgul M, et al. Two cases of subacute thyroiditis after different types of SARS-CoV-2 vaccination. Arch Endocrinol Metab 2022: 2359-3997000000430.
6. Toft J, Larsen S, Toft H. Subacute thyroiditis after hepatitis B vaccination. Endocr J. 1998; 45:135.
7. Hsiao JY, Hsin SC,Hsieh MC, Hsia PJ, Shin SJ. Subacute thyroiditis following influenza vaccine (Vaxigrip) in a young female. Kaohsiung J Med Sci 2006; 22: 297-300.
8. Plaza-Enriquez L, Khatiwada P, Sanchez-Valenzuela M, Sikha A. A case report of subacute thyroiditis following mRNA COVID-19 vaccine. Case Reports in Endocrinology 2021; 11; 8952048.
9. Aemaz Ur Rehman M, Farooq H, Ali MM, Ebaad Ur Rehman M, Dar QA, Hussain A. The association of subacute thyroiditis with COVID-19: a systematic review. SN Compr Clin Med 2021; 1-13.
10. Christensen J, O'Callaghan K, Sinclair H, et al. Risk factors, treatment and outcomes of subacute thyroiditis secondary to COVID-19: a systematic review. Intern Med J 2021: 10.1111/imj.15432.
11. Campos-Barrera E, Alvarez-Cisneros T, Davalos-Fuentes M. Subacute Thyroiditis associated with COVID-19. Case Rep Endocrinol 2020; 2020: 8891539.
12. Bahçecioğlu AB, Karahan ZC, Aydoğan BI, Kalkan IA, Azap A, Erdoğan MF. Subacute thyroiditis during the COVID-19 pandemic: a prospective study. J Endocrinol Invest 2022; 13:1-10.
13. Coronavirus vaccinations, Our World in Data, https://ourworldindata.org/covid-vaccinations?country=OWID_WRL, accessed 10 October, 2021.
14. Iremli BG, Sendur SN, Unluturk U. Three cases of subacute thyroiditis following SARS-CoV-2 vaccine: postvaccination ASIA syndrome. J Clin Endocrinol Metab 2021; 106: 2600-5.
15. Bornemann C, Woyk K, Bouter C. Case report: two cases of subacute thyroiditis following SARS-CoV-2 vaccination. Front Med (Lausanne) 2021; 8: 737142.
16. Sözen M, Topaloğlu Ö, Çetinarslan B, et al. COVID-19 mRNA vaccine may trigger subacute thyroiditis. Hum Vaccin Immunother 2021; 10:1-6.
17. Coronavirus vaccinations, Our World in Data, https://ourworldindata.org/covid-vaccinations?country=OWID_WRL, accessed 19 September, 2021.
18. Barron E, Bakhai C, Kar P, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol 2020; 8: 813-22.
19. Kumar B, Gopalakrishnan M, Garg MK, et al. Endocrine dysfunction among patients with COVID-19: A single-center experience from a tertiary hospital in India. Indian J Endocr Metab 2021; 25: 14.
20. Brancatella A, Ricci D, Viola N, Sgro D, Santini F, Latrofa F. Subacute thyroiditis after Sars-COV-2 infection. J Clin Endocrinol Metabi 2020; 105: 7.
21. Ippolito S, Dentali F, Tanda ML. SARS-CoV-2: a potential trigger for subacute thyroiditis? Insights from a case report. J Endocrinol Invest 2020; 43: 1171-2.
22. Brancatella A, Ricci D, Cappellani D, et al. Is subacute thyroiditis an underestimated manifestation of SARS-CoV-2 infection? insights from a case series. J Clin Endocrinol Metab 2020; 105: 10.
23. Abreu R, Miguel R, Saieg M. Subacute (De Quervain) thyroiditis during the COVID-19 pandemic. Cancer Cytopathol 2021.
24. Sohrabpour S, Heidari F, Karimi E, Ansari R, Tajdini A, Heidari F. Subacute thyroiditis in COVID-19 patients. Eur Thyroid J 2021; 9: 321-3.
25. Muller I, Cannavaro D, Dazzi D, et al. SARS-CoV-2-related atypical thyroiditis. Lancet Diabetes Endocrinol 2020; 8: 739-41
26. Trimboli P, Camponovo C, Franscella S, et al. Subacute thyroiditis during the COVID-19 pandemic: searching for a clinical association with SARS-CoV-2. Int J Endocrinol 2021; 2021: 5588592.
27. Pirola I, Gandossi E, Rotondi M, et al. Incidence of De Quervain's thyroiditis during the COVID-19 pandemic in an area heavily affected by Sars-CoV-2 infection. Endocrine 2021; 74: 215-8.
28. Lamers MM, Beumer J, Van der Vaart J, et al. SARS-CoV-2 productively infects human gut enterocytes. Science 2020; 369: 50-4.
29. Lindner D, Fitzek A, Brauninger H, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol 2020; 5: 1281-5.
30. Puelles VG, Lutgehetmann M, Lindenmeyer MT, et al. Multiorgan and renal tropism of SARS-CoV-2. New Engl J Med 2020; 383: 590-2.
31. Abreu R, Miguel R, Saieg M. Subacute (De Quervain) thyroiditis during the COVID-19 pandemic. Cancer Cytopathol 2021.Abreu R, Miguel R, Saieg M. Subacute (De Quervain) thyroiditis during the COVID-19 pandemic. Cancer Cytopathol 2021.
32. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty 2020; 9: 45.
33. Ruggeri RM, Campenni A, Deandreis D, et al. SARS-COV-2-related immune-inflammatory thyroid disorders: facts and perspectives. Expert Rev Clin Immunol 2021; 17: 737-59.

34. Altay FA, Guz G, Altay M. Subacute thyroiditis following seasonal influenza vaccination. Hum Vaccin Immunother 2016; 12: 1033-4.
35. Girgis CM, Russo RR, Benson K. Subacute thyroiditis following the H1N1 vaccine. J Endocrinol Invest 2010; 33:506.
36. Oyibo SO. Subacute Thyroiditis After receiving the adenovirus-vectored vaccine for Coronavirus disease (COVID-19). Cureus 2021; 13: e16045.
37. Das L, Bhadada SK, Sood A. Post-COVID-vaccine autoimmune/inflammatory syndrome in response to adjuvants (ASIA syndrome) manifesting as subacute thyroiditis. J Endocrinol Invest 2021.
38. Desailloud R, Hober D. Viruses and thyroiditis: an update. Virol J 2009; 12: 5.

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Changing profile of infective endocarditis during 31-year time course in a tertiary care hospital

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ABSTRACT

Aim: Infective endocarditis (IE), infection of the endocardial surface of heart, may cause mortality up to 30% despite advancements in medical care. Epidemiology of IE and profile of causative organism has changed in the last years. We aimed to investigate the changing profile of IE over a 31-year period in a tertiary care hospital

Material and Method: Medical records of 290 patients treated with the diagnosis of IE between 1974 and 2005 were re-evaluated according to Modified Duke criteria. Forty seven cases were classified as rejected cases.

Results: Of the 243 patients 109 was female (44.8%) and 134 male (55.2%). The mean age of the patients was 38±16.4 years (Table). The mean age of the patients showed an increasing trend throughout the time ($p< 0.001$) ; it was 29 years between 1974-1980 but increased to 54 years in 2001-2005 period. Rheumatic valvular disease (RVD) was the most frequent underlying heart disease (60%) but showed a declining trend especially in the last years. *S. aureus* was the most common pathogen in all the time periods (15.2%). Blood cultures were negative in 90 (43%) patients. But the percentage of blood culture negativitiy decreased significantly from 63% in 1981-1985 periods to 28% in 2001-2005 period. (p: 002). Mitral valve was the most common affected valve (52, 44%). Surgery was performed in 74 of the 243 cases (30.5%). In-hospital mortality rate was 30.6. Mortality rate was significantly lower in patients who underwent surgery compared to ones who did not (19.2% vs. 35.8%, $p< 0.005$). Mortality rate was also lower in patients with community acquired infection compared to ones with nosocomial infection (27% vs 45%). Embolic events, nosocomial infections and surgery were independent risk factors for mortality.

Conclusion: The mean age of IE population is increasing, RVD disesase is less commonly seen as an underlying heart and *S. aureus* is the most common pathogen. These findings are compatible with the reports from developed countries. Surgery displays a protective effect on the prognosis of IE

Keywords: Infective endocarditis, mortality, epidemiology

INTRODUCTION

Infective endocarditis (IE) is an infectious disease that affects the endocardial surface of the heart. Native or prosthetic valves and also implanted intracardiac devices may be involved (1). Annual incidence of IE approaches 10/100,000 of the general population where mortality risk may reach 30% despite the advancements in medical care (2,3).

Epidemiology of the disease has changed in the last years. Rheumatic valvular disease is currently less common in developed countries but is still an important predisposing factor in developing countries. On the other hand prosthetic valves and intracardiac devices constitute major risk factors for IE in developed countries. In industrialized countries older individuals are more commonly affected; the percentage of younger individuals affected by IE is higher in developing countries or in low socioeconomic groups. Intravenous drug use in young individuals is also an increasing risk factor (1,4).

Staphylococcus aureus has become more prominent among causative microorganisms, accounting for up to %30 percent of cases (1). This may be due to the fact that most cases of IE are hospital acquired or health care related (5). Due to the decreased incidence of rheumatic heart disesase, incidence of viridians group *streptococci* causing subacute IE has also decreased. Growing incidence of *enterococcal* IE is also seen worldwide (2).

In this study we aimed to investigate the changing profile of IE during 31-year time course in a tertiary care hospital.

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MATERIAL AND METHOD

The study was a thesis study. It was completed with the approval of Academic Board of Deparment of Internal Medicine, Hacettepe University (Date: 2014, Decision No: 87). This study was a retrospective thesis study for Internal Medicine residency graduation which was approved by Department of Internal Medicine of Hacettepe University in 05.05.2006. All procedures were performed in accordance with the ethical rules and principles of the Helsinki Declaration.

Study Population

Medical records of patients treated in Hacettepe University Hospital with the diagnosis of IE between January 1974 and June 2005 were retrospectively examined.

Data collected were as follows: age, sex, signs, duration of hospitalization, comorbidities, source of infection, haemoglobin level, white-blood cell counts (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein, rheumatoid factor, presence of; any murmurs, petechiae, splinter haemorrhage, conjuctival haemorrhage, Janeway lesions, splenomegaly, Roth spots, Osler's nodes, clubbing, neurological signs, embolic phenomenia, transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) findings, blood culture results, history of prior antibiotic treatments, medical or surgical treatment and mortality.

Cases were re-evaluated according to modified Duke Criteria.

Statistical Analysis

SPSS software version 10.0 was used for statistical analysis. Data were presented as mean±standard deviation for continous variables. For categorical variables frequencies were calculated. Chi-square test ($\chi 2$) was performed for comparing qualitative variables. Mann-Whitney U test was used to establish the relationship between mean age and mortality. Spearman Correlation test was applied for demonstrating the relationship between age and mortality. For time trends, linear ratios were analyzed by χ linear trend test ($\chi 2LT$).

RESULTS

Two hundred and ninety cases treated between January 1974 and June 2005 with IE diagnosis was identified during the search. When these cases were re-evaluated using modified Duke Criteria: 145(50%) cases were classified as definite endocarditis, and 98(33%) cases were as possible endocarditis. Forty-seven cases (16.2%) were rejected as they did not fulfil the criteria.

Of the 243 patients 109 were female (44.8%) and 134 male (55.2%). The mean age of the patients was 38±16.4 years (**Table 1**). The mean age of the patients showed an increasing trend throughout the time (p< 0.001); it was 29 years between 1974- 1980 but increased to 54 years in 2001-2005 period (**Figure 1**).

Table 1. Baseline caharacteristics of patients with infective endocarditis

Age, mean±SD	38±16
Gender; Female/Male n (%)	109/134 (44.8/55.2)
Predisposing factors	**n (%)**
Rheumatic valvular disease	124 (60)
Prosthetic valve	51 (21)
Congenital heart disease	14 (5.7)
Sclerotic aortic disease	9 (3.6)
Previous IE	2 (0.8)
Cardiac pacemaker	2 (0.8)
Intravenous drug abuse	1 (0.4)
Laboratory findings	
Haemoglobin (g/dl), mean	10.3± 1.86
White blood cells (/mm³), mean	12.1± 2.45
Erythrocyte sedimentation rate (mm/hour), mean	71±27.8
Rheumatoid factor positivity, %	37
Clinical findings	**n (%)**
Fever	219 (90)
Murmurs	218 (89)
Splenomegaly	108 (44)
Petechiae	23 (9.4)
Splinter hemorrhage	22 (9)
Clubbing	14 (5.7)
Roth's spots	8 (3.2)
Osler nodes	7 (2.9)
Janeway lesions	4 (1.6)
Embolic event	89 (36)
Involved valve	**n (%)**
Mitral valve	52 (44)
Aortic valve	36 (40)
Mitral + aortic valve	11 (9.6)
Prosthetic valve	16 (13.5)
Pulmonary valve	1 (0.9)
Tricuspid valve	2 (1.7)
Causative microoarganism	**n (%)**
S. aureus	37 (15.2)
S. viridans	25 (10.3)
S. epidermidis	16 (6.6)
E. faecalis	18 (7.4)
Brucella	13 (5.3)
P. aeruginosa	7 (2.9)
S. haemolyticus	4 (1.6)
Prior antibiotic use, n (%)	120 (49)
Nosocomial infection, n (%)	45 (18.5)
Surgical treatment, n (%)	74 (30)
Mortality, n (%)	71 (29)

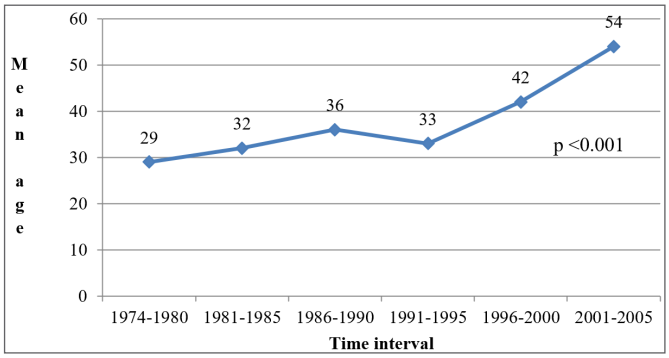

Figure 1. Mean age of patients in consecutive time periods

Underlying Heart Disease

In 207 cases (85%) at least one underlying heart disease was identified; rheumatic valvular disease (RVD)was the most frequent underlying heart disease (60%) followed by prosthetic valve(21%). Underlying heart diseases are shown in **Table 1**. While rheumatic valvular disease seems the most frequent underlying heart disease, substantial changes have occured throughout the time; a decrease has been observed in the frequency of RVD. In the 2001-2005 periods prosthetic valves have become more frequent than RVD. In this last period no structural heart disease has been identified in 40% of the cases (**Figure 2**).

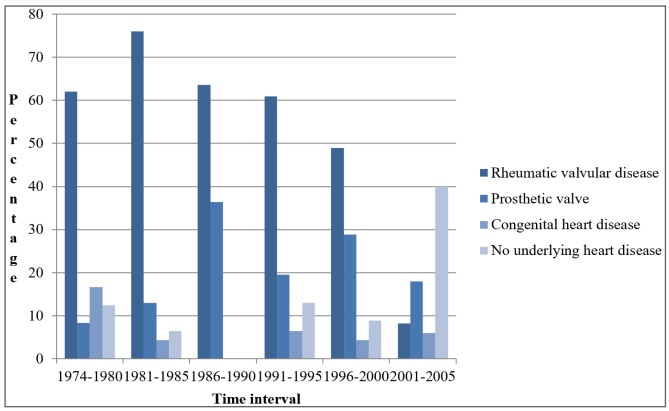

Figure 2. Distribution of underlying heart diseases in consecutive time periods

Causative Microorganisms

Blood cultures were positive in 138/243 (57%) of patients with diagnosis definite or possible IE. The most common pathogen was *S. aureus* in 37 patients (15.2%), followed by *S. viridans* in 25 patients (10.3%), *E. faecalis* in 18 patients (7.4%) and *Brucella* in 13 patients (5.3%) (**Table 1**). In all time periods *S. aureus* was more common than *S. viridans* except for the 1986-1990 period (**Figure 3**).

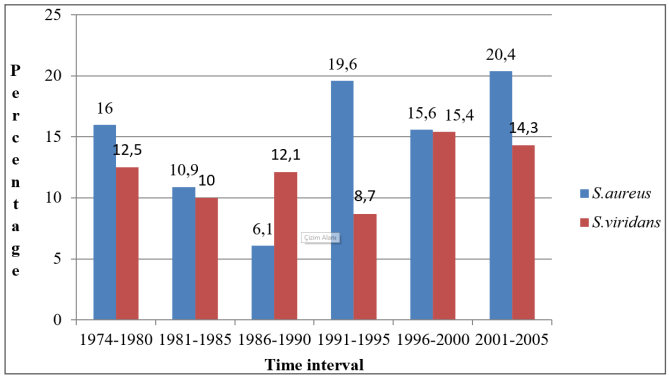

Figure 3. Comparison of incidences of *S. aureus* and *S. viridans* in consecutive time periods

Blood cultures were negative 90 patients (43%). The percentage of culture negative cases decreased throughout the time, from 63% in 1981-1985 period to 28% in 2001-2005 period (**Figure 4**). The decrease was statistically significant (χ2LT= 3.26, p=0.002).

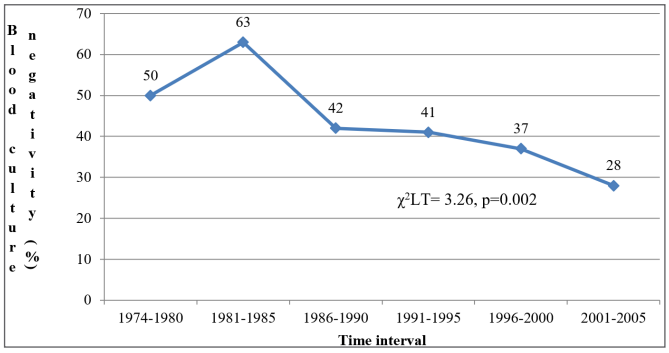

Figure 4. Percentage of blood culture negativity in consecutive time periods

Echocardiographic Findings

From 1990 all cases were evaluated by transthoracic echocardiography (TTE). Transoesophageal echocardiography (TE) was available since 1995. Since then TEE was performed in 56 /110 (50%) of cases. Echocardiographic findings compatible with modified Duke criteria was found in 118 patients of the 243 patients (48%) clasified as IE. TEE detected vegetations in 24(20%) cases which could not be detected by TTE. Vegetations were most commonly seen on mitral valve in 52(44%) patients followed by aortic valve in 36(30%) patients (**Table 1**).

Complications

Complications were present in 111of the 243 cases (**Table 2**). The most frequent complication was embolic events (96, 39.5%). Heart failure was the second most frequent complication (16, 6%). Cerebral embolism was the most common embolic events occurring in 65 cases (26.7%). Spleen (13 cases, 5.3%), extremities (10 cases, 4.1%) and lungs (3 cases, 1.2%) were also affected by embolic events.

Surgery

Surgery was performed in 74 of the 243 cases (30.5%) diagnosed with IE. Surgery was indicated most commonly for heart failure (21.6%) followed by embolic events (18.9%), valve dysfunction (17.6%), prosthetic valve failure (14.9%). Indications for surgery are given in detail in **Table 2**.

Mortality

In-hospital mortality rate was 30.6%. Major causes of death were as follows: sudden death (14 cases, 19.7%), cerebral embolism (13 cases, 18.3%), cardiogenic shock (9 cases, 12.6%), pulmonary embolism (2 cases, 2.8%). A marked decrease in mortality has been observed over the time. Mortality rate decreased from 47.5 % in the 1974-1980 periods to 22.7 % in 1996-2000 periods. But

in 2001-2005 period there was an unexpected increase in the mortality rate (**Figure 5**).

Table 2. Complications of infective endocarditis and indications for surgery

Complication	**n, (%)**
Embolic event	93 (38.3)
Congestive heart failure	13 (5.3)
Embolic event +congestive heart failure	3 (1.2)
Chordae tendineae rupture	2 (0.8)
Indications for surgery	**n, (%)**
Congestive heart failure	16 (21.6)
Embolic events	14 (18.9)
Valve dysfunction	13 (17.6)
Prosthetic valve failure	11 (14.9)
Mobile vegetation > 10 mm	6 (8.1)
Congenital heart defect	4 (5.4)
Perivalvular abscess	2 (2.7)
Brucella endocarditis	1 (1.4)
Uncontrolled infection	1 (1.4)
Prosthetic valve failure + perivalvular abscess	1 (1.4)
Candida endocarditis	1 (1.4)
Valvular obstruction	1 (1.4)

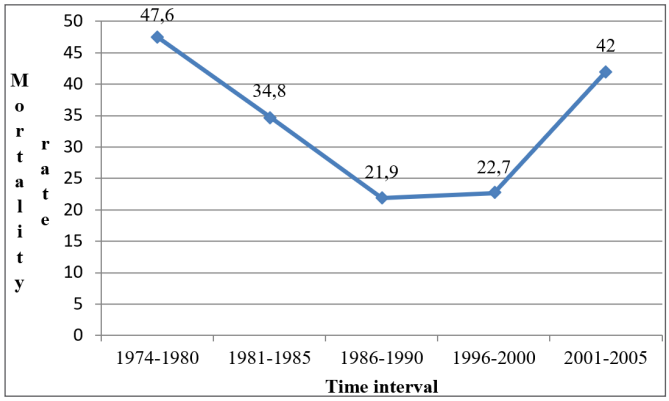

Figure 5. Mortality trend in consecutive time periods

Mean age of patients who died were higher compared to the surviving patients (42.44±16.70 vs. 37.79 ±16.15, p< 0.005)

Mortality rate was significantly lower in patients who underwent surgery compared to ones who did not (19.2% vs. 35.8%, p< 0.005). Mortality rate was also significantly lower in patients with community acquired infection compared to ones with nosocomial infection (27% vs 45%,p< 0.005). Mortality rate was higher but not significant in patients >60 years compared to patients ≤ 60years (38.9% vs 29.3%, p=0.078).

Mutivariate analysis (**Table 3**) showed that embolic events (OR=3.304, 95% CI: 1.703-5.404, p =0.047) nosomial infection (OR=2.24, 95% CI: 1.140-4.396, p=0.019) and surgery (OR=0.425, 95% CI: 0.218-0827, p=0.012) were independent risk factor for mortality, but not *S. aureus* (OR=3.304, 95% CI:0.499-1.856, p =0.901) or blood culture positivity (OR=1.7, 95% CI: 0.655-3.054, p =0.071).

Table 3. Multivariate analysis of factors predicting in-hospital mortality of patients with infected endocarditis

	Odds'ratio	**95%CI**	**p-value**
Embolic events	3.034	1.703-5.404	0.047
Nosocomial infection	2.24	1.140-4.396	0.019
Surgery	0.425	0.218-0.827	0.012
S. aureus	0.962	0.499-1.856	0.901
Blood culture positivity	1.7	0.655-3.054	0.071

DISCUSSION

The features of IE over a 31-year period in a tertiary care hospital are analyzed in this retrospective study. The mean age was 38±16.4 years in this period but showed an increasing trend throughout the time. In 2001-2005 period mean age increased to about 54 years. The mean age was found to be 45 in a study from our country which included 2002- 2004 period (6). In a recent study of IE from our country median age was 58 (7). The increase in age is considered to be associated with the decrease in rheumatic heart diseases and increase in degenerative heart diseases (5). In our series RVD was the leading predisposing factor until 2000, but a striking decrease in the incidence of RVD was observed in 2001-2005 period which is in concordance with the literature (1,4). Interestingly in the last period most of IE cases occurred in patients with no underlying structural heart disease. In this period the mean age of the patients increased to about 54 years. We may postulate that the individuals in this group may have more chronic illnesses necessitating more medical interventions predisposing them to IE.

S. aureus was the most common isolated microorganism in IE cases. It was followed by viridians group *streptococci*. Our results are in concordance with a pooled analysis of 1270 IE cases in Turkey (8) and a consensus report on IE (9). *S. aureus* is also the most common pathogen in Western countries and United States of America (2,5). In the study by Correa et al. (10), which included the period between 1970 and 2006, a similar period to our study, viridians group *streptococci* was more common than *S. aureus* except for the 2001-2006 period. The decrease in the incidence of viridians group *streptococci* was suggested to be associated with significant decrease in the proportion of rheumatic heart disease as a result of successful treatment of streptococcal pharyngitis. But unlike their findings *S. aureus* was more common than viridians group *streptococci* in all periods in our study, except for the 1986-1990 periods.

Overall, blood cultures were negative in 43.2% of cases. Although we observed a significant decrease in culture negative cases throughout the time; in 2001-2005 period culture period cases consisted 28% percent of all the cases, the number is still high. Recent European and American studies report rates ranging between 5%-20% (11,12). In our study group 58% of blood culture negative cases had a history of antibiotic use in two weeks time prior to diagnosis which may explain such high rate. In the above mentioned pool analysis of IE cases in Turkey, incidence of negative blood culture was 31.1 % (8). In two studies conducted at tertiary care hospitals from Turkey culture negative cases were reported at similar high rates 48% (4,7). Authors explain this undesired high rate as a consequence of being a referral hospital where patients have a history of antibiotic use prior to referral.

Surgery was performed in 30.5% of the cases, comparable to the rate reported (36.9%) in a study from Portugal (13). In that study main indication for surgery was heart failure similar to our study. Higher surgery rate (69.7%) was reported in a study from our country which is explained as a possible result of selection bias by the author (7).

Embolic events were the most frequent complication identified in our study. Most emboli were seen in the brain. Mostaghim et al. (2) also reported a similar finding. They have two explanations for this finding. First one is ordering more brain imaging as result of increased awareness of physicians for the neurologic symptoms. Second one is the upward direction of the branches of aorta supplying the brain which makes it easier for embolism .

In-hospital mortality rate found in our study (30.6%) was within the limits reported in the literature (2,3). Over the 31-year period a substantial decrease was observed in mortality rate in our patients except 2001-2005 periods where mortality rate increased to 42%. This unexpected increase may be explained by the fact that the patients in this period were older; older age is associated with more chronic medical conditions making individuals more vulnerable.

Surgical therapy in IE was reported to be lower mortality rates in the literature (13,14). We found a significant lower mortality rate in patients who underwent surgery.

This study is not without limitations. Retrospective nature of this study is the major limitation. The high rate of culture negative cases may have precluded us detecting the real incidence of microorganisms, especially viridians group *streptococci*. As the study is conducted at a tertiary care hospital, it will not be proper to generalize the results to the whole population. But 31-year study period in our study gives a good perspective to observe the changes occurred in the profile of IE.

CONCLUSION

We studied the changing profile of IE over a 31-year period in a tertiary care hospital. We found out that the mean age of patients with IE has dramatically increased evidently increased and that the incidence or RVD has decreased. The rate of culture negative cases has also decreased. Embolic events and nocomial infections were independent predictors of mortality. But it was encouraging to see the improvement in survival rates throughout the time; surgery was associated with improved survival rates.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was a thesis study. It was completed with the approval of Academic Board of Deparment of Internal Medicine, Hacettepe University (Date: 05.05.2006, Decision No: 2).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Mostaghim AS, Lo HYA, Khardori N. A retrospective epidemiologic study to define risk factors, microbiology, and clinical outcomes of infective endocarditis in a large tertiary-care teaching hospital. SAGE Open Med 2017; 5: 2050312117741772.
2. Rajani R, Klein JL. Infective endocarditis: A contemporary update. Clin Med (Lond) 2020; 20: 31-5.
3. Hubers SA, DeSimone DC, Gersh BJ, Anavekar NS. Infective endocarditis: a contemporary review. Mayo Clin Proc 2020; 95: 982-97.
4. Yilmaz Ak H, Özşahin Y, Yesiltas MA, et al. Comparison of demographic profile, laboratory, epidemiology and clinical outcomes in patients with native valve and prosthetic valve endocarditis. Heart Surg Forum 2021; 24: E534-43.
5. Selton-Suty C, Célard M, Le Moing V, et al. Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based survey. Clin Infect Dis 2012; 54: 1230-9.
6. Leblebicioglu H, Yilmaz H, Tasova Y, et al. Characteristics and analysis of risk factors for mortality in infective endocarditis. Eur

J Epidemiol 2006; 21: 25-31.

7. Zencirkiran Agus H, Kahraman S, Arslan C, et al. Characterization, epidemiological profile and risk factors for clinical outcome of infective endocarditis from a tertiary care centre in Turkey. Infect Dis (Lond) 2019; 51: 738-44.
8. Vahabi A, Gül F, Garakhanova S, Sipahi H, Sipahi OR. Pooled analysis of 1270 infective endocarditis cases in Turkey. J Infect Dev Ctries 2019; 13: 93-100.
9. Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2015; 132: 1435-86.
10. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). G Ital Cardiol (Rome) 2016: 17: 277-319.
11. Şimşek-Yavuz S, Akar AR, Aydoğdu S, et al. Diagnosis, treatment and prevention of infective endocarditis: Turkish consensus report-2019. Turk Kardiyol Dern Ars 2020; 48: 187-226.
12. Correa de Sa DD, Tleyjeh IM, Anavekar NS, et al. Epidemiological trends of infective endocarditis: a population-based study in Olmsted County, Minnesota. Mayo Clin Proc 2010; 85: 422-6.
13. Ilhão Moreira R, Coutinho Cruz M, Moura Branco L, et al. Infective endocarditis: Surgical management and prognostic predictors. Rev Port Cardiol (Engl Ed) 2018; 37: 387-94.
14. Ferraris L, Milazzo L, Rimoldi SG, et al. Epidemiological trends of infective endocarditis in a single center in Italy between 2003-2015. Infect Dis (Lond) 2018; 50: 749-56.

Original Article

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Determination of the effect of glucose, sucrose and sodium chloride addition in different culture media on biofilm formation of methicillin resistant *Staphylococcus aureus*

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ABSTRACT

Aim: *Staphylococcus aureus* is the most clinically important bacterium among *Staphylococci*, colonizing 15-36% of the entire population. Biofilm formation is an important virulence factor of *S. aureus*. Treatment of biofilm-associated *S. aureus* infections is difficult. This study aimed to investigate the effects of glucose, sucrose, and sodium chloride (NaCl) addition to seven different media on biofilm formation capacity of methicillin resistant *S. aureus* (MRSA) strains.

Material and Method: Biochemical and molecular methods (spa, nuc, coa, and mecA PCR) were used to identify *S. aureus* strains. Cefoxitin resistance was determined by the agar disc diffusion method. Biofilm formation of the strains was investigated in 7 different media (Tryptone soya broth (TSB), TSB+1% sucrose, TSB+1% glucose, TSB+4% NaCl, Brain Heart Infusion broth (BHI), BHI+1% glucose, and BHI+4% NaCl) using the microplate test. The growth of strains in 7 different media was determined at 600 nm, and then 96-well microplates were stained with crystal violet and their biofilm formation abilities were determined by measuring absorbance values at 590 nm.

Results: In this study, 53 strains containing spa, nuc, coa, and mecA genes were identified as MRSA with resistance to cefoxitin. When biofilm formation was examined in seven different media using the microplate test, the biofilm formation ability of MRSA strains increased significantly with glucose and sucrose addition to TSB and BHI ($P<0.05$), while the addition of 4% NaCl decreased the biofilm formation ($P<0.05$). When the media were compared, it was determined that BHI increased bacterial growth and biofilm formation compared to TSB.

Conclusion: It was concluded that the biofilm formation abilities of MRSA strains increased especially in the presence of glucose. The results showed that biofilm production capacity is affected by environmental factors, especially nutrient content in used media.

Keywords: MRSA, biofilm, microplate test

INTRODUCTION

Staphylococcus aureus, one of the most clinically important species among *Staphylococci*, is a commensal bacterium that colonizes 15-36% of the entire population (1). *S. aureus* may cause severe diseases such as wound infections, toxic shock syndrome, scalded skin syndrome, skin abscesses, deep tissue abscesses, styes, impetigo, pneumonia, emesis, meningitis, pericarditis, endocarditis, sinusitis, cellulitis, osteomyelitis, diarrhea, urinary tract infections, bacteremia, and sepsis (2-4). The mortality rate is quite high in invasive *S. aureus* infections. On the other hand, due to the resistance of MRSA strains to other antibiotics, the treatment of infections caused by multidrug-resistant *S. aureus* strains may be difficult, and the length of hospital stay may be prolonged (5).

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Biofilm forming ability is an important virulence factor of *S. aureus*. Biofilm is characterized as a collection of surface-associated microbial cells (6-7). *S. aureus* is accepted as one of the most important causes of biofilm-related infections (8). *S. aureus* adheres to material surfaces by using its rolling motion and sticky extensions, thus it constantly attaches to the surfaces, causing micro aggregation to form, resulting in a biofilm layer (9). *S. aureus* strains from different sources have been shown to produce biofilms (10). When *S. aureus* biofilm-related infections occur, it is very difficult to treat and eradicate with antibiotics and other disinfectants (11). Studies have reported that MRSA strains also form strong biofilms (12-13).

Nutrient-rich Brain Heart Infusion broth (BHI) and Tryptone soya broth (TSB), which is less nutrient-rich compared to BHI, are frequently used in *in vitro* biofilm studies (14). Previous studies have shown that the choice of medium strongly affects the biofilm development of *S. aureus* (15,16). It is known that substances such as glucose, sucrose, and NaCl at different concentrations added to the nutrient media have a significant effect on the biofilm production capacity (17).

In this study, the bacterial stocks that have been previously isolated from blood culture samples were used as the materials. The effects of glucose, sucrose, and NaCl addition to TSB and BHI media on biofilm formation of identified MRSA strains were investigated quantitatively.

MATERIAL AND METHOD

Within the scope of the study, clinical bacteria (n:100) grown on blood agar medium from blood culture samples studied in the Clinical Microbiology Laboratory of Ege University Medical Faculty Hospital were used as the materials. The clinical bacterial stocks (n:100) containing 40% glycerol have been previously stored at -80°C. Ethics committee approval is not required as the study was conducted on the stock bacteria. Any clinical specimen were not used in this study. All procedures were performed in accordance with the ethical rules and principles of the Helsinki Declaration.

Identification of Bacteria

Bacterial stocks were cultivated on Mannitol Salt Agar (CM0085 Oxoid, UK) and grown bacteria were subcultured to obtain pure colonies in the same medium. Gram staining, microscopy, and catalase test using 3% (v/v) hydrogen peroxide were applied for the biochemical identification of the bacteria. Gram-positive, cocci-shaped, and catalase-positive bacteria, which were determined as Staphylococci, were included in the study. Then, Staphylococci were grown in TSB (CM0129, Oxoid), followed by DNA isolation using lysostaphin (L7386, Sigma, Germany) and proteinase K (P2308, Sigma) (18). Molecular identification of the isolates was performed by Polymerase Chain Reaction (PCR) using primers specific to the spa gene (19) encoding surface A protein, the nuc gene responsible for thermonuclease activity (20), the coa gene (21) responsible for coagulase activity, and mecA (22) genes responsible for methicillin resistance. The agar disc diffusion method was used to determine the methicillin resistance of the strains and the disc zone diameters of cefoxitin (30 µg) were measured and evaluated according to the CLSI 2020 standards (23). The reference strains *S. aureus* ATCC 25923 and MRSA ATCC 43300 were used as the positive control strains for antibiotic susceptibility and PCR experiments.

Biofilm Test

The microplate method was used to determine the ability of bacteria to form biofilms in different media (24). For this purpose, TSB, TSB containing 1% (w/v) sucrose, TSB containing 1% (w/v) glucose, TSB containing 4% (w/v) NaCl and BHI (CM1135, Oxoid), BHI containing 1% (w/v) glucose and BHI containing 4% (w/v) NaCl were used as test media. Bacterial strains were grown overnight on Tryptone Soya Agar (TSA, CM0131, Oxoid) at 37 °C and then their concentration was adjusted to McFarland0.5 using a densitometer (Den-1B, Biosan, Latvia) in 10 ml of 0.9% (w/v) NaCl. After that, 180 µl of each medium and 20 µl of bacterial suspension in McFarland 0.5 turbidity were inoculated in triplicate wells in a 96-well flat-bottom sterile microplate (3599 Corning Costar, USA). The microplates were incubated at 37 °C for 24 hours and then, bacterial growth was measured using a microplate reader (Epoch, BioTek, the USA) at 600 nm. After that, the microplates were emptied and washed 3 times with sterile 0.9% NaCl to remove bacteria that did not attach to the surface and did not form biofilm. The bacteria attached to the surface were fixed with 200 µl methanol for 15 minutes. The methanol in the microplates was removed by decanting. The microplates were then dried at 55 °C for 1 hour. The attached bacteria were stained with crystal violet (1159400 Merck, Germany) for 5 minutes to visualize biofilm formation, and excess dye was removed by washing the microplates with tap water. For quantification of the biofilm formation of bacteria on the surface, the microplates were dried at 55 °C for 1 h and 200 µl of 33% (v/v) acetic acid (Merck) was added to each well. The dye was completely dissolved in a microplate mixer (Vortex 4 digital, Ika, Germany) at 500 rpm for 5 minutes. The absorbance values of the microplates were measured at 590 nm using a microplate reader (Epoch, BioTek, USA). *S.*

epidermidis YT-169a strain, which produced biofilm in microplate tests, was used as a positive control strain (25).

Statistics

Mean, standard deviation, minimum and maximum values, frequency, and descriptive statistics were used for the data analysis. In addition, the Kruskal-Wallis test, which is a nonparametric test, was used to determine whether there was a statistically significant relationship between different media and glucose, sucrose and NaCl added to the media on the biofilm formation of isolated MRSA strains. Another nonparametric test, the Mann-Whitney test, was used to determine the significant relationship between different media and additives to these media. For all these tests, $p<0.05$ was considered statistically significant. These tests were performed in IBM SPSS statistical program version 22.0 for Windows (2020).

RESULTS

Within the scope of the study, a total of 53/100 strains were identified as Staphylococci by biochemical tests, including spa, nuc and coa genes by molecular identification. The strains (n:53) were mecA gene positive and resistant to cefoxitin by agar disc diffusion method. When the growth of 53 MRSA strains in seven different media was examined with measurements performed at 600 nm. It was determined that MRSA strains developed better in BHI medium and BHI medium to which NaCl was added, compared to only TSB and TSB medium containing sucrose or glucose, and their OD 600 nm values were higher (**Figure 1**).

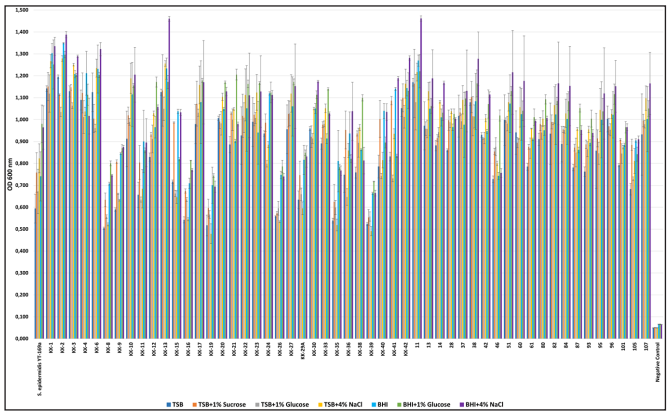

Figure 1. Growth of MRSA strains after incubation at 37 °C for 24 hours in seven different media. *S. epidermidis* YT-169a is indicated as the biofilm positive control strain and the bacteria-free medium as the negative control.

The biofilm formation abilities of the bacteria were determined using the microplate test. In general, higher adhesion and biofilm formation were detected in BHI medium containing 1% glucose (**Figure 2**). In the evaluation made based on the strains, it was determined that MRSA 38 strain showed the highest biofilm formation in BHI containing 4% NaCl.

As a result of the nonparametric Kruskal-Wallis and Mann-Whitney statistical tests based on the microplate test results at 590 nm, no significant relationship was found between TSB and BHI, in terms of biofilm formation ($P>0.05$). Only 1% sucrose and 1% glucose supplementation to TSB medium were found to be significantly associated with the biofilm formation ($P<0.05$), and 1% sucrose and 1% glucose added to TSB medium were found to increase the biofilm formation, compared to TSB alone (**Figure 2**). Compared to TSB, 4% NaCl added to TSB medium was also found to be significantly associated with the biofilm formation ($P<0.05$), and 4% NaCl added to TSB medium was found to reduce the biofilm formation. While there was no significant relationship between 1% sucrose and 1% glucose added to TSB medium on the biofilm formation ($P>0.05$), they were found to be significantly different with 4% NaCl ($P<0.05$) (**Figure 3**).

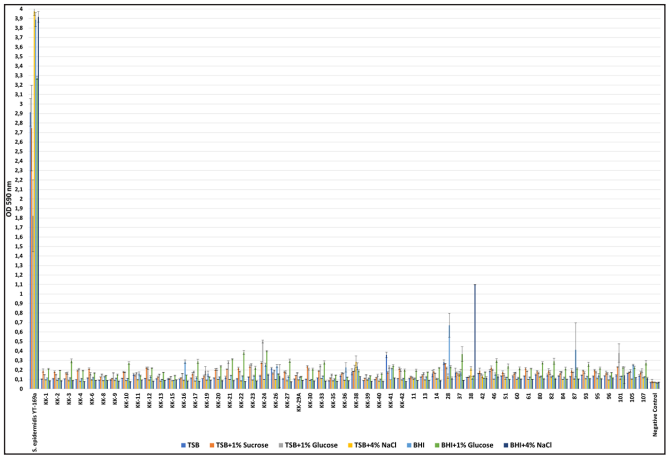

Figure 2. Determination of biofilm formation abilities of MRSA strains in seven different media by the microplate test. *S. epidermidis* YT-169a is indicated as a biofilm positive control strain and a bacteria-free medium as a negative control.

It was also found that 1% glucose added to BHI medium was significantly associated with the biofilm formation compared to BHI alone ($P<0.05$), and 1% glucose added to BHI medium was found to increase the biofilm formation. According to BHI, 4% NaCl added to BHI medium was found to be significantly associated with the biofilm formation ($P<0.05$), and 4% NaCl added to BHI medium was found to reduce the biofilm formation. Significant differences were found on the biofilm formation between 1% glucose and 4% NaCl added to BHI medium ($P<0.05$) (**Figure 3**).

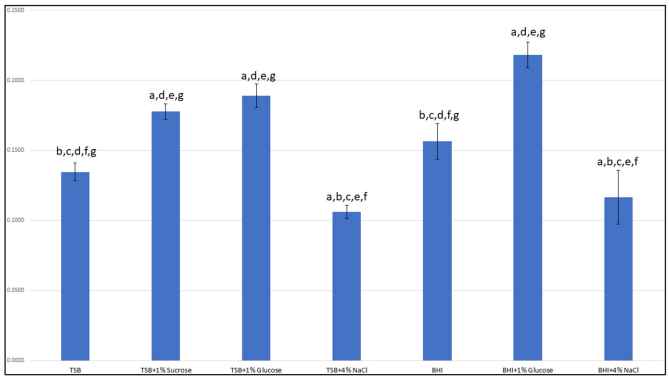

Figure 3. The relationships of glucose, sucrose and NaCl supplementation to TSB and BHI media with the biofilm formation of MRSA strains. (a) TSB, (b) TSB+1% Sucrose, (c) TSB+1% Glucose, (d) TSB+4% NaCl, (e) BHI, (f) BHI+1% Glucose, (g) BHI+4% NaCl. The results were recorded as mean values with±standard deviations of three independent measurements. Mean values with different letters show statistically significant difference ($P<0.05$).

DISCUSSION

The pathogenicity of *S. aureus*, which is the causative agent of various acute or chronic infections, depends on biofilm formation along with other virulence factors. The first stage of biofilm formation, which takes place in at least three stages, is the adhesion of microorganisms. The second stage is cell proliferation and exopolysaccharide synthesis on the surfaces, and the third stage is microaggregation and thick biofilm layer formation (26).

The choice of medium in which bacteria are cultivated and the use of glucose, sucrose, and NaCl at different concentrations influence the biofilm formation of *S. aureus* cells. The previous studies have reported that the increase in NaCl (27), sucrose (28), glucose (29), supplementation with combination glucose and NaCl (28-30) stimulate the biofilm formation capacity. It has also been reported that substances such as glucose and NaCl added to different media for MRSA strains, which are also known to form biofilms, significantly increase the biofilm production capacity of MRSA strains (31).

In this study, we found that the addition of glucose and sucrose in TSB and BHI media increased the biofilm production capacity of MRSA strains, while the addition of NaCl to TSB and BHI media decreased the biofilm formation. In addition, no significant difference was found between the BHI medium and the TSB medium in terms of biofilm production. Singh et al. (32) investigated the effect of glucose, sucrose, and NaCl on the biofilm production capacity of *S. aureus* strains and they stated that these added substances did not have any effect on increasing biofilm production alone, but increased biofilm production when given together. Vázquez-Sánchez et al. (33) examined the biofilm formation of 26 *S. aureus* strains isolated from seafood in the presence of 5% glucose, 5% NaCl, their combination, and 0.1 mM and 1 mM $MgCl_2$. Similar to our glucose supplementation to test media, their results showed that the highest biofilm formation was obtained in 5% glucose supplementation of TSB alone. Meanwhile, glucose increased biofilm formation with increasing incubation temperature from 25°C to 37°C. NaCl had negative correlation with biofilm formation at 37°C. The combination of glucose with NaCl slightly increased the biofilm formation compared to the absence of supplements. Moreover, $MgCl_2$ did not affect significantly the biofilm formation of the strains concerning for to the absence of $MgCl_2$. Lade et al. (16) conducted a study with 40 strains including 21 MRSA and 19 methicillin-susceptible *S. aureus* (MSSA), selected from blood samples. Similar to our study, they stated that biofilm formations of both MRSA and MSSA strains increased in TSB + 0.5% glucose and TSB + 1% glucose media compared to TSB alone. Unlike us, they found that biofilm formations of both MRSA and MSSA strains increased at TSB + 1% NaCl and TSB + 2% NaCl concentrations. In addition, there was no significant difference between MRSA and MSSA at different glucose concentrations, while biofilm formation of MRSA strains was stronger than MSSA strains at TSB + 2% NaCl concentration. In another study, Sugimoto et al. (15) studied 47 clinical *S. aureus* strains (23 MRSA and 24 MSSA) and their results were demonstrated that glucose supplementation increased biofilm formation in most of the strains (42/47). Moreover, NaCl supplementation stimulated biofilm formation of mostly MSSA strains (15/24) than MRSA strains (1/23). The main difference in the results of Sugimoto et al. with our data was the stimulatory effect of NaCl on biofilm formation of MSSA strains rather than MRSA strains. Furthermore, Xu et al. (34) analyzed the effects of NaCl concentrations (0%, 2%, 4%, 6%, 8%, and 10%) on biofilm formation ability of *S. aureus* at 37 °C. Adherence of *S. aureus* cells to polystyrene microplate surface was starting to decrease after 4 days of incubation at 37 °C in all tested NaCl concentrations. Their results demonstrated that high concentrations of NaCl from 4% to 10% continuously increased adherence of bacteria. Ionic nature of NaCl could impact on biofilm formation of the strains. In this respect, surface charge of bacteria could be affected due to environmental Na and Cl ions. In our study, 4% NaCl tested and only one MRSA strain 38 was determined with inreased biofilm formation. Further studies are needed to elucidate the affect of NaCl on clinical MRSA strains with higher and lower concentrations in different growth media.

In the determination of biofilm formation abilities of bacteria, mostly microplate test is used. This test is easy, convenient, and gives quantitative results. Bacterial physicochemical properties especially surface charge, hydrophobicity, and auto-aggregation capacity play important roles in biofilm formation. When we compared our results with previously reported studies

the main difference is the bacterial surface characteristics. Adhesion capacity depends on each bacterial surface characteristic in both MRSA and MSSA strains. Another parameter is test conditions. Incubation time, temperature, test surface (polystyrene, polypropylene, glass, or metal) and surface properties (surface charge, hydrophobicity, and roughness), used media and their ingredients (supplementation with glucose, sucrose, and different type of salts) influence biofilm formation of bacteria (25, 35-36). These test conditions differ from lab to lab with the used test materials and chemicals. This is the main reason for discrepancies in the results.

CONCLUSION

As a result of our study, it was determined that 53 MRSA strains originating from blood culture had the potential to produce biofilms. While the biofilm feature of MRSA strains increases significantly with glucose and sucrose added to different media such as TSB and BHI, the addition of 4% NaCl decreases the biofilm feature. In only one MRSA strain, NaCl stimulated biofilm formation compared to other supplements. The main contribution of our results to the literature was to use different media (TSB and BHI) and supplements (glucose, sucrose and NaCl) together to test biofilm forming abilities of clinical MRSA strains isolated in Turkey. Biofilm formation was controlled both genetic and physicochemical properties of each bacteria. For this reason, each individual bacterium can behave differently to adhere material surfaces.

Contamination of polymeric catheter and percutaneous endoscopic gastrostomy equipment with Staphylococci, which can form a biofilm, poses a great risk of infection for patients. Our results also showed that biofilm production capacity was affected by environmental factors such as nutrient content and type. Using a large number of MRSA and MSSA strains, meanwhile analyzing their physicochemical properties, biofilm-forming ability of clinical strains should be elucidated. These results will be a guide in the development of anti-biofilm surfaces and materials.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval is not required as the study was conducted on the stock bacteria. Any clinical specimen were not used in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Botelho-Nevers E, Gagnaire J, Verhoeven PO, et al. Decolonization of *Staphylococcus aureus* carriage. Med Mal Infect 2017; 47: 305-10.
2. Horn J, Stelzner K, Rudel T, Fraunholz M. Inside job: *Staphylococcus aureus* host-pathogen interactions. Int J Med Microbiol 2018; 308: 607-24.
3. Zainulabdeen SMS, Dakl AA. Pathogenicity and virulence factors in *Staphylococcus aureus*. Muthanna J Pure Sci 2021; 8: 109-19.
4. Jin T, Mohammad M, Pullerits R, Ali A. Bacteria and host interplay in *Staphylococcus aureus* septic arthritis and sepsis. Pathogens 2021; 10: 1-25.
5. Kanyo EC, Nowacki AS, Gordon SM, Shrestha NK. Comparison of mortality, stroke, and relapse for methicillin-resistant versus methicillin-susceptible *Staphylococcus aureus* infective endocarditis: a retrospective cohort study. Diagn Microbiol Infect Dis 2021; 100: 115395.
6. Naicker PR, Karayem K, Hoek KGP, Harvey J, Wasserman E. Biofilm formation in invasive *Staphylococcus aureus* isolates is associated with the clonal lineage. Microb Pathog 2016; 90: 41-9.
7. O'Neill E, Pozzi C, Houston P, et al. A novel *Staphylococcus aureus* biofilm phenotype mediated by the fibronectin-binding proteins, FnBPA and FnBPB. J Bacteriol 2008; 190: 3835-50.
8. Pourzal F, Haghkhah M. Prevalence of biofilm associated genes in different isolates of *Staphylococcus aureus*. J Med Bacteriol 2020; 9: 9-15.
9. Taj Y, Essa F, Aziz F, Kazmi SU. Study on biofilm-forming properties of clinical isolates of *Staphylococcus aureus*. J Infect Dev Ctries 2012; 6: 403-9.
10. Oniciuc EA, Cerca N, Nicolau AI. Compositional analysis of biofilms formed by *Staphylococcus aureus* isolated from food sources. Front Microbiol 2016; 7: 2014-7.
11. Otto M. Staphylococcal biofilms. Microbiol Spectrum 2018; 6: GPP3-0023-2018.
12. Avila-Novoa MG, González-Gómez JP, Guerrero-Medina PJ, et al. *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) strains isolated from dairy products: Relationship of ica-dependent/independent and components of biofilms produced *in vitro*. Int Dairy J 2021; 119: 105066.
13. Azmi K, Qrei W, Abdeen Z. Screening of genes encoding adhesion factors and biofilm production in methicillin resistant strains of *Staphylococcus aureus* isolated from Palestinian patients. BMC Genomics 2019; 20: 1-12.
14. Nyenje ME, Green E, Ndip RN. Evaluation of the effect of different growth media and temperature on the suitability of biofilm formation by Enterobacter cloacae strains isolated from food samples in South Africa. Molecules 2013; 18: 9582-93.
15. Sugimoto S, Sato F, Miyakawa R, et al. Broad impact of extracellular DNA on biofilm formation by clinically isolated methicillin-resistant and -sensitive strains of *Staphylococcus aureus*. Sci Rep 2018; 8: 2254.
16. Lade H, Park JH, Chung SH, et al. Biofilm Formation by *Staphylococcus aureus* clinical isolates is differentially affected by glucose and sodium chloride supplemented culture media. J Clin Med 2019; 8: 1853.
17. Tang J, Chen J, Liu J, Zhang R, Yang R, Chen L. Effects of different cultivation conditions on *Staphylococcus aureus* biofilm formation and diversity of adhesin genes. J Food Safety 2012; 32: 210-8.

18. Sudagidan M, Çavuşoğlu C, Bacakoğlu F. Investigation of the virulence genes in methicillin-resistant *Staphylococcus aureus* strains isolated from biomaterial surfaces. Mikrobiyol Bul 2008; 42: 29-39.
19. Aires-De-Sousa M, Boye K, De Lencastre H, et al. High interlaboratory reproducibility of DNA sequence-based typing of bacteria in a multicenter study. J Clin Microbiol 2006; 44: 619-21.
20. Sudagidan M, Aydin A. Screening virulence properties of *Staphylococci* isolated from meat and meat products. Wien Tierärztl Mschr 2009; 96: 128-34.
21. Hookey J V, Richardson JF, Cookson BD. Molecular typing of *Staphylococcus aureus* based on PCR restriction fragment length polymorphism and DNA sequence analysis of the coagulase gene. J Clin Microbiol 1998; 36: 1083-9.
22. Lem P, Spiegelman J, Toye B, Ramotar K. Direct detection of mecA, nuc and 16S rRNA genes in BacT/Alert blood culture bottles. Diagn Microbiol Infect Dis 2001; 41: 165-8.
23. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing Document M100. 30th ed. Pennsylvania, USA; 2020: 58-66.
24. Stepanović S, Djukić V, Djordjević V, Djukić S. Influence of the incubation atmosphere on the production of biofilm by *Staphylococci*. Clin Microbiol Infect 2003; 9: 955-8.
25. Sudagidan M, Erdem İ, Çavuşoğlu C, Çiftçioğlu M. Investigation of the surface properties of Staphylococcus epidermidis strains isolated from biomaterials. Mikrobiyol Bul 2010; 44: 93-103.
26. Şahin R, Kaleli İ. Comparison of genotypic and phenotypic characteristics in biofilm production of *Staphylococcus aureus* isolates. Mikrobiyol Bul 2018; 52: 111-22.
27. Lee S, Choi KH, Yoon Y. Effect of NaCl on biofilm formation of the isolate from *Staphylococcus aureus* outbreak linked to ham. Korean J Food Sci Anim Resour 2014; 34: 257-61.
28. Knobloch JKM, Horstkotte MA, Rohde H, Mack D. Evaluation of different detection methods of biofilm formation in *Staphylococcus aureus*. Med Microbiol Immunol 2002; 191: 101-6.
29. Waldrop R, McLaren A, Calara F, McLemore R. Biofilm growth has a threshold response to glucose *in vitro*. Clin Orthop Relat Res 2014; 472: 3305-10.
30. Agarwal A, Jain A. Glucose & sodium chloride induced biofilm production & ica operon in clinical isolates of *Staphylococci*. Indian J Med Res 2013; 138: 262-6.
31. McCarthy H, Rudkin JK, Black NS, Gallagher L, O'Neill E, O'Gara JP. Methicillin resistance and the biofilm phenotype in *Staphylococcus aureus*. Front Cell Infect Microbiol 2015; 5: 1-9.
32. Singh A, Prakash P, Achra A, Singh G, Das A, Singh R. Standardization and classification of *in vitro* biofilm formation by clinical isolates of *Staphylococcus aureus*. J Glob Infect Dis 2017; 9: 93-101.
33. Vázquez-Sánchez D, Habimana O, Holck A. Impact of food-related environmental factors on the adherence and biofilm formation of natural *Staphylococcus aureus* isolates. Curr Microbiol 2013; 66: 110-21.
34. Xu H, Zou Y, Lee HY, Ahn J. Effect of NaCl on the biofilm formation by foodborne pathogens. J Food Sci 2010; 75: 580-5.
35. Lee J-S, Bae Y-M, Lee S-Y, Lee S-Y. Biofilm formation of *Staphylococcus aureus* on various surfaces and their resistance to chlorine sanitizer. J Food Sci 2015; 80: M2279-86.
36. Sudagidan M, Ozalp VC, Öztürk O, et al. Bacterial surface, biofilm and virulence properties of *Listeria monocytogenes* strains isolated from smoked salmon and fish contact surfaces. Food Biosci 2021; 101021.

Original Article

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Breast cancer patients with delayed radiotherapy during the pandemic process

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ABSTRACT

Aim: In this study; We wanted to examine the changes and delays in radiotherapy of all our breast cancer patients diagnosed with COVID-19

Material and Method: Radiotherapy delays of our breast cancer patients who had COVID-19 infection before and during radiotherapy between March 2020 and March 2021 were evaluated retrospectively.

Results: Sixteen of a total of 642 breast cancer patients, 472 operated and 165 metastatic, who underwent radiotherapy were diagnosed with COVID-19. All patients were women, ages were between 40 and 77 (mean 54.6). Five patients had a mastectomy, 8 had breast-conserving surgery, and 3 had breast cancer with bone metastases. Different radiotherapy schemes were applied at different treatment duration according to the clinical stage and disease status. The first breast cancer patient with COVID-19 infection was diagnosed on 27 June 2020. Our other patients were diagnosed from June to December (n=15) in 2020. Treatment of patients infected during radiotherapy was interrupted after a mean of 10 fractions (2-24 fractions) and treatment was started after a mean of 25 days (21-44 days). Post-operative patients who could not start treatment because they were SARS-CoV-2 PCR positive were able to start treatment after a mean of 22 days (14-30 days).

Conclusion: Radiotherapy could not be started at the recommended times for breast cancer patients infected with COVID-19 during the pandemic and the treatments had to be interrupted. Therefore, more care should be taken in the follow-up of these patients; should be considered as patients at risk for local recurrence and metastasis.

Keywords: Breast cancer, radiotherapy, COVID-19, pandemic

The study presented as an oral presentation in "Ankara Hematoloji ve Onkoloji Günleri 2021", Ankara, 4-6 February 2021.

INTRODUCTION

COVID-19 outbreak; caused unwanted delays in cancer diagnosis and treatment (1,2). Radiation therapy of breast cancer patients is also affected by up to 30% of the pandemic (3). It is shown that interruption of radiotherapy is related to lower local control (4). However, it takes some time to evaluate the scale and consequences of this pandemic. Various recommendations and guidelines have been prepared for each disease group. Health associations and authorities made different recommendations for general surgery, medical oncology, and radiation oncology clinics to treat breast cancer and started to be applied in a short time. The first COVID-19 case was diagnosed in Turkey on March 11, 2020. In our clinic, recommendations of national and international guidelines have been followed (5). Our aim in arranging the clinical approach was to evaluate and treat cancer patients' radiotherapy indications while preventing exposure to hospital-acquired COVID-19 infection. This study retrospectively examined the changes and delays in radiotherapy of all breast cancer patients diagnosed with COVID-19 after March 11, 2020.

MATERIAL AND METHOD

Our study was approved by the COVID-19 Scientific Research Evaluation Commission within the General Directorate of Health Services of our Ministry and Dr. Abdurrahman Yurtaslan Ankara Onkoloji Training and Research Hospital Ethics Commitee (Date: 2021, Decision No:2021-04/1139). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Breast cancer patients who had COVID-19 infection between March 2020 and March 2021 in the Radiation Oncology Clinic of -censored- hospital were identified from the records kept by the COVID-19 pandemic unit of our clinic. Both clinical and radiotherapy plan characteristics of each patient were recorded. Delays in patients infected before and during radiotherapy and treated/quarantined were evaluated retrospectively.

When calculating the delay time, the weekend is added to the total delay time for delays that include the weekend. For example, the 4 days from Thursday to Sunday were calculated as the delay period for the patient who could not enter treatment on Thursday and Friday. Otherwise, only the day without treatment was evaluated as the delay time.

All data were analyzed using SPSS (version 22) and Microsoft Excel programs. Descriptive statistics were used to determine the general characteristics of the groups. Frequency tables were used for ordinal variables, median and minimum/maximum values were used for non-parametric variables. Conformity of variables to normal distribution was analyzed using visual and analytical (Kolmogorov-Smirnov/Shapiro-Wilk) methods.

Table 1. Patients Characteristics (n=16)

Age	Median Age 55 (40-77)
Type of Surgery	
	Mastectomy (n=5)
	Breast-Conserving Surgery (n=8)
Staging (TNM)	
	Stage 0 (n=1)
	Stage I (n=2)
	Stage II (n=6)
	Stage III (n=4)
	Stage IV (n=3)
Histopathology	
	Invasive breast carcinoma (n=9)
	Invasive lobular carcinoma (n=3)
	Medullary carcinoma (n=3)
	Insitu Ductal carcinoma (n=1)
Chemotherapy/Hormonotherapy	
	Postoperative chemotherapy (n=7)
	Neoadjuvant chemotherapy (n=4)
	Hormonotherapy (n=5)
Radiotherapy Dose/Fractionization/Duration	
	50 Gy/25 fx (5 Wk) (n=5)
	50 Gy/25 fx (5 Wk) + 10-16 Gy/5-8 fx (2 Wk) (n=6)
	48 Gy/20 fx (4 Wk) + 12.5 Gy/5 fx (1 Wk) (n=1)
	48Gy/18 fx (4 Wk) + 16 Gy/6 fx (1 Wk) (n=1)
	20 Gy/5 fx (1 Wk) (n=3)

*fx: fraction, Wk: week, n: patient number

RESULTS

Sixteen (2.5%) of 642 breast cancer patients, including 472 operated breast cancer and 165 metastatic breast cancer, were diagnosed with COVID-19 on the specified dates. Of the patients with a mean age of 54.6 (40-77), 5 were mastectomized, 8 had breast-conserving surgery, and 3 had bone metastatic breast cancer. One patient was Stage 0, 2 patients were Stage I, 4 patients were Stage IIA, 2 patients were Stage IIB, 1 patient was Stage IIIA, 2 patients were Stage IIIB, 1 patient was Stage IIIC, and 3 patients were Stage IV. Nine patients had invasive breast carcinoma, 3 had invasive lobular carcinoma, 3 had medullary carcinoma, and 1 had ductal carcinoma in situ histopathology. Thirteen patients were hormone positive, 4 patients were HER2 positive. Only hormonotherapy was started in 5 patients. Postoperative chemotherapy was applied to 7 patients, and neoadjuvant chemotherapy was applied to 4 patients. In mastectomized patients (n=5); to chest wall +/- lymph nodes 50 Gy/25 fractions in 5 weeks, in breast-conserving surgery patients; In 6 patients, the breast +/- lymph nodes 50 Gy/25 fractions in 5 weeks and the tumor bed 10-16 Gy/5-7 fractions boost, 1 patient 48 Gy/20 fractions to the breast and 12.5 Gy to the tumor bed/5 fractions boost and 1 patient 48 Gy/18 fractions and 16 Gy/6 fraction boost adjuvant radiotherapy was planned to the tumor bed. Palliative radiotherapy (RT) was planned 20 Gy/5 fractions in 1 week for metastatic patients (**Table 1**).

The first patient with COVID-19 infection was a breast cancer patient with fever and sore throat on June 27, 2020. Our other patients were found in June (n=1), August (n=2), September (n=1), October (n=3), November (n=5) and December (n=4) 2020. 8 of the patients were diagnosed with COVID-19 during RT and 8 before radiotherapy. The treatment of patients infected during radiotherapy was prolonged after the 10th fraction, as the median (2-24 fractions) and a mean of 25 days (21-44 days). Patients who were scheduled for postoperative radiotherapy but infected before radiotherapy were able to start treatment after a mean of 22 days (14-30 days) (**Table 2**). Three patients with bone metastases were diagnosed before RT and started treatment after a mean of 20 days (14-30 days). The treatment was discontinued since 1 patient infected in the 18th fraction of RT (25 fractions were planned) and 1 infected in the 27th fraction (33 fractions were planned) did not want the remaining treatments. It was determined that a patient who was infected in the 5th fraction of RT completed his remaining treatment in another center after about 4 months. Other patients (n=5) completed their treatment as planned. The mean follow-up period of the patients was 11.6 months (4-17 months). Three patients with bone metastases were alive with metastatic disease in a mean follow-up of 8 months (4-13 months), and non-metastatic patients were alive without disease with a mean follow-up of 12.3 months (6-17 months).

Table 2. Parameters of Delays in COVID-19 Infection (n=16)
SARS Cov-2-PCR + Timing
During RT (n=8)
Before RT (n=8)
SARS Cov-2-PCR + time interval
June 2020 (n=1)
August 2020 (n=2)
September 2020 (n=1)
October 2020 (n=3)
November 2020 (n=5)
December 2020 (n=4)
SARS Cov-2-PCR + delay time during radiotherapy
25 days (21-44 days) Median after 10th fx (2-24 fx)
SARS Cov-2-PCR + delay time before radiotherapy
22 days (14-30 days) post-op RT
20 days(14-30 days) palliative RT
*fx: fraction n=patient number

DISCUSSION

The diagnosis of COVID-19 with polymerase chain reaction (PCR) was made in November and December 2020 in routine examinations, one of which was symptomatic during radiotherapy and eight asymptomatic patients before radiotherapy. Our hospital was a clean hospital which means SARS Cov-2-PCR positive patients were referred to another pandemic hospital and clean hospital precautions were taken (6). As in other radiation oncology clinics in Turkey, the treatment of patients was not interrupted or clinically delayed during any period of the pandemic. Therefore, more often seen as the cause of this date, the number of cases occurring in Turkey increased, and before radiotherapy, the decision to have a negative result of the SARS Cov-2-PCR test of the patients was applied (7). Performing a SARS Cov-2-PCR test before treatment for every radiotherapy patient is controversial. Some publications suggest that cancer patients and their staff need SARS Cov-2-PCR testing twice a week (8). Our clinical approach is to perform a SARS Cov-2-PCR test the day before starting treatment and to repeat the test if it is symptomatic for COVID-19 during radiotherapy and similar to other clinics that practice it caused a delay of up to 1 day per patient (9). The rationale for routine SARS Cov-2-PCR testing before radiotherapy is that cancer patients are more susceptible to infections, more than one cancer patient is present in the same room and device at the same time or one after the other, and the risk of transmission of infection to the hospital personnel who are in constant contact with the patient is reduced.

It is estimated that failure to complete radiotherapy within the specified time due to the COVID-19 pandemic will reduce local control (10,11). In our study, patients with COVID caused a break in radiotherapy for at least 2 weeks of breast cancer patients. Bese et al. (12) study shows that the 5-year local control was reduced by 5% if the radiotherapy interval was longer than 1 week. It means two weeks of COVID-19 quarantine duration is affected radiotherapy efficacy more than 5%. In this case, an additional dose may be considered at the end of the treatment.

Radiotherapy increases the risk of infection of patients and hospital staff in COVID-19 because it is a form of treatment that requires an extended visit to the hospital (13). During this period, suggestions of hypofractionated radiotherapy came to the fore. Long-term results of randomized controlled studies such as START and FAST, which were conducted to investigate the side effects and local control of hypofractionated radiotherapy, especially in early-stage breast cancer, showed that radiotherapy for a shorter time is possible without reducing local control rates (14-17). The use of hypofractionated treatment regimens has increased in our clinic in patients with clinical suitability. Hypofractionated radiotherapy studies in locally advanced breast cancer are still ongoing and are not used in our clinic despite the COVID-19 pandemic. Treatments with fractions of 5 or less are routinely preferred for palliation of metastases (18).

COVID-19 was detected in 2.5% of the patients we applied radiotherapy during this period. This rate is shallow, and the measures we have taken are effective. The pandemic risk assessment determined that the patients had external contact, and there was no intra-clinical transmission. Radiotherapy should be started 1-2 months after surgery in patients with early-stage breast cancer who are not given chemotherapy and patients with locally advanced breast cancer who are operated on after neoadjuvant chemotherapy. In breast cancer patients in whom chemotherapy is started postoperatively, radiotherapy should be started within 7 months after surgery (19,20). One of our patients who received SARS Cov-2-PCR + before radiotherapy and received post-mastectomized chemotherapy 8 months later, and 2 patients who were operated on after neoadjuvant chemotherapy started radiotherapy 2 months later. Treatment continued after a mean of 3 weeks (21, 21, 22, 24, and 44 days) due to the prolonged quarantine period and recovery of those infected during radiotherapy. No dose change was made in patients for whom treatment was interrupted. All patients were treated at the planned doses.

CONCLUSION

Radiotherapy could not be started at the recommended times for patients with breast cancer infected with COVID-19 during the pandemic period, and the treatments had to be interrupted. Therefore, more care should be taken in the follow-up of these patients; they should be considered risky patients in terms of local recurrence and metastasis.

ETHICAL DECLARATIONS

Ethics Committee Approval: Our study was approved by the COVID-19 Scientific Research Evaluation Commission within the General Directorate of Health Services of our Ministry and Dr. Abdurrahman Yurtaslan Ankara Onkoloji Training and Research Hospital Ethics Commitee (Date: 2021, Decision No:2021-04/1139).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Richards M, Anderson M, Carter P, Ebert BL, Mossialos E. The impact of the COVID-19 pandemic on cancer care. Nat Cancer 2020: 1-3.
2. Lee S, Heo J. COVID-19 pandemic: a new cause of unplanned interruption of radiotherapy in breast cancer patients. Med Oncol 2021; 39: 5.
3. Papautsky EL, Hamlish T. Patient-reported treatment delays in breast cancer care during the COVID-19 pandemic. Breast Cancer Res Treat 2020; 184: 249-54.
4. Bese NS, Hendry J, Jeremic B. Effects of prolongation of overall treatment time due to unplanned interruptions during radiotherapy of different tumor sites and practical methods for compensation. Int J Radiat Oncol Biol Phys 2007; 68: 654-61.
5. Coles CE, Aristei C, Bliss J, et al. International Guidelines on Radiation Therapy for Breast Cancer During the COVID-19 Pandemic. Clin Oncol (R Coll Radiol) 2020; 32: 279-81.
6. Göksel F, Güzle Adaş Y. Management of a radiation oncology clinic in a clean oncology hospital during the COVID-19 outbreak. J Surg Med 2020; 4: 925-9.
7. Anacak Y, Onal C, Ozyigit G, et al. Changes in radiotherapy practice during COVID-19 outbreak in Turkey: A report from the Turkish Society for Radiation Oncology. Radiother Oncol 2020; 150: 43-5.
8. Marschner S, Corradini S, Rauch J, et al. SARS-CoV-2 prevalence in an asymptomatic cancer cohort-results and consequences for clinical routine. Radiat Oncol 2020; 15: 165.
9. Ning MS, McAleer MF, Jeter MD, et al. Mitigating the impact of COVID-19 on oncology: Clinical and operational lessons from a prospective radiation oncology cohort tested for COVID-19. Radiother Oncol 2020; 148: 252-7.
10. Benk V, Joseph L, Fortin P, et al. Effect of delay in initiating radiotherapy for patients with early stage breast cancer. Clin Oncol (R Coll Radiol) 2004; 16: 6-11.
11. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJJJoco. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review 2003; 21: 555-63.
12. Bese NS, Sut PA, Ober A. The effect of treatment interruptions in the postoperative irradiation of breast cancer. Oncology 2005; 69: 214-23.
13. Gemici C, Yaprak G. Covid-19 outbreak in a major radiation oncology department; which lessons should be taken? Radiother Oncol 2020; 149: 107-8.
14. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013; 14: 1086-94.
15. Brunt AM, Haviland JS, Sydenham M, et al. Ten-year results of FAST: a randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. J Clin Oncol 2020; 38: 3261-72.
16. Brunt AM, Wheatley D, Yarnold J, et al. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. Radiother Oncol 2016; 120: 114-8.
17. de Azambuja E, Trapani D, Loibl S, et al. ESMO Management and treatment adapted recommendations in the COVID-19 era: Breast Cancer. ESMO Open 2020; 5.
18. Lutz ST, Chow EL, Hartsell WF, Konski AA. A review of hypofractionated palliative radiotherapy. Cancer 2007; 109: 1462-70.
19. Tsoutsou PG, Koukourakis MI, Azria D, Belkacemi Y. Optimal timing for adjuvant radiation therapy in breast cancer: a comprehensive review and perspectives. Crit Rev Oncol Hematol 2009; 71: 102-16.
20. Abdel-Rahman O. Impact of timeliness of adjuvant chemotherapy and radiotherapy on the outcomes of breast cancer; a pooled analysis of three clinical trials. Breast 2018; 38: 175-80.

Original Article

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The role of serum lipoprotein levels in predicting independent short-term mortality in COVID-19 patients

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ABSTRACT

Background: Plasma lipoprotein levels typically change as a result of systemic inflammation in coronavirus disease (COVID-19). These changes have been reported to be related to the severity and prognosis of the disease. The aim of this study was to evaluate the relationship between serum high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, and cholesterol levels andindependent short-term (28-day) mortality in COVID-19 patients with critical disease.

Material and Method: The retrospective study included patients that had a positive result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on real-time reverse transcriptase polymerase chain reaction (RT-PCR) and were followed up in ICU due to pneumonia and acute hypoxemic respiratory failure between March 2020 and January 2021.

Results: The 123 patients comprised 69 (56.1%) women and 54 (43.9%) men with a mean age of 65.41±13.93 years. Mean hospital and ICU stays were 16.07±9.84 and 8.54±8.24 days, respectively. Short-term (28-day) mortality occurred in 33 (26.8%) patients. Mean serum LDL, HDL, triglyceride, and cholesterol levels were 100.61±36.32, 41.57±10.74, 136.67±85.33, and 164.4±40.73 mg/dL, respectively. Short-term (28-day) mortality established a significant relationship with LDL and HDL levels, whereas no significant relationship was established with cholesterol and triglyceride levels (p=0.001, p=0.001, p=0.332, and p=0.222, respectively). The durations of hospital and ICU stay established a significant relationship with LDL levels (p=0.033 and p=0.002, respectively).

Conclusion: Based on our results, we suggest that monitoring HDL and LDL levels with serial measurements in patients with critical and severe COVID-19 pneumonia may be useful for predicting the prognosis.

Keywords: COVID-19, high-density lipoprotein, low-density lipoprotein,cholesterol, triglyceride, mortality

INTRODUCTION

Lipoproteins are classified into five groups based on their density, including chylomicrons, very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). In recent studies, changes in lipid metabolism have been found in cases of infection (1). It has also been reported that HDL play a role in the transport of endotoxins, lipopolysaccharides, and lipotoxins from the liver and that HDL have anti-inflammatory, antioxidant, and immunomodulatory effects (2,3). By contrast, LDL has been shown to facilitate bacterial toxin clearance in sepsis and to play a role in the body's defence against bacterial and viral pathogens. Studies have found that both the HDL and LDL levels decrease in response to gram-negative and positive acute infection and inflammation (3). Additionally, a significant relationship was found between clinical worsening and HDL level in a study conducted on community-acquired pneumonia and a correlation between HDL and acute phase reactants was shown in some other studies. Besides, there are studies aimed at evaluating the prognostic value ofHDL in cases of infection (4).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was named Coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO), is a viral pneumonia causing acute respiratory distress syndrome (ARDS) and is mostly diagnosed by nucleic acid amplification tests (NAAT) such as real-time reverse transcriptase polymerase chain reaction (RT-PCR). Approximately 81% of infected symptomatic patients develop mild infection while 14% of them develop severe disease and 5% of them develop critical disease (5). In addition to these conditions, cytokine storm caused by COVID-19, homeostaticchanges,

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severe vasculitis, changes in plasma lipoprotein levels caused by complications, and changes in endothelial levels have been reported in COVID-19 cases (5,6). Sorokin et al. (6) reported that the changes in HDL levels are due to their anti-inflammatory and antioxidant effects in COVID-19 patients. Wang et al. (7) evaluated 228 COVID-19 patients retrospectively and found that the severity of the disease correlated with the HDL level. Nevertheless, to our knowledge, the relationship between mortality and plasma lipoproteins and the cut-off values for the concentration of these lipoproteins in COVID-19 patients remain unclear. In this study, we aimed to evaluate the relationship between serum HDL, LDL, triglyceride, and cholesterol levels and independentshort-term (28-day) mortality in COVID-19 patients with critical disease followed up in intensive care unit (ICU).

MATERIAL AND METHOD

The retrospective study included patients that had a positive SARS-CoV-2 RT-PCR result and were followed up in ICU due to pneumonia and acute hypoxemic respiratory failure between March 2020 and January 2021. Laboratory results, discharge reports, and short-term (28-day) mortality rates were retrieved from the electronic database and intensive care observation forms after obtaining an approval from the scientific research and ethics committee of the Keçiören Training and Research hospital of Health General Directorate of Health Services (Date: 01/11/2021, Decision No: 2012-KAEK-15/2444). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Inclusion criteria were as follows: HDL, LDL, triglyceride, and cholesterol levels measured in the first hour of ICU admission, age over 18 years, a positive SARS-CoV-2 RT-PCR result, pneumonia and hypoxemic respiratory failure due to COVID-19 (hypoxia or pulmonary involvement in excess of 50% on imaging, tachypnea [respiratory rate>30/min], partial arterial oxygen pressure [PaO_2]/ fraction of inspiration O_2 (FiO_2) ≤300 mmHg) (8,9). Patients with an active infection except for COVID-19, active malignancy, connective tissue disease and vasculitis, use of drugs that could affect HDL, LDL, triglyceride, and cholesterol levels, patients aged under 18 years, and pregnant women were excluded from the study (**Figure 1**). HDL, LDL, triglyceride, and cholesterol concentrations were assessed using a Beckman AU5800 biochemical detector (Beckman Coulter, Inc., Brea, CA, USA) with the turbidimetric method. The reference range for HDL, LDL, triglyceride, and cholesterol concentrations was 40-60, 0-130, 50-200, and 50-200 mg/dL, respectively.

Statistical Analysis

Data were analyzed using SPSS for Windows version 21.0 (Statistical Package for the Social Sciences). Continuous variables were expressed as mean±standard deviation (SD) and categorical variables were expressed as percentages (%). Pearson Chi-square and Fisher's exact test statistics were used compared categorical variables. Normal distribution of data was tested using Shapiro Wilk tests. In groups with normal distribution, binary comparisons were performed using Student's t-tests. In groups with nonnormal distribution, binary comparisons were performed using Mann-Whitney U test.A p value of <0.05 was considered significant. Multiple logistic regression analysis was used with all of the prespecified factors with a p <0.25 in the univariate analysis. Statistical significance in the multivariate analysis was accepted at p <0.05.

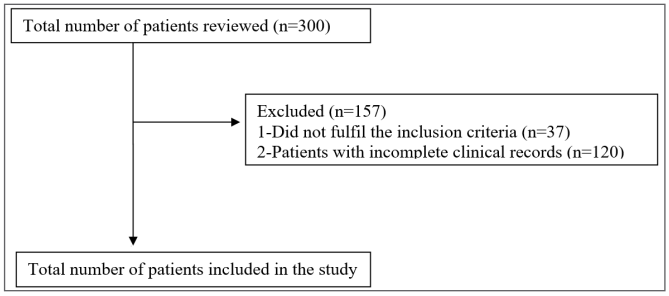

Figure 1. Flow-chart of the study

RESULTS

The 123 patients comprised 69 (56.1%) women and 54 (43.9%) men with a mean age of 65.61±14.05 years. Mean hospital and ICU stays were 16.03±9.81 and 9.28±12.48 days, respectively. Short-term (28-day) mortality occurred in 33 (26.8%) patients. All the patients had hypoxemic respiratory failure and 26 (21.13%) of them were receivinginvasive mechanical ventilation (IMV), 18 (14.64%) were receiving non-invasive mechanical ventilation (NIMV), 56 (45.53%) were receiving high-flow nasal oxygen (HFNO), and 72 (58.54%) were receiving supplementary oxygen support with a reservoir oxygen mask. **Table 1** presents the demographic, clinical characteristics and respiratory support therapies of the patients.The rate of hospital stay (days) ,age, SOFA and APACHE II scores were significantly higher in mortality patients compared to non-mortality patients (p<0.05). ICU stay (days) and gender were found to be insignificant factors affecting 28-day mortality (p=0.394 and p=0.496, respectively).

Mean serum LDL, HDL, triglyceride, and cholesterol levels were 99.298±38.08, 39.6±12.23, 136.59±89.54, and 164.69±48.72 mg/dL, respectively. Short-term (28-day) mortality established a significant relationship with LDL, HDL, cholesterol and triglyceride levels (p=0.001, p=0.008, p=0.016, and p=0.012, respectively) (**Table 2**).

Table 1. Demographic, clinical characteristics

Variables	Mortality Ort.± SD-Median (Min-Max)			P value
	Alln=123	No=90	Yes=33	
Age (year)	65.41±13.935	62.79±14.080	72.58±10.799	<0.001
Gender (Male /Female)	69/54	51/39	18/15	0.496
SOFA	5 [2-12]	4[2-12]	8 [2-12]	<0.001
APACHE II	18 [5-38]	15 [5-31]	24 [10-38]	<0.001
Comorbidity	88 (71.5%)	64 (71.1%)	24 (72.7%)	0.860
Cardiovascular diseases (n %)	27 (22.0%)	18 (20.0%)	9 (27.3%)	0.388
Hypertension (n %)	52 (42.3%)	38 (42.2%)	14 (42.4%)	0.984
Diabetes Mellitus (n %)	33 (26.8%)	27 (30.0%)	6 (18.2%)	0.190
Asthma (n %)	5 (4.1%)	4 (4.4%)	1 (3.0%)	0.725
Congestive heart failure (n %)	8 (6.5%)	5 (5.6%)	3 (9.1%)	0.481
Malignancy (n %)	7 (5.7%)	3 (3.3%)	4 (12.1%)	0.062
Neurological Disease (n %)	11 (8.9%)	8 (8.9%)	3 (9.1%)	0.972
IMV	26 (21.1%)	8 (8.9%)	18 (54.5%)	<0.001
NIMV	18 (14.6%)	9 (10%)	9 (27.3%)	0.016
HFNO	56 (45.5%)	41 (33.3%)	15 (45.5%)	0.969
Reservoir Oxygen Mask	72 (58.5%)	59 (65.5%)	13 (39.4%)	0.012
Hospital stay (days)	13 [2-46]	15[5-46]	11 [2-30]	0.009
ICU stay (days)	5 [1-46]	4[1-36]	2 [2-46]	0.394
LDL (mg/dL)	95 [16-210.4]	103.8 [16.8-210.4]	80 [16-141]	<0.001
HDL (mg/dL)	39.06±11.808	40.74±12.292	34.45±9.028	0.008
Cholesterol (mg/dL)	157 [56-341]	162 [56-341]	144 [56-246]	0.012
Triglyceride (mg/dL)	114 [35-585]	107.5 [35-517]	124 [81-585]	0.016

APACHE II: Acute physiology and chronic health evaluation II, SOFA: Sequential organ failure assessment, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CAD: Coronary artery disease, CHF: Congestive heart failure, HT: Hypertension, CKD: Chronic kidney disease, SD: Standard deviation, IMV: Invasive mechanical ventilation, NIMV: Noninvasive mechanical ventilation, HFNO: High-flow nasal oxygen

Table 2. Logistic regression analysis

	Univariate analyze					Multivariate analyze (backward wald 5. step)				
	Wald	p	OR	95% CI for EXP(B)		Wald	p	OR	95% CI for EXP(B)	
				Lower	Upper				Lower	Upper
Age	10.145	0.001	.061	1.023	1.100	4.049	0.044	0.892	0.799	0.997
APACHE II	18.216	<0.001	1.167	1.087	1.253	9.253	0.002	1.927	1.263	2.940
SOFA	22.101	<0.001	1.544	1.288	1.851					
IMV	24.527	<0.001	12.450	4.589	33.775					
NIMV	5.468	0.019	3.417	1.220	9.569					
Reservoir Oxygen Mask	6.207	0.013	0.353	0.155	0.801					
LOS hospital (days)	7.829	0.005	0.922	0.871	0.976	10.556	0.001	0.714	0.583	0.875
LDL (mg/dL)	11.846	0.001	0.976	0.963	0.990	8.443	0.004	0.923	0.875	0.974
HDL (mg/dL)	2.356	0.125	0.973	0.939	1.008					
Cholesterol (mg/dL)	6.093	0.014	0.987	0.978	0.997					
Triglyceride (mg/dL)	2.913	0.088	1.004	0.999	1.009	4.716	0.030	1.015	1.001	1.028

OR: odds ratio. Multinominal logistic regression (Hosmer ve Lemeshow p>0.05), APACHE II: Acute physiology and chronic health evaluation II, SOFA: Sequential organ failure assessment, IMV: Invasive mechanical ventilation, NIMV: Noninvasive mechanical ventilation

DISCUSSION

The results indicated that serum HDL and LDL levels were significantly associated with 28-day mortality in COVID-19 patients followed up in ICU due to pneumonia, whereas no significant relationship was found between 28-day mortality and triglyceride and cholesterol levels. Moreover, although a significant relationship was found between the durations of hospital and ICU stay and LDL levels, no significant relationship was established with cholesterol, triglyceride, and HDL levels.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a high infection and has different manifestations in every infected individual. Although it typically leads to a mild-to-moderate infection in most cases and recovers within seven days, it can result in severe pneumonia and ARDS in some cases (8). Althoughthe hospital and ICU admission rates differ across studies, approximately 20% of the patients are hospitalized and 25% of them are admitted to ICU. Global mortality rates rangebetween 4.8-11% depending on the elderly population and developing countries. However,

the mortality rate in ICU patients is over 60% (8,9).

In our study, we evaluated COVID-19 pneumonia cases with severe and critical diseasewhorequired ICU care due to hypoxemic respiratory failure. Ourindependent short-term (28-day) mortality rate was found to be 26.8%,whichwas lowerthan those reported in the literature (8,9). This lower rate could be attributed to the longerdurations of hospital and ICU stay in our patients and to our IMV rate (21.13%).In our study age, hospital stay(days) , APACHE II and SOFA scores were found to be significant predictors of independent short-term mortality. These findings of our study were consistent with those reported in the literature (5,7,8). ICU stay (days) and gender were found to be insignifcant predictors of mortality. Therefor our results were thought to be incompatible with the literature (5,7,8).

Lipids and metabolites are major molecules in plasma and their concentrationsmay changein case of infection in the presence of pathophysiological and critical disease (9). Lipids have been shown to play a pathophysiological role in viral infections, fusion of virus membrane with host cell membrane, viral replication, and viral endocytosis and exocytosis. Therefore, lipoproteins are considered to have vital functions in the life cycle of viruses (10,11). HDL have been shown to have anti-inflammatory, antioxidant, immunomodulatory, and antithrombotic effects in virus-related infections (2,4,6). The natural and adaptive immune response against the SARS-CoV-2 plays a role.A cytokine storm termed 'secondary hemophagocytic, lymphohistiocytosis' occurs as a result of exaggerated production of proinflammatory cytokines andthe induction of the activation of proinflammatory macrophages and granulocytes (9). In COVID-19 patients, this cytokine storm leads to immune-mediated inflammatory dyslipoproteinemia, resulting in low HDL and LDL levels and increased triglyceride levels (6). Sorokin et al. (6) showed that the HDL levels decreased in COVID-19 patients due to the anti-inflammatory and antioxidant effectsof HDL and as a result of pulmonary inflammation. The authors also showed that the severity of the disease, including hypoxic pneumonia, reached its peak on the third day of disease onset, the changes in lipid levels were parallel with increases in C-reactive protein (CRP), and these changes were accompanied by lymphocytopeniain COVID-19 patients (6). Cao et al. (11) reported that LDL and total cholesterol levels decreased in COVID-19 patients.In our study, the relationship between plasma lipoproteins and short-term (28-day) mortality was evaluated in COVID-19 pneumonia patients followed up in ICU. Due to the retrospective nature of our study, only the HDL, LDL, cholesterol, and triglyceride levels measured during ICU admission were evaluated and thus, as in other studies, serial measurements could not be performed. Moreover, the effect of disease severity on the changes in serum lipid levels could not be evaluated.

To our knowledge, there are few studies on the relationship between serum lipoproteins and disease severity and mortality in COVID-19. In a prospective study, Tanakeet al. (12) evaluated 48 COVID-19 patients followed up in ICU and reported that the HDL and LDL levels were relatively lower in severe COVID-19 patients.In a retrospective study, Qin et al. (13) evaluated 248 COVID-19 patients and showed that the triglyceride and LDL levels were negatively correlated with the duration of hospitalization. In our study, in a similar way to Tanaka et al. (12), a significant relationship was found between the HDL and LDL levels and 28-day mortality. However, no significant relationship was found between the triglyceride and cholesterol levels and short-term mortality, which could be attributed to the effect of changes in liver functions caused by hemodilution, capillary leakage syndrome, and the medical treatments we used in the treatment of COVID-19 on the triglyceride and cholesterol biosynthesis and their levels (10, 11, and 12). In our study, only LDL was found to be significantlyassociated with the durations of hospital and ICU stay. However, a clear evaluation on this issue could not be made due to the limited number of data and studies on the relationship between plasma lipoproteins andthe durations of hospital and ICU stay in COVID-19 patients. Therefore, we suggest that further multi-center, prospective, randomized controlled studies with largerpatient series are needed.

Our study was limited since it was designed as a retrospective single-center study. Moreover, serum HDL, LDL, cholesterol, and triglyceride levels were not measured prior to hospital admission and no serial measurements were performed, and no comparison could be performed between the measurements performed on admission and inflammatory markers.

CONCLUSION

Based on our results, we has been considered that monitoring HDL and LDL levels with serial measurements in patients with critical and severe COVID-19 pneumonia may be useful for predicting the prognosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval from the scientific research and ethics committee of the Keçiören Training and Research hospital of Health General Directorate of Health Services (Date: 01/11/2021, Decision No: 2012-KAEK-15/2444).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Laurila A, Bloigu A, Nayha S, et al. Chronic Chlamydia pneumoniae infection is associated with a serum lipid profile known risk factor for atherosclerosis. Arterioscler Tromb Vasc Biol 1997; 17: 2910-3.
2. Guirgis FW, Donnelly JP, Dodani S, et al. Cholesterol levels and long-term rates of community-acquired sepsis. Crit Care 2016; 20: 408.
3. Kaysen GA, Ye X, Raimann JG, et al. .Monitoring dialysis outcomes (MONDO) Initiative Lipid levels are inversely associated with infectious and all-cause mortality: international MONDO study results. J Lipid Res 2018; 59: 1519-28.
4. Saballs M, Parra S, Sahun P, et al. HDL-c levels predict the presence of plevral effusion and the clinical outcome of community-acquired pneumonia. Springer plus 2016; 5: 1491.
5. Wu Z, McGoogan JM. Characteristics of and ımportantlessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA 2020; 323: 1239-42.
6. Sorokin AV, Karathanasis SK, Yang ZH, et al. COVID-19 -Associated dyslipidemia: Implications for mechanism of impaired resolution and novel therapeutic approaches. The FASEB Journal 2020; 34: 9843-53.
7. Wang G, Zhang Q, Zhao X, et al. Low high-density lipoprotein level is correlated with the severity of COVID-19 patients: an observational study. Lipids Health Dis 2020; 19: 204.
8. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020; 46: 846-48.
9. Wu D, Shu T, Yang X, et al. Plasma metabolomic and lipidomic alterations associated with COVID-19. Natl Sci Rev2020; nwaa086.
10. Abu-Farha M, Thanarj TA, Qaddoumi MG, et al. The role of lipid metabolism in COVID-19 virus infection and as a drug target. Int J Mol Sci2020; 21: 3544.
11. Cao X, Yin R, Albrecht H, Fan D, Tan W. Cholesterol: a new game player accelerating vasculopathy caused by SARS-CoV-2?.Am J Physiol Endocrinol Metab2020; 319: E197-2.
12. Tanaka S, De Tymowski C, Assadi M, et al. Lipoprotein concentrations over time in the intensive care unit COVID-19 patients: Results from the ApoCOVID study. PLoS One 2020: 15: e0239573.
13. Qin C, Minghan H, Ziwen Z, Yukun L. Alteration of lipid profile and value of lipids in the prediction of the length of hospital stay in COVID-19 pneumonia patients. Food Sci Nutr 2020; 8: 6144-52.

Original Article

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Evaluation of anesthesia methods in percutaneous kyphoplasty procedures in vertebral compression fractures

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ABSTRACT

Aim: Kyphoplasty is a much less invasive technique than conventional methods to strengthen vertebral body fractures. This study aimed to demonstrate a safe and effective anesthesia method by retrospectively investigating the clinical conditions, perioperative pain experiences, and anesthesia methods of patients who underwent kyphoplasty in our institution.

Material and Method: A total of 76 patients who had kyphoplasty operations performed under elective conditions between January 2018 and March 2021 have been enrolled in this research. Demographic data of patients, injury mechanisms, anesthesia method, duration of surgery, severe perioperative complications (heart attack, lung disease, delirium, etc.), duration of postoperative stay in intensive care, pre and postoperative pain degrees with visual analogue scale (VAS) has been interpreted.

Results: There was a statistically significant difference between the groups in terms of duration of operation, duration of anesthesia, postoperative discharge time, postoperative 24-hour VAS score, intraoperative hemodynamic status, and presence in the post-anesthesia care unit (PACU) ($p<0.05$). The operation time, anesthesia time, postoperative discharge time, and the postoperative 24-hour VAS score of individuals with general anesthesia were higher than those under local anesthesia and sedation. Regarding intraoperative hemodynamic status, 37.5% of those under general anesthesia were stable, while 73.5% of individuals under local anesthesia and sedation were stable. While 37.5% of those under general anesthesia were in the post-anesthesia care unit, this rate was 7.4% in those under local anesthesia and sedation.

Conclusion: The most appropriate anesthesia type should be determined according to the patient's individual health status. Each method has its advantages, such as no need for a stable position in general anesthesia and availability of motor functioning evaluation and verbal communication in local anesthesia; hence local anesthesia and sedoanalgesia were together. This seems to be more advantageous with the appropriate sedation.

Keywords: Kyphoplasty, vertebral fractures, local anesthesia, general anesthesia, PACU

INTRODUCTION

It is known that vertebral compression fractures (VCF) can cause severe and long-lasting pain, nerve damage, depression, and even permanent disability without appropriate treatment (1). These patients have long-lasting pain, irregularity in bowel functions, disruption in sleep patterns, and lung problems that cause severe declines in their quality of life (2).

Kyphoplasty is a much less invasive technique than conventional methods to strengthen the vertebral body. Polymethylmethacrylate (PMMA) (popularly called bone cement) is given to the vertebral corpus by the external percutaneous route. With these methods, it has been possible to treat such fractures without open surgery (3). Infection, bleeding, and limitation of movement secondary to long-term surgery are almost non-existent with these methods. Thromboembolism, lung problems, bedsores, long-term drug use, and corset use are avoided due to prolonged lying down (4).

Patients undergoing kyphoplasty procedures usually have significant comorbidities. Therefore, it is difficult to determine the intraoperative anesthesia method. Both local anesthesia and general anesthesia are commonly used. However, it remains unclear which anesthetic method is better for kyphoplasty (5). generally surgeons recognize the advantage of local anesthesia to prevent fragile elderly patients with multiple organ dysfunction (6).

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Surgeons usually assess whether the nerve injury occurred while the patient is awake. Moreover, patients who receive local anesthesia do not need postoperative care and can get out of bed earlier, conducive to postoperative rehabilitation (7-8). On the other hand, there are certain downsides of local anesthesia, such as the prolongation of fluoroscopy time resulting in extended operation or the termination of the surgery due to posture-related discomfort. Moreover, abundant local anesthetic administration may induce a toxic reaction of bone cement and abrupt fluctuation of vital signs (9).

Local anesthesia are an option for pain relief during kyphoplasty. On the other hand, it may be insufficient in pain control. The need for sedation and analgesics may cause complications such as respiratory depression, hypotension, and delirium in the patient in the prone position. Although it is recommended to perform kyphoplasty under general anesthesia due to severe pain, it has been shown that general anesthesia brings life-threatening problems, especially in the elderly and comorbid disease group (10).

Spinal anesthesia and epidural anesthesia are alternative methods, especially in these patients with comorbid diseases. However, the baricity of the chosen local anesthetic and its inadequacy in pain control limit its application. Currently, it remains unclear which anesthesia is ideal for PKP. The anesthesia method may vary according to the clinical findings of the patient and the knowledge and experience of the anesthetist (9,10).

Study Hypothesis

As in every surgery, the main purpose stands for achieving the best possible clinical effect without increasing the incidence of complications. At this stage, a multidisciplinary approach is crucial with a team of surgeons and anesthesiologists for better outcomes in pain improvement rate, vertebral height recovery, and kyphosis correction (11).

This study aimed to demonstrate a safe and effective anesthesia method by retrospectively investigating the clinical conditions, perioperative pain experiences, and anesthesia methods of patients who underwent kyphoplasty in our institution.

MATERIAL AND METHOD

A total of 76 patients who had a kyphoplasty operation performed under elective conditions between January 2018 and March 2021 have been enrolled in this research. The study has a retrospective nature. The study was carried out with the permission of Bursa Training and Research Hospital, Non-interventional Clinical Researches Ethics Committee (Date: 28.04.2021, Decision No: 2011-KAEK-25 2021/04-17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Demographic data of patients, injury mechanisms, anesthesia method, duration of surgery, severe perioperative complications (heart attack, lung disease, delirium, etc.), duration of postoperative stay in intensive care, pre and postoperative pain degrees with visual analogue scale (VAS) has been interpreted.

Inclusion Criteria

Patients classified as ASA Group 1-3, preoperative VAS >5, and subjects with single-level vertebral compression fractures were included in the analysis.

Exclusion Criteria

Patients classified as ASA Group 4-5 (high risk of mortality and morbidity), subjects free of pain, individuals with symptomatic neurological damage, fracture due to secondary osteoporosis, and metastatic cancer have been excluded from the analysis.

Anesthesia & Surgical Procedure

In all kyphoplasties, the surgeon was the same but the anesthesiologists were different. Group G received general anesthesia with endotracheal intubation. General anesthesia was administered via 2 mg/kg propofol, 2 mcg/kg fentanyl, 0.6-1.2 mg/kg rocuronium during the operation. In addition, maintenance was provided with 2-3% sevoflurane. Group L has received 10 ml of bupivacaine at a concentration of 0.25% for local infiltration anesthesia. Double or triple combinations of sedative and hypnotic (midazolam, propofol, pentothal) and analgesic (fentanyl, ketamine) drugs were used for sedoanalgesia.

Fluoroscopy imaging performed a unilateral transpedicular (lumbar vertebrae) or extrapedicular (thoracic vertebra) puncture. After reaching the posterior edge of the vertebral body, the bone needle was replaced with a working cannula. A radiopaque medium balloon was placed over the fractured vertebral body to restore the damaged vertebral body until adequate height restoration, and kyphosis correction were achieved. The balloon was then deflated and withdrawn, and the resulting intravertebral space was filled with polymethylmethacrylate cement.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage were given for categorical data, and median, minimum and maximum descriptive values for continuous data. “Mann Whitney-U Test” was used for comparisons between groups, and “Pearson Chi-square or Fisher’s Exact Test” was used to compare categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

The evaluation of whether there was a difference between demographic and clinical findings of the patients in the study under general anesthesia and local anesthesia and sedation were elaborated in **Table 1.**

When the table was examined, no statistically significant difference was found between the two groups regarding age, gender, and Charlson comorbidity index (p>0.05). This outcome indicates that the study population was homogeneous regarding age, gender, and Charlson comorbidity index result.

There was a statistically significant difference between the groups in terms of duration of operation, duration of anesthesia, postoperative discharge time, postoperative 24-hour VAS score, intraoperative hemodynamic status, and presence in the post-anesthesia care unit (PACU) (p<0.05).

The operation time, anesthesia time, postoperative discharge time, and the postoperative 24-hour VAS score of individuals with general anesthesia were higher than those under local anesthesia and sedation.

Regarding intraoperative hemodynamic status, 37.5% of those under general anesthesia were stable, while 73.5% of individuals under local anesthesia and sedation were stable. While 37.5% of those under general anesthesia were in the post-anesthesia care unit, this rate was 7.4% in those under local anesthesia and sedation.

DISCUSSION

Kyphoplasty surgery has several complications. The most common of them could be elaborated as leakage from the operation zone and the second one is anesthesia related events (12,13). At this point, the medical team's anesthesia method becomes a controversial issue. The surgeons are prone to local anesthesia rather than general anesthesia because it is a safer method for elderly patients who cannot receive general anesthesia and whose general condition is impaired. On the other hand, comorbid diseases are also another decision point for the elderly population (11).

Liu, et al. (10) have previously published that local anesthesia might be an ideal choice for patients who had undergone single vertebra kyphoplasty. They declared that local anesthesia effectively achieved the sufficient efficacy of general anesthesia. Additionally, local anesthesia was a safer option for cardiac situations and older individuals to reduce anesthesia-related complications. Last but not least, local anesthesia also had better postoperative outcomes such as early mobilization, getting out of bed soon, and reducing hospital stay. Similar to their findings, our study found that the operation time, anesthesia time, postoperative discharge time, and postoperative 24-hour VAS score of individuals with general anesthesia were higher than those under local anesthesia and sedation.

Table 1. Distribution of Demographic and Clinical Findings by Types of Anesthesia

Characteristics (N=76)	Total (n=76) n (%) or Median (Min-Max)	GA (n=8) n (%) or Median (Min-Max)	LA+SED (n=68) n (%) or Median (Min-Max)	P Value
Age, years	69 (33-92)	68 (54-83)	69 (33-92)	0.754
Gender				0.234
Male	23 (30.3)	4 (50.0)	19 (27.9)	
Female	53 (69.7)	4 (50.0)	49 (72.1)	
Charlson Comorbidity Index	4 (0-7)	5 (2-7)	4 (0-7)	0.674
Injury Type				0.623
Osteoporosis	4 (5.3)	0 (0.0)	4 (5.9)	
Metastatic Tumor	5 (6.6)	1 (12.5)	4 (5.9)	
Falling	67 (88.2)	7 (87.5)	60 (88.2)	
Pre-op VAS Score	8 (6-10)	8 (7-10)	8 (6-10)	0.257
Operation time, minutes	**45 (20-120)**	**70 (30-120)**	**45 (20-120)**	**0.029**
Anesthesia time, minutes	**60 (30-180)**	**80 (45-140)**	**60 (30-180)**	**0.027**
Severe Complications	16 (21.1)	4 (50.0)	12 (17.6)	0.056
Post-op Discharge, days	**1 (1-44)**	**2,5 (1-44)**	**1 (1-10)**	**<0.001**
Post-op 24 hour VAS Score	**2 (1-5)**	**3 (2-5)**	**2 (1-4)**	**0.001**
Intraoperative Hemodynamic Status				**0.049**
Stable	**53 (69.7)**	**3 (37.5)**	**50 (73.5)**	
Unstable	**23 (30.3)**	**5 (62.5)**	**18 (26.5)**	
PACU	**8 (10.5)**	**3 (37.5)**	**5 (7.4)**	**0.034**

There is also conflicting literature on this subject, indicating that the type of anesthesia did not affect the efficacy of PKP for a single-level OVF. Liu et al. (10) stated that anesthesia type was not a significant parameter of the PKP procedure. This is an important finding as the duration of single kyphoplasty intervention of a single OVF is shorter. On the contrary, our study's patient population mainly consisted of the elderly with several comorbidities, thus considering that general anesthesia will be more risky. Postanesthetic care unit need was less in the local anesthesia sedation group.

One important aspect of comparing local and general anesthesia during PKP surgery lies beneath each individual's vital signs, hemodynamic parameters, and intraoperative situation. However, data on this strategic point is lacking in the previous studies. Fluctuations in these parameters determine the duration of PACU patients with a variety of factors such as cardiac status (mean arterial pressure, heart rate, vital signs during the operation), postoperative cognitive dysfunction, and other complications (14,15). In this study, there was a statistically significant difference in favor of the local anesthesia group between the groups in terms of duration of operation, duration of anesthesia, postoperative discharge time, postoperative 24-hour VAS score, intraoperative hemodynamic status, and presence in the post-anesthesia care unit (PACU) ($p<0.05$).

At this stage, one should consider the differential advantages of each anesthesia method at a patient centric approach. General anesthesia has definite advantages on vital signs (arterial pressure and heart rate) due to narcotic analgesics, sedatives, and muscle relaxants, combined with efficient respiratory ventilation management. This enables the prevention of cardiovascular and cerebral complications via controlling heart rate and blood pressure (16-18). However, this data was challenged in our findings as the intraoperative hemodynamic status of our study population has been found as 37.5% of those under general anesthesia were stable, while 73.5% of individuals under local anesthesia and sedation were stable.

Another technical advantage of general anesthesia is reducing surgery period and fluoroscopy exposure, especially in multiple vertebral PKP. During local anesthesia, the patient needs to change his/her position frequently due to body position-related discomfort or stimulation of intraoperative pain. Due to the combination of muscle relaxation and analgesia, it seems appropriate to prefer general anesthesia at this point (19).

The downside of local anesthesia could be elaborated as inadequate efficacy leading to severe pain during the surgery. Multiple osteoporotic vertebral fracture surgery such as rib, humerus, or intertrochanteric fracture requiring a prone position at the operation might lead to discomfort. At this point, the patient may need sedation and analgesia. However, it is difficult for anesthesiologists to adjust the appropriate sedation level without causing respiratory depression and unconsciousness in the patient population (elderly and patients with comorbid diseases) and prone position. The experience of the surgeon is also another aspect. If the puncture point angle could not be achieved at one time, repeated puncture increases the damage to surrounding soft tissue and nerve injury, resulting in muscle tension in the intraoperative period (20). In our study, the same surgeon has performed the operations, but the anesthetists were different. The main challenge has been preserving patient cooperation while administering sedation without respiratory depression. Although there was no statistically significant difference in the study analyses, complications in the local anesthesia sedoanalgesia group (respiratory distress in 4 patients, hypertensive crisis in 2 patients, hypotension in 3 patients, nausea and vomiting in 1 patient) were life-threatening.

One should also admit the proven advantages of local anesthesia. The major strength could be emphasized as no requirement for postoperative PKP recovery. The patients get out of bed very soon, thus alleviating wound healing. Another strength is no impairment in cognitive functions compared to general anesthesia, which is essential for elderly patients (21). The results of our study have provided supportive outcomes on this aspect. The 37.5% of those under general anesthesia were in the post-anesthesia care unit while this rate was 7.4% in those under local anesthesia and sedation.

The surgery team's skills and the patient's positive motivation increase the success rate. The experienced surgeon and an individual who has been informed about the surgery, position, and sedation/analgesia requirement case can be attributed as the best possible combination. Hence, physicians prefer local anesthesia in single OVF repair by kyphoplasty (10).

Limitations of the Study

The main limitation of this study could be attributed to its retrospective nature. The second limitation was the lack of comparison between local and general anesthesia during PKP surgery in terms of each individual's vital signs, hemodynamic parameters, and intraoperative situation. However, one should mention that this was the most significant gap in published literature up to date.

In our study, the type of anesthesia was decided with the surgical team. Regional anesthesia methods, neuraxial blocks (spinal, epidural), ultrasonography-assisted trunk blocks were not performed. Prospective studies are needed to compare these methods to determine the advantageous anesthesia method for kyphoplasties.

CONCLUSION

Regarding the results of this study, one can say that the most appropriate anesthesia type should be determined according to the patient's individual health status. Thus each method has its advantages, such as no need for a stable position in general anesthesia and availability of motor functioning evaluation and verbal communication in local anesthesia. When the anesthesia method was compared, since local anesthesia and sedoanalgesia were together, local anesthesia seemed to be more advantageous with the appropriate sedation level.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bursa Training and Research Hospital, Non-interventional Clinical Research Ethics Committee (Date: 28.04.2021, Decision No: 2011-KAEK-25 2021/04-17).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Briot K, Kolta S, Fechtenbaum J, et al. Increase in vertebral body size in postmenopausal women with osteoporosis. Bone 2010; 47: 229-34.
2. Iolascon G, Moretti A, Giamattei MT, et al. Prevalent fragility fractures as risk factor for skeletal muscle function deficit and dysmobility syndrome in post-menopausal women. Aging Clin Exp Res 2015; 27: 6-11.
3. Deandrea S, Lucenteforte E, Bravi F, et al. Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. Epidemiology 2010; 21: 658-68.
4. Müller CW, Gösling T, Mameghani A, et al. Vertebral fractures due to osteoporosis. Kyphoplasty and vertebroplasty vs conservative treatment. Orthopade 2010; 39: 417-24.
5. Iolascon G, Cisari C, Moretti A, et al. NSAIDs and opioids in management of fragility fractures. Aging Clin Exp Res 2013; 25: 97-100.
6. Migliaccio S, Francomano D, Romagnoli E, et al. Persistence with denosumab therapy in women affected by osteoporosis with fragility fractures: a multicenter observational real practice study in Italy. J Endocrinol Investig 2017; 40: 1321-6.
7. Migliaccio S, Resmini G, Buffa A, et al. Evaluation of persistence and adherence to teriparatide treatment in patients affected by severe osteoporosis (PATT): a multicenter observational real life study. Clin Cases Miner Bone Metab 2013; 10: 56-60.
8. Zhu RS, Kan SL, Ning GZ, et al. Which is the best treatment of osteoporotic vertebral compression fractures: balloon kyphoplasty, percutaneous vertebroplasty, or non-surgical treatment? A Bayesian network metaanalysis. Osteoporos Int 2019; 30: 287-98.
9. Ru XL, Jiang ZH, Song BS, Treatment of senile osteoporotic vertebral compression fractures with percutaneous kyphoplasty under local anesthesia. Zhong guo Gu Shang 2013; 26: 824-8.
10. Jie Liu, Lin Wang, Mei Chai, et al. Analysis of anesthesia methods in percutaneous kyphoplasty for treatment of vertebral compression fractures. J Healthc Eng 2020: 3965961.
11. Luginbühl M. Percutaneous vertebroplasty, kyphoplasty and lordoplasty: implications for the anesthesiologist [J]. Curr Opin Anaesthesiol 2008; 21: 504-13.
12. Key BM, Symanski J, Scheidt MJ, Tutton SM. Vertebroplasty, Kyphoplasty, and Implant-Based Mechanical Vertebral AugmentationSemin. Musculoskelet Radiol 2021; 25: 785-794.
13. Chen WC, Tsai SHL, Goyal A. Comparison between vertebroplasty with high or low viscosity cement augmentation or kyphoplasty in cement leakage rate for patients with vertebral compression fracture: a systematic review and network meta-analysis. Eur Spine J 2021; 30: 2680-90.
14. Razek AA, Ashmalla GA. Assessment of paraspinal neurogenic tumors with diffusion-weighted MR imaging. Eur Spine J 2018; 27: 841-6.
15. Staender SEA, Mahajan RP. Anesthesia and patient safety: have we reached our limits? Curr Opin Anaesthesiol 2011; 24: 349-53.
16. Urman RD, Punwani N, Shapiro FE. Patient safety and office-based anesthesia. Curr Opin Anaesthesiol 2012; 25: 648-53.
17. Tosi F, Genovese O, Jovanovic T, Visocchi M. Management of Anaesthesia. Acta Neurochir Suppl 2019; 125: 381-6.
18. Yeom JS, Kim WJ, Choy WS, et al. Leakage of cement in percutaneous transpedicular vertebroplasty for painful osteoporotic compression fractures. J Bone Joint Surg (Br) 2003; 85: 83-9.
19. Harrington KD. Major neurological complications following percutaneous vertebroplasty with polymethylmethacrylate : a case report. J Bone Joint Surg Am 2001; 83: 1070-3.
20. Park JW, Park SM, Lee HJ, et al. Infection following percutaneous vertebral augmentation with polymethylmethacrylate. Arch Osteoporos 2018; 13: 47.
21. Razek AA, Sherif FM. Diagnostic accuracy of diffusion tensor imaging in differentiating malignant from benign compressed vertebrae. Neuroradiology 2019; 61: 1291-6.

Original Article

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Evaluation of the effects of two different anesthesia methods on postoperative renal functions in geriatric patients undergoing hip fracture surgery: a prospective randomized trial

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ABSTRACT

Aim: The choice of anesthesia management for hip fracture surgery is among the modifiable risk factors that can affect the outcome. This study aims to investigate the effects of two different anesthesia techniques on kidney functions with the RIFLE (Risk, Injury, Failure, Loss, and End-stage renal failure) risk score in patients who were operated on for hip fracture.

Material and Method: Serum creatinine values lower than 1.5 times (Normal value: 1.2 mg/dL) and glomerular filtration rate (GFR) below 60 mg/dl, over 65 years old, without serious comorbidity, hemoglobin (Hb) value over 9 g/dl 60 patients were included. The demographic data and biochemical parameters of the patients were recorded. The patients were randomized into two groups as spinal anesthesia (Group S) and general anesthesia (Group G). During the surgery, a urinary catheter was applied to the patients and urine output was monitored. Balance liquid electrolyte regimen was applied and after Hb control, an appropriate blood regimen was planned with Hb above 9 g/dl. Postoperatively, patients were followed at 6th, 12th, and 24th hours on the first day, and then at 24-hour intervals in the first postoperative week, and were evaluated with the RIFLE risk scores.

Results: There was no statistically significant difference between the groups in terms of demographic data, fracture type, laboratory values, and urine volumes ($p > 0.05$). In the comparison of intragroup urea values, the decrease in the 5th time interval compared to the baseline value was statistically significant in Group G. There was no statistically significant difference between the measurement times in Group S ($p > 0.05$). Preoperative creatinine values were found to be statistically significantly higher than other measurement times in the patient group in Group S ($p < 0.05$). In both groups, it was found that all measurement time urine amounts were statistically different from each other ($p < 0.05$). In comparisons between groups, There was no statistically significant difference in terms of RIFLE risk score and postoperative outcome at all measurement times ($p>0.05$).

Conclusion: There is no difference between the anesthesia method applied in hip fracture surgery and the change in renal function of patients, based on RIFLE criteria and laboratory parameters. In addition, a significant improvement in renal functions was observed in both groups, especially during the discharge period, according to preoperative values, which may indicate that the stress response to surgery can be effectively limited in both anesthesia methods.

Keywords: General anesthesia, spinal anesthesia, hip fracture, renal functions, geriatric, RIFLE criteria

INTRODUCTION

Fracture of the femur in the bone region just distal to the hip articular cartilage, up to about five centimeters below the lower border of the lesser trochanter, is referred to as "hip fracture" and these patients are generally in the advanced age group (1-3). The presence of cardiac, endocrine, renal, cerebral, and respiratory diseases increases perioperative and postoperative morbidity and mortality in geriatric patients (2,4). The choice of anesthesia management for hip fracture surgery is among the modifiable risk factors that may affectpatient mortality (4). Anesthesia used is either general anesthesia; with the airway maintained by a face mask,

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laryngeal mask airway (LMA), or endotracheal tube (ET) induction and ventilation being spontaneous or mechanical; or regional where a spinal injection of a local anesthetic or an epidural is used (5). In many studies on mortality, different results have been obtained regarding the superiority of anesthesia methods over each other, and a clear consensus has not been reached (6-8).

Acute kidney injury (AKI) is a sudden, sustained decrease of renal function, causing damage to its excretion capacity and maintenance of fluid/electrolytic homeostasis and urea and creatinine accumulation with or without urinary output reduction. This renal function decrease is observed with a reduction of the glomerular filtration rate (GFR), resulting in an elevation of serum creatinine and urea levels, which are often used to clinically evaluate the renal function (9,10). AKI is a common complication in patients undergoing major surgery (11). For this reason, fluid monitoring and stabilization of hemodynamics are very important in these patients. Studies of AKI in patients with hip fractures have reported an 8% to 24% risk of developing acute renal failure within 72 hours after surgery or during hospitalization (9,12,13). Renal failure studies were standardized by a consensus in 2004 that defined ARF based on separate criteria of creatinine and/or urinary output (14). AKI was classified, by this consensus, in three different severity categories (risk, injury, and failure) and two clinical categories (renal loss and end-stage of renal disease), and the acronym RIFLE (Risk, Injury, Failure, Loss, and End-Stage) identifies this classification as follows (9):

•Risk: increase of 1.5 times of serum creatinine concerning basal creatine and/or urinary debt of 0.5 mL · kg−1 h−1 for six hours;

•Injury: increase of two times of serum creatinine to basal creatinine and/or urinary debt of 0.5 mL · kg−1 h−1 for 12 hours;

•Failure: increase of three times of serum creatinine in relation to basal creatinine and/or urinary debt of 0.3 mL · kg−1 h−1 for 24 hours (oliguria), 12 hours (anuria), or when the creatinine values are above 4.0 mg · dL−1;

•Renal loss: acute renal failure for more than four weeks; and

•End-stage: renal failure for more than three months.

In this study, we hypothesized that spinal anesthesia applied in geriatric patients undergoing hip surgery may be a more protective technique than general anesthesia in the early postoperative period in terms of acute renal failure. This study, it is aimed to evaluate this effect by using the RIFLE criteria. The primary outcome of this study is to investigate the effects of two different anesthesia techniques on kidney functions by using the RIFLE criteria in patients who will be operated on for hip fracture. The secondary outcome, on the other hand, is to investigate the mortality and morbidity of patients through the early detection of renal dysfunction using RIFLE criteria.

MATERIAL AND METHOD

This study was planned as prospective, randomized, controlled, and double-blind. After the approval of the Ankara Numune Training and Research Hospital Clinical Researches Ethics Committee (ID: E.Kurul-E-16-1025, Date: 10.08.20016). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. It was planned for geriatric patients who applied to the orthopedics clinic of the high volume tertiary medical center with hip fracture between September 2016 and September 2017. Those who were less than 1.5 times the normal serum creatinine values according to the hospital reference values (Normal value: 1.2 mg/dL) and GFR below 60 mg/dl, over 65 years of age, without a previous history of liver, kidney and heart failure, were included in the study. Sixty patients with hemoglobin (Hb) values over 9 g/dl were included. The patients were randomized using the random.org method and divided into two groups as spinal anesthesia (Group S) and general anesthesia (Group G). Allocation was done by the closed envelope method.

Those with liver, kidney, and heart failure, unregulated hypertension and diabetes mellitus, those with a history of regular non-steroidal anti-inflammatory drug use in the last 6 months, and those with a history of drug use affecting kidney functions were excluded from the study.

Demographic data and biochemical parameters (Hb, serum creatinine, and blood urea nitrogen (BUN)) values of the patients who were preoperatively prepared were recorded. Isolyte S (balanced solution) infusion at 10 ml/kg/h was given to the patients. In Group S, a unilateral spinal block was applied to the patients using 1.5 ml 0.5% Heavy Bupivacaine with a 25 G spinal needle (Egemen, 11 cm, Quince 25G) with the patient lying on their side through the L 4-5 intervertebral space. Balance anesthesia induction 0.3 mg/kg midazolam, 0.25-0.50 µg/kg remifentanil, 2% propofol 1.5-2 mg/kg, 0.6 mg/kg rocuronium intravenous (iv) bolus was administered to the patients in Group G and appropriate endotracheal (7-8.0 cuffed) tube was intubated. Sevoflurane 1.0-1.2 MAC, and 0.5 µg/kg/h remifentanil infusion were administered for anesthesia maintenance. During the surgery, urine output was monitored by applying a urinary catheter to the patients, and recording was started when the urine in the first bag was emptied and the bladder was empty. After the balance fluid electrolyte regimen and Hb

control, an appropriate blood regimen was planned with Hb above 9 g/dl. The urinary catheter was removed after the first 48 hours in the patients. Following the removal of the urinary catheter, the patient's urine was collected in a measurable urine cup and a 24-hour follow-up was performed. Postoperatively, patients were followed up at 6th, 12th, and 24th hours on the first day, and then at 24-hour intervals in the first postoperative week and were evaluated with a RIFLE risk score. Patients from the risk group were consulted to the nephrology clinic.

Statistical Analysis

Analysis of the data was done using IBM SPSS 25.0 statistical package program. While evaluating the study data, the Chi-Square ($\chi 2$) test was used to compare the qualitative data as well as descriptive statistical methods (frequency, percentage, mean, standard deviation, median, min-max). The suitability of the data to the normal distribution was evaluated with Kolmogorov-Smirnow and Shapiro-Wilk tests. The Mann-Whitney U test was used for the intergroup comparisons of the data that did not show normal distribution, and the Friedman test was used for the intragroup comparisons. Dunn's post-hoc test was used to find the source of the difference in cases where there was a difference in group comparisons. Values with a probability (P) less than $\alpha=0.05$ were accepted as significant and there was a difference between groups, values with a higher probability were considered as insignificant and there was no difference between groups.

Sample Size And Power Analysis

The sample size was calculated using G*Power© software version 3.1.9.2 (Institute of Experimental Psychology, Heinrich Heine University, Dusseldorf, Germany). The sample size was calculated for the Mann Whitney U-test, which was used for testing the main hypothesis of (RIFLE score for 24 hours) the present study. Depending on previous research results with two-sided (two tails) type I error 0.05 and power of 80% ($1-\beta=0.8$), effect size (d) factor 0.5, should involve ≥ 112 subjects.

Power analysis was done with the G*Power 3.1.9.2 statistical package program; n1=49, n2=56, $\alpha=0.05$, Effect Size d=0.65; Power $(1-\beta)=0.90$.

RESULTS

Our study included 157 patients who applied to the orthopedics clinic of our hospital between September 2016 and September 2017. 112 of these patients who met the criteria agreed to participate in the study. Afterward, 7 patients in the general anesthesia group were excluded from the study before the operation because they wanted to drop out of the study. The operations of the patients were planned with general anesthesia and one of the spinal anesthesia methods. In the spinal anesthesia group, all 56 patients were included in the study. The study was completed by 49 patients in the general anesthesia group and 56 patients in the spinal anesthesia group (**Figure 1**).

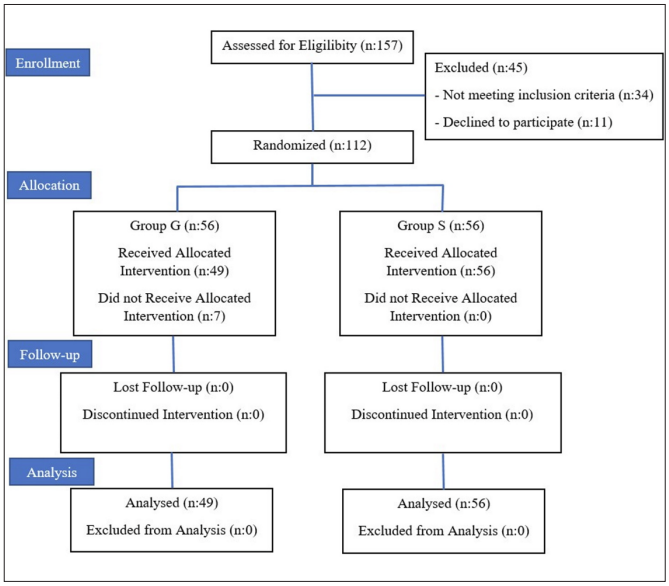

Figure 1. Flowchart of patients. Group G: general anesthesia, Group S: spinal anesthesia.

There was no statistically significant difference between the groups in terms of gender, age, and fracture type ($p > 0.05$) (**Table 1**).

Table 1. Comparison of patient characteristics between groups

		Group G (n=49)	Group S (n=56)	P
Gender	Female	29 (% 59.2)	40 (% 71.4)	0.266 a
	Male	20 (% 40.8)	16 (% 28.6)	
Age, (year)	80 (65-96)	79 (65-100)	0.969 b	
Fracture type	Femur neck	11 (% 22.4)	22 (% 39.3)	0.103 a
	Intertrochanteric	30 (% 61.2)	30 (% 53.6)	
	Subtrochanteric	8 (% 16.3)	4 (% 7.1)	
Operation	Endoprothesis	12 (% 24.5)	18 (% 32.1)	0.103 a
	Proximal Femoral Nail	37 (% 75.5)	38 (% 67.9)	

Continuous variables are expressed as either the mean±standard deviation (SD) or median (Q1-Q3) and categorical variables are expressed as either frequency (percentage). a: Chi-Square Test, b: Mann-Whitney U Test. Group G: general anesthesia, Group S: spinal anesthesia.

In comparison between groups, there was no statistically significant difference between the groups in terms of urea, serum creatinine, GFR, and urine values at all measurement times ($p > 0.05$).

In group comparisons; in the comparison of urea values, the decrease in the 5th time interval compared to the baseline value in the general patient group was statistically significant. In the spinal patient group, there was no statistically significant difference between the measurement times ($p > 0.05$). In the comparison of serum creatinine values, it was observed that there

was no statistically significant difference between the measurement times in the general patient group in terms of serum creatinine values ($p > 0.05$). In the spinal patient group, preoperative serum creatinine values were found to be statistically significantly higher than the other measurement times ($p < 0.05$). In the comparison of GFR values, it was observed that there was no statistically significant difference between the measurement times in both general and spinal patient groups ($p > 0.05$). In the comparison of urine volumes, a statistically significant difference was observed between the measurement times in both general and spinal patients ($p < 0.05$). In both groups, it was found that the urine volumes at all measurement times were statistically different from each other ($p < 0.05$) (**Table 2**) (**Figure 2**).

Table 2. Comparison of renal function tests between groups

		Group G (n=49)	Group S (n=56)	P a
Urea (mg/dL)	Preoperative1	58.2±28.2	57.0±27.1	0.946
	PO 6. hour2	55.1±26.6	54.9±26.6	0.944
	PO 24. hour 3	55.9±27.8	57.2±25.0	0.738
	PO 48. hour 4	56.9±31.4	58.5±28.1	0.761
	Discharge5	43.3±21.5	52.1±30.3	0.119
	P b	0,000	0,166	
	Difference	1 with 5	--	
Creatinin (mg/dL)	Preoperative1	1.1±0.5	1.2±0.6	0.772
	PO 6. hour 2	1.1±0.6	1.0±0.5	0,169
	PO 24. hour 3	1.1±0.6	1.1±0.6	0.977
	PO 48. hour 4	1.1±0.8	1.1±0.5	0.644
	Discharge5	0.9±0.4	1.0±0.7	0.606
	P b	0.002	0.048	
	Difference	1 with 5	1 with 5	
GFR (ml/min)	Preoperative1	61.8±23.6	58.2±21.5	0.383
	PO 6. hour 2	63.7±24.8	63.3±21.1	0.944
	PO 24. hour 3	65.3±24.9	61.4±19.9	0.458
	PO 48. hour 4	80.6±36.2	69.6±31.7	0.115
	Discharge5	91.1±33.9	78.1±31.5	0.091
	P b	0.000	0.000	
	Difference	1 with 4-5	1 with 4-5	
Urine volumes (mL)	PO 6. hour	669.4±211.6	594.6±187.2	0.068
	PO 12. hour	1333.7±356.5	1293.8±377.2	0.505
	PO 24. hour	1878.6±493.9	1885.7±514.0	0.870
	P b	0.000	0.000	
	Difference	All	All	

Continuous variables are expressed as the mean±standard deviation (SD).
a: Mann-Whitney U Test, b: Chi-Square Test, c: FriedmanTest
Group G: general anesthesia, Group S: spinal anesthesia, GFR: Glomerular filtration rate; PO: Postoperative.

In comparisons between groups; There was no statistically significant difference between the groups in terms of GFR values at all measurement times ($p > 0.05$).

In group comparisons; In the comparison of GFR values, it was observed that there was no statistically significant difference in terms of GFR values between the measurement times in both the general and spinal patient groups ($p > 0.05$).

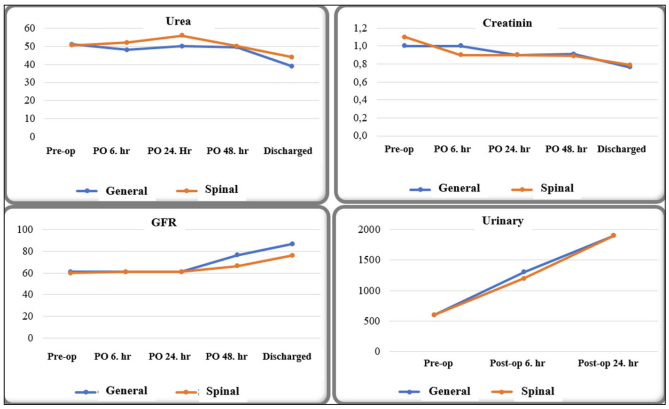

Figure 2. Comparison of renal function tests between groups. GFR: Glomerular filtration rate; Pre-op: Preoperative; PO: Postoperative

In comparisons between groups; It was found that there was no statistically significant difference between the groups in terms of RIFLE values at all measurement times ($p > 0.05$) (**Table 3**) (**Figure 3**).

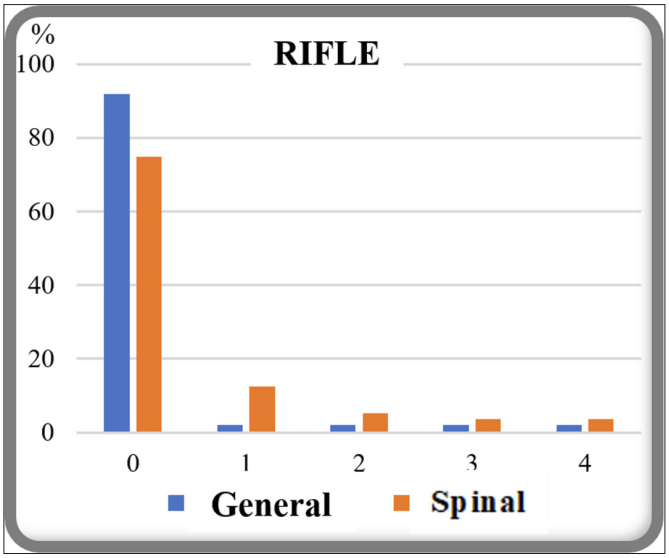

Figure 3. Comparison of RIFLE scores and groups. RIFLE: Risk, Injury, Failure, Loss, and End-stage renal failure.

Table 3. Comparison of RIFLE scores and groups

		Group G (n=49)	Group S (n=56)	P a
RIFLE	0	45(%91.8)	42(%75.0)	0.212
	1	1(%2.0)	7(%12.5)	
	2	1(%2.0)	3(%5.4)	
	3	1(%2.0)	2(%3.6)	
	4	1(%2.0)	2(%3.6)	
Complication	Yes	5(%10.2)	8(%14.3)	0.736

Continuous variables are expressed as either the mean±standard deviation (SD) or median (Q1-Q3) and categorical variables are expressed as either frequency (percentage). a: Chi-Square Test. Group G: general anesthesia, Group S: spinal anesthesia, RIFLE: Risk, Injury, Failure, Loss, and End-stage renal failure.

In comparisons between groups; It was found that there was no statistically significant difference between the groups in terms of hospitalization time, hospitalization time after surgery, postoperative anesthesia care unit (PACU) requirement, time in PACU, time in hospital ward, intensive care unit (ICU) requirement and time in ICU values ($p > 0.05$) (**Table 4**).

Table 4. Comparison of time and requirements between groups			
	Group G (n=49)	**Group S (n=56)**	**P**
Hospitalization time (day)	11.5±6.2	10.0±4.7	0.376 a
Hospitalization time after surgery (day)	3.3±3.0	3.3±3.4	0.858 a
PACU requirement	30 (% 61.2)	38 (% 67.9)	0.614 b
Time in PACU (day)	0.7±0.6	0.7±0.6	0.442 a
Time in hospital ward (day)	8.4±4.8	7.9±4.0	0.644 a
ICU requirement	13 (% 26.5)	18 (% 32.1)	0.678 b
Time in ICU (day)	2.4±5.8	1.3±2.7	0.792 a

a: Mann-Whitney U Test, b: Friedman test. Group G: general anesthesia, Group S: spinal anesthesia, PACU: postoperative anesthesia care unit, ICU: intensive care unit

In both groups; It was found that the relations between RIFLE variables and PACU need, PACU time, ICU need and ICU time values were not statistically significant (p>0.05) (**Table 5**).

Table 5. Comparison of groups with correlation test in terms of time and needs								
	PACU Need		**PACU Time**		**ICU Need**		**ICU Time**	
	r	Pa	r	Pa	r	Pa	r	Pa
GA RIFLE	0.212	0.144	0.212	0.143	0.172	0.237	0.218	0.132
SA RIFLE	-0.134	0.325	-0.153	0.259	0.234	0.083	0.226	0.095

a: Spearman's Rho Correlation Test. PACU: postoperative anesthesia care unit, GA: General anesthesia, SA: Spinal anesthesia, ICU: intensive care unit, RIFLE: Risk, Injury, Failure, Loss, and End-stage renal failure.

DISCUSSION

The results of this study showed that there was no difference between the anesthesia method applied in patients who were operated on for hip fracture and the change in renal functions of the patients, based on RIFLE criteria and laboratory parameters. In addition, a significant improvement in renal functions was observed in both groups, especially during the discharge period, according to preoperative values.

Hip fractures have serious consequences, especially in frail elderly individuals, and are associated with decreased quality of life and increased morbidity and mortality (15-17). The most important of these complications is AKI, which is defined as a sudden decrease in kidney function, which is a common postoperative complication. AKI is a comprehensive clinical syndrome involving intrarenal and extrarenal pathologies. Postoperative AKI is associated with a longer hospital stay, increased hospital costs, and a significantly high rate of morbidity and mortality (18-20).

The relationship between anesthesia technique and mortality in surgeries performed after hip fractures has been evaluated (21,22). However, studies on the effect of anesthesia type on AKI are limited (23,24). Weingarten et al. (24) reported that general anesthesia was an independent risk factor for the development of postoperative renal failure in patients who underwent joint arthroplasty. Regional anesthesia techniques can be associated with avoidance of airway management, reduced blood loss, potentially reduced risk of deep vein thrombosis, and improved postoperative analgesia. Conversely, it may be associated with a more stable hemodynamic condition in general anesthesia, unlike regional anesthesia (3,25). Considering these effects of general and regional anesthesia, the stable hemodynamics provided in general anesthesia and the limited blood loss provided by regional anesthesia may limit the deterioration of renal functions by keeping the pre-renal blood flow stable, which has a serious effect on renal functions (26). This situation is especially important in fragile geriatric patients. In this study, limited changes and similarities in RIFLE and renal function parameters in both groups show that both anesthesia methods can be used safely in hip fracture surgery in patients.

Stress response to surgery and trauma is an important problem in patients. If this situation cannot be controlled well, it causes acceleration of the catabolic process in patients and deterioration in organ functions with long-term hospitalization (27-29). As a result, this condition is associated with increased morbidity and mortality (29). It has been reported that regional anesthesia limits the stress response more with its central blocking effect. However, it has been reported that this stress response suppressive effect is more limited in general anesthesia (29). This catabolic process is more pronounced, especially in situations that significantly increase the stress response, such as a hip fracture (30). When the fragile geriatric population of this patient group is added to the stress response caused by pain, malnutrition, and trauma, the already borderline organ functions may deteriorate further. Limiting the time to surgery and effective perioperative management may limit this deterioration in these patients. In this study, the higher preoperative renal functions in both groups and the return of these values to more normal levels, especially during discharge, can be explained by the fact that the two anesthetic methods are used to reduce the surgical stress in these patients. As a result, general and spinal anesthesia can be considered as the anesthetic methods preferred in these patients and do not have superiority over each other.

In previous studies, advanced age, low preoperative GFR, emergency surgery, liver disease, obesity, high-risk surgery, and peripheral vascular occlusive disease were accepted as preoperative predictors of AKI in noncardiac surgeries (13,31,32). Intraoperative problems such as bleeding due to anesthesia and hypovolemia have also

been shown to be risk factors for postoperative AKI (33). In addition, hypotension is a common condition during hip surgery, but it has been suggested that this may also lead to AKI. In this study, patients in both groups had similar characteristics in terms of demographic data and comorbidities. In addition, in order to limit the negative effects of possible perioperative hypotension on renal functions, a balance liquid electrolyte regimen was applied to the patients and an appropriate blood regimen was planned with Hb above 9 g/dl after Hb control.

Postoperative complications are more important especially in major surgeries such as hip surgery. This situation may adversely affect the outcome of the patients and may also cause deterioration of renal functions. Various studies have been conducted to determine whether regional anesthesia provides benefits over general anesthesia for surgeries in general, but the evidence remains conflicting (34). Meta-analyses of randomized clinical trials comparing regional anesthesia versus general anesthesia for hip fracture surgery have found borderline significant results on reductions in the risk of short-term complications and mortality associated with regional anesthesia, whereas there is no evidence of a reduction in risk at three months postoperatively (25). In this study, complications developed at a similar rate in both groups, while an intraoperative patient developed death, while 2 patients in the spinal anesthesia group and 1 patient in the general anesthesia group needed dialysis.

There are some limitations to this study. Initially, the study was designed as a single center. This may cause limitations in the evaluation of the general population. Therefore, multicenter prospective and large series studies may be more useful in evaluating the difference of anesthetic methods. Secondly, the use of only RIFLE criteria in addition to the parameters that evaluate renal function in the study may limit objective results. Finally, the relationship of these two anesthesia types with long-term mortality and complications could not be demonstrated, since long-term postoperative follow-up of the patients could not be performed.

CONCLUSION

In conclusion, there is no difference between the anesthesia method applied in patients who were operated on for hip fracture and the change in renal functions of the patients, based on RIFLE criteria and laboratory parameters. In addition, a significant improvement in renal functions was observed in both groups, especially during the discharge period, according to preoperative values, which may indicate that the stress response to surgery can be effectively limited in both anesthesia methods. The effects of the type of anesthesia applied in the patients in terms of postoperative complications and dialysis needs are similar. Large series of prospective randomized studies on this subject will contribute to the emergence of clearer results on the effects of anesthesia methods on renal functions and AKI development.

ETHICAL DECLARATION

Ethics Committee Approval: The study was initiated with the approval of the Ankara Numune Training and Research Hospital Clinical Researches Ethics Committee (ID: E.Kurul-E-16-1025, Date: 10.08.2016).

Informed Consent: All patients were informed about the application and their informed consent was obtained.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Karaca S, Ayhan E, Kesmezacar H, Uysal O. Hip fracture mortality: is it affected by anesthesia techniques? Anesthesiology Research and Practice 2012.doi: 10.1155/2012/708754
2. Ersoy A, Ervatan Z, Ali A, Kara D, Sağ E, Adaş M. Kalça cerrahisinde anestezi deneyimlerimiz. Okmeydanı Tıp Dergisi 2013; 29: 33-6.
3. Beaupre LA, Jones CA, Saunders LD, Johnston DW, Buckingham J, Majumdar SR. Best practices for elderly hip fracture patients. A systematic overview of the evidence. J Gen Intern Med 2005; 20: 1019-25.
4. Brox WT, Chan PH, Cafri G, Inacio MC. Similar mortality with general or regional anesthesia in elderly hip fracture patients. Acta Orthop 2016; 87: 152-7.
5. Rashid RH, Shah AA, Shakoor A, Noordin S. Hip fracture surgery: does type of anesthesia matter? Biomed Res Int. 2013; 2013: 252356.
6. Pugely AJ, Martin CT, Gao Y, Klocke NF, Callaghan JJ, Marsh JL. A risk calculator for short-term morbidity and mortality after hip fracture surgery. J Orthop Trauma 2014; 28: 63-9.
7. Patorno E, Neuman MD, Schneeweiss S, Mogun H, Bateman BT. Comparative safety of anesthetic type for hip fracture surgery in adults: retrospective cohort study. BMJ. 2014; 348: g4022.
8. Neuman MD, Silber JH, Elkassabany NM, Ludwig JM, Fleisher LA. Comparative effectiveness of regional versus general anesthesia for hip fracture surgery in adults. Anesthesiology 2012; 117: 72-92.
9. Azevedo VL, Silveira MA, Santos JN, Braz JR, Braz LG, Módolo NS. Postoperative renal function evaluation, through RIFLE criteria, of elderly patients who underwent femur fracture surgery under spinal anesthesia. Ren Fail 2008; 30: 485-90.
10. Singri N, Ahya SN, Levin ML. Acute renal failure. JAMA 2003; 289: 747-51.

11. Pedersen AB, Christiansen CF, Gammelager H, Kahlert J, Sørensen HT. Risk of acute renal failure and mortality after surgery for a fracture of the hip: a population-based cohort study. Bone Joint J 2016; 98-B: 1112-8.
12. Kateros K, Doulgerakis C, Galanakos SP, Sakellariou VI, Papadakis SA, Macheras GA. Analysis of kidney dysfunction in orthopaedic patients. BMC Nephrol 2012; 13: 101.
13. Ulucay C, Eren Z, Kaspar EC, et al. Risk factors for acute kidney injury after hip fracture surgery in the elderly individuals. Geriatr Orthop Surg Rehabil 2012; 3: 150-6.
14. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute Dialysis Quality Initiative Workgroup. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8: R204-12.
15. Mullen JO, Mullen NL. Hip fracture mortality. A prospective, multifactorial study to predict and minimize death risk. Clin Orthop Relat Res 1992; 280: 214-22.
16. Gong Y, Zhang F, Ding F, Gu Y. Elderly patients with acute kidney injury (AKI): clinical features and risk factors for mortality. Arch Gerontol Geriatr 2012; 54: e47-51.
17. Bennet SJ, Berry OM, Goddard J, Keating JF. Acute renal dysfunction following hip fracture. Injury 2010; 41: 335-8.
18. Noyez L. Influence of the definition of acute renal failure post-cardiac surgery on incidence, patient identification, and identification of risk factors. Eur J Cardiothorac Surg 2011; 39: e8-12.
19. Abelha FJ, Botelho M, Fernandes V, Barros H. Determinants of postoperative acute kidney injury. Crit Care 2009; 13: R79.
20. Kheterpal S, Tremper KK, Englesbe MJ, et al. Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. Anesthesiology 2007; 107: 892-902.
21. O'Hara DA, Duff A, Berlin JA, et al. The effect of anesthetic technique on postoperative outcomes in hip fracture repair. Anesthesiology 2000; 92: 947-57.
22. Desai V, Chan PH, Prentice HA, et al. Is anesthesia technique associated with a higher risk of mortality or complications within 90 days of surgery for geriatric patients with hip fractures? Clin Orthop Relat Res 2018; 476: 1178-88.
23. Hassan BK, Sahlström A, Dessau RB. Risk factors for renal dysfunction after total hip joint replacement; a retrospective cohort study. J Orthop Surg Res 2015; 10: 158.
24. Weingarten TN, Gurrieri C, Jarett PD, et al. Acute kidney injury following total joint arthroplasty: retrospective analysis. Can J Anaesth 2012; 59: 1111-8.
25. Parker MJ, Handoll HH, Griffiths R. Anaesthesia for hip fracture surgery in adults. Cochrane Database Syst Rev 2004; 4: CD000521. Update in: Cochrane Database Syst Rev 2016; 2: CD000521.
26. Zengin M, Dogan G, Karaca O, et al. Retrospective Review of Anesthesia Methods in Total Knee Arthroplasty Surgeries, Osmangazi Journal of Medicine 2021; 43: 633-9.
27. Weinberg L, Pritchard A, Louis M, Jones D, Hardidge A, Churilov L. Rapid response team activation after major hip surgery: A case series. Int J Surg Case Rep 2022; 90: 106699.
28. Desborough JP. The stress response to trauma and surgery. Br J Anaesth. 2000 Jul;85(1):109-17
29. Cusack B, Buggy DJ. Anaesthesia, analgesia, and the surgical stress response. BJA Educ 2020; 20: 321-8.
30. Kendrisic M, Surbatovic M, Djordjević D, Jevdjic J. Please cite this article: surgical stress response following hip arthroplasty regarding choice of anesthesia and postoperative analgesia. Vojnosanitetski Pregled (Military Medical Journal).doi: 10.2298/VSP160416153K.
31. Braüner Christensen J, Aasbrenn M, Sandoval Castillo L, et al. Predictors of acute kidney injury after hip fracture in older adults. Geriatr Orthop Surg Rehabil 2020; 11:2151459320920088.
32. Khetepal S, Tremper KK, Englesbe MJ, et al. Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. Anesthesiology 2007; 107: 892-902.
33. Onuigbo MA, Agbasi N. Association of intraoperative hypotension with acute kidney injury after elective non-cardiac surgery-prevention is better than cure. Ren Fail 2016; 38: 168-9.
34. Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000; 321: 1493.

Original Article

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Comparison of continuous thoracic epidural block and continuous thoracic paravertebral block for management of post thoracotomy pain: a randomised trial

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ABSTRACT

Aim: Pain after thoracotomy is one of the most severe in clinical practice and more effective analgesia can be achieved by combining systemic and regional techniques. Though thoracic epidural analgesia (TEA) is the gold standard in the treatment, its application can be restricted due to side effects and contraindications. We investigated the hypothesis that thoracic paravertebral block (TPVB) reduced morphine consumption, pain scores, and side effects as much as TEA after thoracotomy.

Material and Method: Fifty patients who underwent elective posterolateral thoracotomy were included in this study. Patients were randomly allocated into two groups as TEA (group I, n = 25) and TPVB (group II, n = 25). Postoperative consumption of patient-controlled morphine, visual analog scores (VAS), hemodynamic parameters, and side effects were collected in 72 hours. Additionally, pulmonary function tests (PFT) values were recorded.

Results: Postoperative VAS values during rest were comparable between the groups ($p > 0.005$) and they did not have significantly difference postoperative VAS values during coughing ($p > 0.005$). The cumulative morphine consumption was higher in Group 2 ($p < 0.05$). Side effects were comparable between the groups II ($p > 0.05$).

Conclusion: We conclude that TEA provided more effective analgesia than TPVB in thoracotomy patients in the early postoperative period with comparable side effects.

Keywords: Paravertebral block; post-thoracotomy pain; thoracic epidural block; visual analog scale

INTRODUCTION

Pain after thoracotomy is one of the most severe in clinical practice, and inadequate pain management may be related to outcome (1). Many methods such as systemic analgesia, thoracic epidural analgesia (TEA), cryoanalgesia, thoracic paravertebral blockade (TPVB), intercostal nerve block, and intrapleural analgesia have been used to prevent thoracotomy pain (2-4). Furthermore, more efficient analgesia can be achieved by combining systemic and regional techniques (4,5). Although many new methods such as serratus plane block are used for pain after thoracotomy, TEA and TPVB are still acknowledged (5). Although the epidural block technique is considered to be a gold standard for the treatment of pain after thoracotomy, paravertebral blockade technique has fewer side-effects (2). So, the paravertebral blockade is considered to be a good alternative to epidural analgesia (3,4,6).

Morphine is widely used in the treatment of postoperative pain. Thus, it is an important component of multimodal analgesia to prevent severe pain after thoracotomy (4). However; the potential side effects of this agent are a major concern while using it. The regional techniques used for postoperative pain management can reduce the morphine consumption and the possible side effects associated with these drugs (4,7-10).

Primary and secondary outcomes were determined as morphine consumption for postoperative 24 hours, visual analog scale (VAS) scores, and side effects. In this study, we tested the hypothesis that TPVB reduces morphine consumption, pain scores, and side effects as much as TEA after thoracotomy.

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MATERIAL AND METHOD

The study was conducted with a randomized, prospective design after obtaining approval from the Keçiören Training and Research Hospital Ethics Committee (Date: 04.02.2013, Decision No: B.10.4.ISM.4.06.68.49/). All patients were informed about the procedure and informed consent was also obtained from all patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Fifty patients aged 18-65 years who were in the American Society of Anesthesiologists (ASA) I-III physical status. Patients were randomly assigned to two groups as TEA (Group I, n = 25) and TPVB (Group II, n = 25). Randomization was performed using computer-generated random numbers. Blinding was performed by concealing information in closed opaque envelopes.

Patients who have chronic pain, mental illnesses, anticoagulation therapy, bleeding disorder; alcohol-illicit drug abuse, allergy to local anesthetics, patients with infection in the intervention area, and patients who did not permit regional anesthesia were excluded from the study.

Midazolam 0.03 mg kg-1 was administered to all patients intravenously (iv) in the premedication room 30 minutes before the operation to prevent anxiety. Preoperative systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), and heart rate (HR) were monitored. 25 mcg IV fentanyl citrate was given to prevent anxiety and pain during the regional intervention.

The catheter insertion site was covered with a sterile technique after the skin was cleaned with povidone-iodine. Group I received 3 mL of 1% prilocaine for skin anesthesia, then an epidural catheter (Perifix®, Braun, Melsungen, Germany) was inserted through the thoracic (Th) Th5-6 or Th6-7 intervertebral space with median approach using the hanging drop technique, and the catheter was advanced 3 cm to cephalad. Later on, the patients were positioned in the supine position, and 5 ug/ mL-1 (1: 200.000) adrenaline and 3 mL 2% lidocaine were administered through the epidural catheter to exclude vascular or intrathecal injection. Group I was given 5 mL-1 of 0.5% bupivacaine for thoracic epidural anesthesia. The bilateral blockade was assessed by the pin-prick test. Infusion of bupivacaine at a concentration of 0.166% with a 270 mL elastomeric infusion pump was initiated for epidural analgesia at a rate of 7 mL/h during and for three days after the operation.

The insertion site was identified as 2.5 cm laterally of the spinous process at the level of Th5- Th7 and 3 mL of 1 % prilocaine was applied for skin anesthesia in group II. The nerve stimulator (Plexygon, Vycon®, Padova, Italy) was set up at 0.1 ms, a frequency of 2 Hertz, and a current of 2.5 mA. The 100 mm and 18 gauge (G) peripheral nerve stimulator needle (Techniplex, Vygon, Ecouen, France) was advanced. After the transverse process was felt with the needle, the needle was pulled back and directed 1 cm towards the upper side of the transverse process. The current was gradually reduced to 0.5 mA, and the paravertebral space was expanded with 10 ml of normal saline after determining that contractions were present in the intercostal muscles. The catheter was advanced 3 cm from the needle tip. Then, the catheter was fixed on the skin. The patients were supine and 5 ug/ mL-1 (1: 200,000) adrenaline and 3 mL 2% lidocaine were administered through the paravertebral catheter to avoid vascular or intrathecal injection. Using a pinprick test, to determine of block level after TPVB. Infusion of bupivacaine at a concentration of 0.25% with a 270 mL elastomeric infusion pump was initiated for paravertebral analgesia at a rate of 7 mL / h during and for three days after the operation.

Anesthesia induction was performed using 2 mg kg-1 propofol, 0.1 mg kg-1 vecuronium bromide and 1.5 μg / kg-1 fentanyl citrate. Anesthesia management was maintained with 2-3% sevoflurane in oxygen/ air mixture and fentanyl boluses in both groups. A 0.03 mg kg-1 vecuronium was administered for the management of neuromuscular blockade. The HR < 50 beats/min which lasted longer than 1 min was defined as bradycardia and hypotension as 20% decrease compared to the preoperative value of MAP. The fluid infusion was increased in case of hypotension. Ephedrine 5-10 mg IV was administered if there was no response. Atropine sulfate 0.015 mg kg-1 IV was planned to be administered in case of bradycardia.

The SAP, DAP, MAP, HR, SpO_2, visual analog scale (VAS) measurements; VAS rest (VASR), and VAS coughing (VASC) scores were recorded on the postoperative 30th minutes and 1st, 2nd, 6th; 12th, 20th, 24th; 36th, 48th, and 72nd hours. Pulmonary function test (PFT) (One Flow Soft V 1.2, Clement Clarke Int, Harlow Essex, England) was performed on the first, second, and third postoperative days, and the results were recorded.

In the early postoperative period, patients received 1 mg morphine IV bolus as an additional analgesic until the first VAS score was less than four, and these were recorded as additional analgesic requirements. A patient-controlled analgesia pump, which was programmed to deliver morphine 1 mg boluses with a lockout interval of 15 min, was attached to the patient for rescue analgesia. A total of 24 hours of morphine consumption was recorded for every patient. Each group received dexketoprofen 50

mg IV every twelve hours and paracetamol 1 gr IV every six hours on the postoperative first day. Paracetamol tablets (500 mg) were administered four times a day, and dexketoprofen tablets (25 mg) twice daily in addition to paravertebral and epidural infusion on the second and third postoperative days. Possible side effects such as hypotension, bradycardia, nausea-vomiting; itching, urinary retention, sedation, and motor block were also recorded. The suprascapular block was performed in case of ipsilateral shoulder pain. The block was applied to all patients by the same anesthesiologist. VAS follow-ups of patients were performed by a pain management nurse; who was blinded to the type of block applied to the patient.

Statistical Analysis

The distribution of continuous variables was investigated with the Shapiro-Wilk test. Descriptive statistics were expressed as mean±standard deviation or median (minimum-maximum) for continuous variables, and the number of cases (%) for nominal variables. The significance of the difference between the groups in terms of means was investigated with the student's t-test and the significance of the difference in terms of median values was investigated with the Mann-Whitney U test. Nominal variables were assessed by Pearson's Chi-Square, Fisher's Exact Result Chi-Square, or Likelihood Ratio test. Analysis of variance was used in repeated measures in evaluating hemodynamic measurements. The Greenhouse-Geisser test was used to examine the importance of group-time interaction. The percentages of change between the observation times which were considered clinically important were calculated and compared among the groups when the group-time interaction was found to be significant. The results with a p-value of < 0.05 were considered significant. However, Bonferroni correction was performed to examine type I error in all possible sub-analyses.

A sample size of 25 patients by the group was calculated to detect a significant difference of 20% or more in morphine consumption with a power of 80% and a significance level of 5% error to test the statistical importance by using G-Power for Mac OS X (Universitat Düsseldorf version 3.1). Data were analyzed using SPSS (Statistical Package for Social Science) software package program for Windows 11.5.

RESULTS

In the present study, 76 patients undergoing thoracotomy were allocated randomly into two groups. 26 patients were excluded from the study. Fifty patients were eligible for the study (**Figure**).

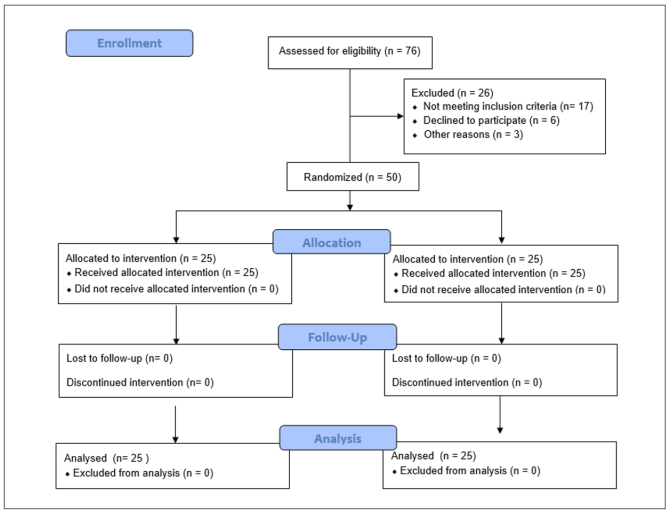

Figure. Flow diagram of the participants.

No significant difference was found between the groups in demographic data, type of surgery, and duration of surgery (p > 0.05) (**Table 1**).

Table 1. Demographic and clinical characteristics of the patients

	TEA group	TPVB Group	p
Age(year)	52.2±11.9	47.7±15.0	0.240
Male	16 (64.0%)	18 (72.0%)	0.544
Female	9 (36.0%)	7 (28.0%)	
Weight (kg)	71.9±11.8	72.3±12.1	0.906
Height (meter)	1.68±0.08	1.69±0.07	0.669
BMI (kg/m^2)	25.3±3.4	25.2±3.4	0.847
Duration of Surgery (min)	180 (75-240)	150 (90-210)	0.555
Intraoperative fentanyl consumption (µg)	119.1±25.3	115.3±22.5	0.560

Data were presented as mean±standard deviation, median range, or percent. BMI: Body mass index; TEA: Thoracic epidural analgesia; TPVB: Thoracic paravertebral block.

The morphine consumption was higher in Group II at the 2nd, 6th, 12th, 20th, and 24th hours (p < 0.05) (**Table 2**). Preoperative and postoperative PFT values were comparable between groups (p>0.05). There was no significant difference in the postoperative MAP measurements between Group I and Group II at each follow-up time (p > 0.005). There was no significant difference at VASR scores between Group I and Group II at each follow-up time (p > 0.005) (**Table 3**). There was no significant difference between the groups in terms of VASC scores (p > 0.005) (**Table 4**).

Table 2. Groups' cumulative morphine consumption in the first postoperative 24 hours.

Follow up times	TEA group		
Mean±SD	TPVB group		
Mean±SD	p		
30th min	1.0±0.9	1.5±1.0	0.090
1st hour	2.5±1.7	3.4±1.8	0.081
2nd hour	4.4±3.8	6.6±3.6	0.042*
6th hour	7.4±5.8	12.1±6.4	0.009*
12th hour	10.6±8.3	16.3±9.0	0.023*

Table 3. Visual Analog Scale scores during rest

VASR	Group I		Group II		P
Follow up times	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
30th min	2.8±2.1	2 (0-7)	4.0±2.2	4 (0-7)	0.049
1st hour	1.8±1.4	2 (0-5)	2.6±1.0	3 (1-4)	0.020
2nd hour	1.6±1.1	2 (0-3)	2.0±0.9	2 (0-3)	0.160
6th hour	1.4±1.0	2 (0-3)	1.9±1.0	2 (0-3)	0.112
12th hour	1.1 1.0	1 (0-3)	1.6±0.9	2 (0-3)	0.055
20th hour	0.9±1.0	1 (0-3)	1.4±1.3	1 (0-5)	0.204
24th hour	1.2 1.0	1 (0-3)	0.7±0.9	0 (0-3)	0.064
36th hour	0.8±0.9	1 (0-3)	0.6±0.8	0 (0-2)	0.331
48th hour	1.1 1.1	1 (0-3)	0.5±0.7	0 (0-2)	0.039
72th hour	0.8±0.8	1 (0-2)	0.2±0.4	0 (0-1)	0.005

Data presented as mean±Standard deviation and minimum-maximum. TEA: Thoracic epidural analgesia; TPVB: Thoracic paravertebral block; VASR: Visual Analog Scale during rest.

Table 4. Visual analogue pain scale at coughing.

(VASC)	Group I		Group II		P
Follow up times	Mean±sd	Median (Min-Max)	Mean±sd	Median (Min-Max)	
30th min	2.8±2.1	2 (0-7)	4.2±2.0	4 (1-7)	0.019
1st hour	2.1±1.5	2 (0-5)	2.0 ±0.9	3 (1-4)	0.034
2nd hour	1.9±1.1	2 (0-4)	2.5 ±0.7	3 (1-3)	0.030
6th hour	1.7±1.1	2 (0-3)	2.4±1.0	3 (1-4)	0.033
12th hour	1.7±1.0	2 (0-3)	2.2±0.9	2 (1-3)	0.075
20th hour	1.7±1.1	2 (0-4)	2.1±1.4	2 (0-6)	0.512
24th hour	1.7±1.2	1 (0-4)	1.5±0.9	1 (0-4)	0.705
36th hour	1.5±1.1	1 (0-4)	1.2±1.0	1 (0-4)	0.403
48th hour	1.6±1.0	1 (0-3)	1.0±0.9	1 (0-3)	0.028
72th hour	1.4±0.9	1 (0-3)	0.7±0.7	1 (0-2)	0.006

Data presented as mean±Standard deviation and minimum-maximum.
TEA: Thoracic epidural analgesia; TPVB: Thoracic paravertebral block; VASC:Visual analogue pain scale at coughing.

20th hour	14.2 ±11.1	22.9±13.8	0.018*
24th hour	16.3±11.0	24.5±14.2	0.027*

*($p < 0.05$): The results were statistically significant between the groups. Data presented as mean + standart deviation. TEA: Thoracic epidural analgesia; TPVB: Thoracic paravertebral block; SD: Standard deviation

Hypotension and bradycardia, which were not significant, were more frequently observed in Group I ($p > 0.05$). One patient in Group I had nausea and vomiting while two had motor blockade. No itching and urinary retention were observed in both groups. When patients were evaluated in terms of ipsilateral shoulder pain 6 patients Group 1, and 2 patients in Group 2 had shoulder pain ($p > 0.05$).

DISCUSSION

The present study showed that bupivacaine infusion through the elastomeric infusion pump had better analgesic effects in TEA patients who underwent thoracotomy. However, the complication rate was lower in the TPVB group than the TEA group.

Effective treatment of acute post-thoracotomy pain is very important in terms of patient comfort and pulmonary functions (10,11). Atelectasis and pneumonia may develop due to difficulty in breathing and effective coughing, and the respiratory functions of the patient may deteriorate postoperatively. The protection of postoperative respiratory functions after thoracotomy is crucial to prevent potential complications (10-15). In a study comparing the effect of TEA and TPVB on pulmonary functions in patients with post-thoracotomy pain, spirometry values were better on the postoperative 72nd hour in the epidural group (16).

However, Richardson et al. (10) found that postoperative pain scores were significantly lower in patients with preoperative TPVB in thoracotomies and postoperative pulmonary functions were better preserved in these patients. Davies et al. (13) reported that respiratory functions in patients receiving paravertebral analgesia were statistically better at only 24 hours. Gülbahar et al. (17) reported no difference in postoperative respiratory function between the epidural and paravertebral groups in the study conducted in 44 patients who underwent thoracotomy. Respiratory functions were comparable in both groups preserved similarly in the postoperative period in the present study. This was also supported by the low requirement and usage of 24-hour morphine. Thus, impairment of pulmonary function due to the use of morphine in high doses was also avoided.

The efficacy of TPVB and TEA methods on hemodynamic parameters was investigated by many authors. Richardson et al. (14) found that hypotension was observed more frequently in the TEA group when compared to the TPVB method. Karmakar (18) stated that TPVB is a functional method because of the inhibition of neuroendocrine response to surgery by unilateral somatic and sympathetic block. Continuous TPVB administration is a part of balanced analgesia after thoracotomy and due to the lack of side effects; it may be a safe alternative to the TEA method which is considered the gold standard. Lönnqvist et al. (19) observed a 4.6% risk of hypotension due to TPVB catheterization in their trial investigating TPVB complications on 367 patients. In the present study even if hypotension was observed frequently in the TEA group, it was not significant. The high incidence of hypotension in the TEA group can be attributed to the TEA-dependent hemodynamic suppression due to the bilateral blockade of cardiac sympathetic fibers. Morphine and its derivatives are very effective in the treatment of severe pain due to thoracotomy. However, parenteral administration of opioids is known to cause undesirable effects such as respiratory depression, nausea, vomiting, decreased intestinal motility, and increased sphincter tone (20). Postoperative pulmonary

complications were reported to be 64% after parenteral opioid administration and 24% in the cases of epidural analgesia (21). Wu et al. compared the systemic and epidural administration of opioids. The epidural group had lower nausea, vomiting, and sedation scores than the IV opioid group. Nevertheless, complications such as itching, urinary retention, and motor block were more common in the epidural group. Although the mechanism of action was different, the incidence of nausea and vomiting in epidural and intrathecal opioid use was claimed to be similar to that of parenteral usage (22). Complications due to IV morphine administrated in the postoperative 24 hours were very limited in our study. Although morphine consumption was higher in the TPVB group in 24 hours, the average amount of morphine consumption in both groups was quite low. We think that low morphine consumption resulted from multimodal analgesia methods. We also did not encounter paracetamol and dexketoprofen-related adverse reactions in both groups.

Messina et al. (16) compared the efficacy of epidural and paravertebral block in patients undergoing thoracic surgery. They reported that postoperative IV rescue morphine use was underestimated and less morphine consumption was achieved in epidural block cases. Contrarily, Richardson et al. (14) assessed the efficacy of epidural block and TPVB in patients undergoing thoracotomy. Patients in the epidural group needed additional analgesics. Richardson et al. (10) showed that postoperative pain scores were significantly lower in the paravertebral group in another study comparing postoperative continuous epidural and TPVB methods after thoracotomy. In our study, morphine consumption was lower in the TEA group. Considering morphine requirement, effective analgesia was thought to be achieved TEA group.

Ipsilateral shoulder pain common complication in post-thoracotomy patients (23,24). While shoulder pain is often caused by diaphragm irritation due to surgical manipulation, inappropriate positioning of the patients during surgery can also cause shoulder pain. The non-steroid anti-inflammatory drugs administration, suprascapular block, intraoperative phrenic nerve block, or interscalene block might be used for the management of shoulder pain (23-25). In our study, shoulder pain was observed in eight out of 50 patients. Six of these patients were in the TEA group. We performed suprascapular block in patients with shoulder pain, and pain relief was provided to all patients.

Compared with the TEA and TPVB studies (2, 3, 10), the rate of side effects such as hypotension, nausea, vomiting, bradycardia, and motor block was within clinically acceptable limits in this study, and there was no statistically significant difference between the TEA and TPVB groups. Based on this result, we think that TEA is still a preferred method in terms of side effects, especially in patients with thoracotomy.

We have some limitations in this study. First of all the sample size of this study is small and results may need to be confirmed with a larger number of subjects. Even though we evaluate acute postoperative pain, the follow-up of chronic post-thoracotomy pain that may develop can give significant results in comparing TEA and TPVB. In our study, thoracic paravertebral catheter insertion was not performed under US guidance. However, the localization was confirmed using a nerve stimulator. In addition, since the procedure was performed while the patient was awake, the success of the block was evaluated with the pinprick test. The location of the catheter in the intraoperative period was also evaluated by direct observation.

CONCLUSION

Even if morphine consumption was within the clinically limits in both groups, patients who received TPVB needed more morphine doses to achieve sufficient analgesia. We think that TEA is a good alternative in thoracotomy with less morphine consumption and clinically acceptable incidence of side effects.

ETHICAL DECLARATION

Ethics Committee Approval: The study was initiated with the approval of the Keçiören Training and Research Hospital Ethics Committee (Date: 04.02.2013, Decision No: B.10.4.ISM.4.06.68.49/).

Informed Consent: All patients were informed about the application and their informed consent was obtained.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Mesbah A, Yeung J, Gao F. Pain after thoracotomy. BJA Education 2016; 16: 1-7.
2. Komatsu T, Sowa T, Takahashi K, Fujinaga T. Paravertebral block as a promising analgesic modality for managing post-thoracotomy pain. Ann Thorac Cardiovasc Surg 2014; 20: 113-6.

3. Júnior Ade P, Erdmann TR, Santos TV, et al. Comparison between continuous thoracic epidural and paravertebral blocks for postoperative analgesia in patients undergoing thoracotomy: Systematic review. Braz J Anesthesiol 2013; 63: 433-42.
4. Romero A, Garcia JE, Joshi GP. The state of the art in preventing postthoracotomy pain. Semin Thorac Cardiovasc Surg 2013; 25: 116-24.
5. Thompson C, French DG, Costache I. Pain management within an enhanced recovery program after thoracic surgery. J Thorac Dis 2018; 10: 3773-80.
6. Gerner P. Postthoracotomy pain management problems. Anesthesiol Clin 2008; 26: 355-67, vii.
7. Yokoyama Y, Nakagomi T, Shikata D, Goto T. Combined analgesic treatment of epidural and paravertebral block after thoracic surgery. J Thorac Dis 2017; 9: 1651-7.
8. Chin JWE, Valchanov K. Pharmacological management of post-thoracotomy pain. Open Med J 2016; 3: 255-64.
9. Mathews TJ, Churchhouse AM, Housden T, Dunning J. Does adding ketamine to morphine patient-controlled analgesia safely improve post-thoracotomy pain? Interact Cardiovasc Thorac Surg 2012; 14: 194-9.
10. Richardson J, Sabanathan S, Jones J, Shah RD, Cheema S, Mearns AJ. A prospective, randomized comparison of preoperative and continuous balanced epidural or paravertebral bupivacaine on post-thoracotomy pain, pulmonary function and stress responses. Br J Anaesth 1999; 83: 387-92.
11. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 2016; 17: 131-57.
12. Yeung JH, Gates S, Naidu BV, Wilson MJ, Gao Smith F. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. Cochrane Database Syst Rev 2016; 2: CD009121.
13. Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy--a systematic review and meta-analysis of randomized trials. Br J Anaesth 2006; 96: 418-26.
14. Richardson J, Cheema S. Thoracic paravertebral nerve block. Br J Anaesth 2006; 96: 537.
15. Alzahrani T. Pain relief following thoracic surgical procedures: A literature review of the uncommon techniques. Saudi J Anaesth 2017; 11: 327-31.
16. Messina M, Boroli F, Landoni G, et al S. A comparison of epidural vs. paravertebral blockade in thoracic surgery. Minerva Anestesiol 2009; 75: 616-21.
17. Gulbahar G, Kocer B, Muratli SN, et al. A comparison of epidural and paravertebral catheterisation techniques in post-thoracotomy pain management. Eur J Cardiothorac Surg 2010; 37: 467-72.
18. Karmakar MK. Thoracic paravertebral block. Anesthesiology 2001; 95: 771-80.
19. Lönnqvist PA, MacKenzie J, Soni AK, Conacher ID. Paravertebral blockade. Failure rate and complications. Anaesthesia 1995; 50: 813-5.
20. Cuschieri RJ, Morran CG, Howie JC, McArdle CS. Postoperative pain and pulmonary complications: comparison of three analgesic regimens. Br J Surg 1985; 72: 495-8.
21. Wu CL, Cohen SR, Richman JM, et al. Efficacy of postoperative patient-controlled and continuous infusion epidural analgesia versus intravenous patient-controlled analgesia with opioids: a meta-analysis. Anesthesiology 2005; 103: 1079-88; quiz 1109-10.
22. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984; 61: 276-310.
23. Blichfeldt-Eckhardt MR, Andersen C, Ørding H, Licht PB, Toft P. Shoulder Pain After thoracic surgery: type and time course, a prospective cohort study. J Cardiothorac Vasc Anesth 2017; 31: 147-51.
24. Burgess FW, Anderson DM, Colonna D, Sborov MJ, Cavanaugh DG. Ipsilateral shoulder pain following thoracic surgery. Anesthesiology 1993; 78: 365-8.
25. MacDougall P. Postthoracotomy shoulder pain: diagnosis and management. Curr Opin Anaesthesiol 2008; 21: 12-5.

Original Article

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The usability of shock index and lactate in predicting mortality in multitrauma patients presenting to the emergency department

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ABSTRACT

Objectives: This study was conducted to evaluate two simple and quickly assessed parameters such as shock index (SI) and lactate to predict in-hospital mortality in multi-trauma patients admitted to the emergency department (ED).

Material and Methods: The study included a total of 93 patients who presented to the ED with multitrauma. In our retrospective study, SI was calculated by taking blood pressure and pulse values from the files of the patients recorded at the time of admission to the ED, and lactate values obtained from blood gas were recorded. The results were compared with the in-hospital mortality rates after admission. SI ($p<0.001$) and lactate ($p<0.001$) values in patients discharged as exitus were significantly higher ($p<0.05$). The predictive diagnostic value of SI and lactate levels in terms of mortality in the patients included in the study was analyzed by using ROC curve analysis.

Results: The area under the ROC curve for SI was 0.738. The SI cut-off value for patients' mortality findings was 1.14. The area under the ROC curve for the lactate value was 0.941. The lactate cut-off value for mortality findings was 4.5.

Conclusion: In conclusion, SI and lactate values obtained at ED admission can be used to predict mortality in multitrauma patients.

Keywords: Multitrauma, Shock index, Lactate, Emergency Department, Mortality

INTRODUCTION

Trauma is a public health problem that causes serious economic and medical burdens worldwide (1). The arrival of trauma patients with serious injuries, the presence of many symptoms at the same time, and the rapid and variable progression of the disease pose the risk of death at any time. The three distinct death peaks occur within the first hour in approximately 50% of trauma patients, within the first 3 hours in approximately 30%, and within 1-4 weeks in approximately 15%. The first two death peaks with the highest rates occur in the crime scene and emergency department(ED), where the first few hours are spent in the early stage of trauma. Therefore, it is very important to predict early deaths quickly and to identify high-risk trauma patients to reduce the rate of trauma-related deaths. Activating the trauma team and preparing them for surgery as soon as necessary is of vital importance for the prevention of mortality.

The data that can be obtained in triage in the ED are vital parameters. The shock index (SI), which is the ratio of heart rate to systolic pressure, can be easily calculated based on vital signs and has proven to be a good predictor in clinical practice. A study has shown that a high SI value recorded in the ED increases the probability of both hospitalization and inpatient mortality in the general adult ED population (2). Some studies suggest the use of SI to predict the prognosis of trauma patients (3-5). The increase in SI in trauma patients mainly indicates acute hypovolemia and circulatory failure and is significantly associated with hospitalization, intensive care, mechanical ventilation, and the risk of mortality (6,3).

It has been reported that determining the treatment according to the early lactate value reduces mortality in critically ill patients (7). In addition, lactate has been reported as a useful prognostic indicator of occult hypoperfusion

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and a predictor of outcome in the acute care setting and following trauma (8,9). Serum lactate values are commonly used in the treatment of sepsis and trauma. Serial lactate measurements are also important during the treatment of these patients. As lactate has an estimated half-life of 20 minutes, the persistence of lactic acidosis may indicate a persistent hypoxic state. Serial lactate measurements may be useful in predicting sepsis and death in trauma patients, and lactate clearance (using serial lactate measurements) may provide data on the adequacy of resuscitation and prognosis for trauma patients (10,11).

Therefore, our study was conducted to evaluate simple, useful, and quick methods that can quickly predict mortality in multitrauma patients in the ED. In the study, we aimed to investigate the predictions of SI and lactate, which can be easily and quickly assessed in the ED, in detecting in-hospital mortality in multitrauma patients. Thus, we tried to contribute to early diagnosis and treatment planning with accurate triage in this patient group with a high mortality rate.

MATERIAL AND METHOD

This study was carried out by reviewing the files of multi-trauma patients aged 18 and over who visited Balıkesir University Medical Faculty Hospital between February 1, 2019 and December 1, 2021. Approval of the Balıkesir University Medical Faculty Clinical Researches Ethics Committee was obtained for the retrospective study (Decision date: 08.12.2021 and issue: 2021/265). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patients who were younger than 18 years of age, had non-traumatic organic pathologies in addition to trauma, or were referred to another hospital for any reason were not included in the study. In the study, patients' vital values (beats per minute (BPM), blood pressure (BP), lactate levels in blood gas) were obtained from archive records. Data were collected by trained researchers. SI score was calculated from vital parameters and recorded. The blood pressure values of all patients were evaluated with the Erka D.83646 Bad Tölz sphygmomanometer and blood gas values with epoc Reader 6246 device. Patients' age, gender, and final results (alive, exitus) during hospitalization were recorded. Patients whose data were not available in the records were excluded from the study.

Statistical Analysis

The SPSS (Statistical Package for the Social Sciences) 25.0 software package was used for the statistical analysis of the data. Categorical measurements were presented as numbers and percentages, and continuous measurements as mean and standard deviation values (median and minimum-maximum where appropriate). A chi-square test was used to compare categorical data. Shapiro-Wilk test was used to determine the normality of the parameters in the study. The independent samples t-test was used for normally distributed parameters, and the Mann Whitney U test was used for non-normally distributed parameters. The sensitivity and specificity values of SI and lactate values were calculated based on the mortality findings of the patients included in the study, and the cut-off value was determined by examining the area under the ROC curve. Statistical significance level was taken as $p<0.05$ in all tests.

RESULTS

Most of the patients admitted to the ED are caused by traffic accidents. The rates of admission to the ED and mortality are given in **Figure-1**.

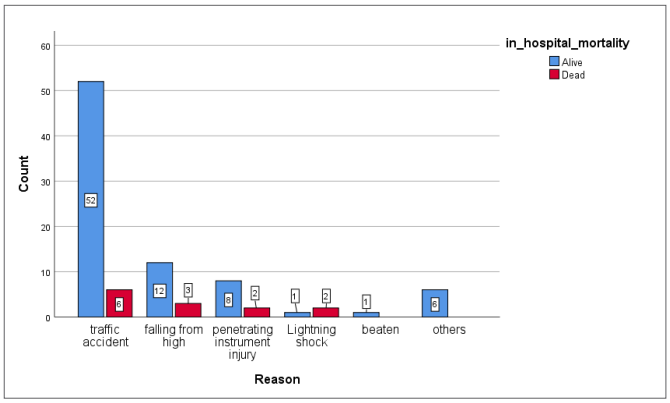

Figure-1: Causes of trauma and in-hospital mortality rates according to the cause

Demographic and basic characteristics of the patients are as in the table (**Table-1**). SI ($p<0.001$) and lactate level ($p<0.001$) findings were significantly higher in patients who were exitus ($p<0.05$). It was observed that the lactate level ($p<0.001$) and SI value ($p<0.001$) of the patients who were exitus were significantly higher than the patients who survived ($p<0.05$) (**Table-2**).

Table 1. Demographics and baseline characteristics of patients

	Alive (n=80) n(%)	Dead (n=13) n(%)	Total (n=93) n(%)
Gender			
Male	61 (76.3)	9 (69.2)	70 (75.3)
Female	19 (23.8)	4 (30.8)	23 (24.7)
Age	43.1±17.1 39 (20-89)	50.0±21.8 45 (22-81)	44.0±17.8 40 (20-89)
Pulse rate	92.3±17.9 92 (44-130)	112.9±16.4 115 (67-132)	95.2±19.1 95 (44-132)
Systolic pressure	121.8±23.8 120 (60-185)	112.5±31.8 100 (70-166)	120.5±25.1 120 (60-185)
Diastolic pressure	74.0±14.8 70 (40-118)	71.5±18.3 70 (50-109)	73.7±15.3 70 (40-118)
Lactate level	2.37±1.3 2.4 (0.5-6.6)	8.95±3.5 8.7 (1.2-14.2)	3.29±2.9 2.4 (0.5-14.2)

Data given as *mean±standard deviation, &median (minimum-maximum) or #n (%)

Table 2: Comparison of patient characteristics in terms of in-hospital mortality

	Alive (n=80)	Dead (n=13)	Total (n=93)	p
	n(%)	n(%)	n(%)	
Shock Index (SI)				
Low	72 (90)	6 (46,2)	78 (83,9)	<0,001
High	8 (10)	7 (53,8)	15 (16,1)	
Lactate Level				
Low	77 (96,3)	1 (7,7)	78 (83,9)	<0,001
High	3 (3,8)	12 (92,3)	15 (16,1)	
Lactate level	2,37±1,3 2,4 (0,5-6,6)	8,95±3,5 8,7 (1,2-14,2)	3,29±2,9 2,4 (0,5-14,2)	<0,001
Shock Index (SI)	0,79±0,25 0,74 (0,34-1,67)	1,08±0,36 1,2 (0,64-1,86)	0,83±0,28 0,76 (0,34-1,86)	<0,001

The predictive diagnostic value of SI and lactate levels in terms of mortality in the patients included in the study was evaluated by the ROC curve analysis. The area under the ROC curve for SI was 0.738 (95% confidence interval (CI): 0.637-0.824; p=0.002). The SI cut-off value for patients' mortality findings was 1.14 (specific: 53.85%, 95% CI: 25.1-80.8, sensitive: 91.25%, 95% CI: 82.8-96.4). The area under the ROC curve for lactate was 0.941 (95% CI: 0.873-0.979; p<0.001). The lactate cut-off (threshold) value for mortality findings was 4.5 (specificity: 92.31%, 95% CI: 64.0-99.8, sensitivity: 96.25%, 95% CI: 89.4-99.2) (**Table-3, Figure-2, Figure-3**).

Table 3. ROC curve analysis results for SI and lactate

	Shock Index (SI)	Lactate Level
AUC	0.738	0.941
95%-Cl (%)	0.637-0.824	0.873-0.979
Cut-off	>1.14	>4.5
Specificity	53.85	92.31
95%-Cl (%)	25.1-80.8	64.0-99.8
Sensitivity (%)	91.25	96.25
95%-Cl (%)	82.8-96.4	89.4-99.2
p	0.002	<0.001

AUC: Area under the curve, CI: Confidence interval

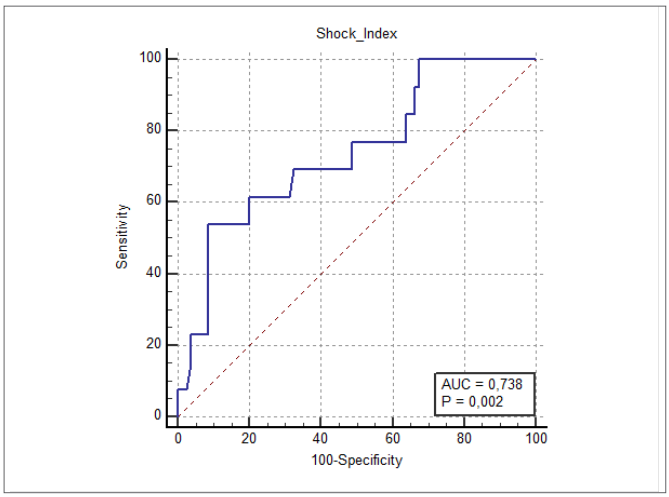

Figure-2: ROC curves of SI for hospital mortality

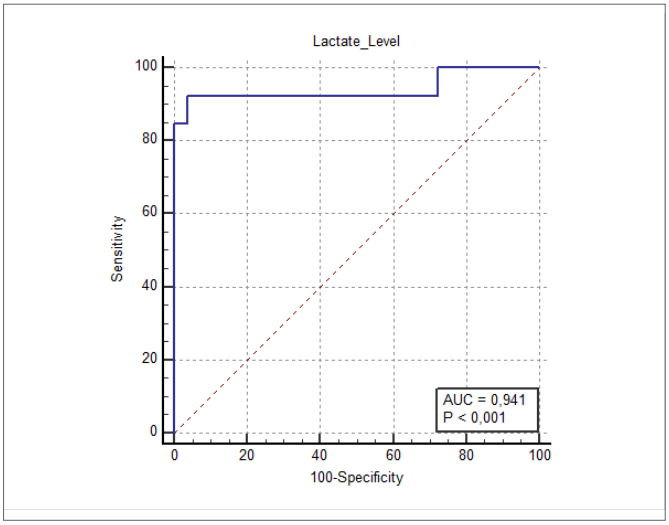

Figure-2: ROC curves of SI for hospital mortality

DISCUSSION

Our study defined the use of SI and lactate as an independent predictor of mortality in multitrauma patients in the ED. The use of SI and lactate may be considered as a good choice for the assessment and triage of the severity of multitrauma patients in the ED.

The SI is a classical indicator that is more sensitive than traditional vital signs for assessing shock. Numerous studies have been conducted on the practical value of SI in trauma patients in recent years. A retrospective cohort study of 16269 trauma patients elucidated the relationship between prehospital SI and hospital stay, length of stay in intensive care and mechanical ventilation, and the use of blood products. It has been shown that patients with an SI value of > 0.9 have a higher risk of transfer to the intensive care unit, emergency surgery, or death (3). A study of 1419 patients indicated that after fluid resuscitation with 1 liter of crystalloid, patients with a high SI value had a higher blood transfusion demand, higher mortality, and worse outcomes (12). This result was also confirmed by a study showing that there would be a significant increase in mortality if the SI did not improve within six hours (13). One study reported that an abnormally elevated SI measured at any time indicated that trauma patients had a higher risk of death within 28 days (14). Charlie et al. (15) reported that an SI value of >0.9 predicted a worse prognosis after trauma. All of these studies highlight the finding of a statistically significant association between SI and mortality in trauma patients. In our study, SI>1.14 was found to be significant in terms of predicting mortality in multitrauma patients. The use of SI as an indicator of severity and poor prognosis in trauma patients is indisputable, and abnormally high levels often indicate a worse outcome in trauma patients. However, in our study, it was evaluated to determine in-hospital mortality, not premature death at the time of stay in the ED.

Lactate has been shown to be a prognostic biomarker in trauma, even in patients with normal vital signs (16,17). This relationship has been confirmed in experimental studies (18,19). High blood lactate levels have been demonstrated in all types of shock (20). Alcohol or drug use, which is frequently encountered in trauma patients, does not change the estimation accuracy of baseline blood lactate levels (21). In our study, we observed that in-hospital mortality increased in multitrauma patients with a lactate value of >4.5. Also, in our study, in-hospital mortality was evaluated, not early mortality in the ED.

CONCLUSION

When SI and lactate parameters were used separately at the first admission to the hospital for a condition with high mortality such as multitrauma, it was observed that they predicted mortality significantly. We argue that early examination of these parameters in multitrauma patients admitted to the ED can determine the severity of the condition and may guide the patient management.

Limitations

Our study is retrospective, and it was conducted with a limited number of patients in a single center. We think that it is necessary to support our results with multicenter studies to be conducted with a larger patient population.

ETHICAL DECLARATIONS

Ethics committee approval: The study was approved by Ethics Committee of Balıkesir University Faculty of Medicine and was conducted in accordance with the principles of the Declaration of Helsinki (Decision date: December 8, 2021 and Issue: 2021/265).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

REFERENCES

1. Jin WYY, Jeong JH, Kim DH, et al. Factors predicting the early mortality of trauma patients. Ulusal Travma Ve Acil Cerrahi Dergisi-Turkish Journal of Trauma & Emergency Surgery 2018; 24: 532-8.
2. Balhara KS, Hsieh Y-H, Hamade B, Circh R, Kelen GD, Bayram JD. Clinical metrics in emergency medicine: the shock index and the probability of hospital admission and inpatient mortality. Emergency Medicine Journal 2017; 34: 89-94.
3. McNab A, Burns B, Bhullar I, Chesire D, Kerwin A. A prehospital shock index for trauma correlates with measures of hospital resource use and mortality. Surgery 2012; 152: 473-6.
4. McNab A, Burns B, Bhullar I, Chesire D, Kerwin A. An analysis of shock index as a correlate for outcomes in trauma by age group. Surgery 2013; 154: 384-7.
5. Singh A, Ali S, Agarwal A, Srivastava RN. Correlation of shock index and modified shock index with the outcome of adult trauma patients: a prospective study of 9860 patients. North American journal of medical sciences 2014; 6: 450-2.
6. Mutschler M, Nienaber U, Muenzberg M, et al. The Shock Index revisited—a fast guide to transfusion requirement? A retrospective analysis on 21,853 patients derived from the TraumaRegister DGU (R). Critical Care 2013; 17.
7. Jansen TC, van Bommel J, Schoonderbeek FJ, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med 2010; 182: 752-61.
8. Kjelland CB, Djogovic D. The role of serum lactate in the acute care setting. J Intensive Care Med 2010; 25: 286-300.
9. Uzoigwe CE, Venkatesan M, Smith R, et al. Serum lactate is a prognostic indicator in patients with hip fracture. Hip Int 2012; 22: 580-4.
10. Dübendorfer C, Billeter AT, Seifert B, Keel M, Turina M. Serial lactate and admission SOFA scores in trauma: an analysis of predictive value in 724 patients with and without traumatic brain injury. Eur J Trauma Emerg Surg 2013; 39: 25-34.
11. Régnier MA, Raux M, Le Manach Y, et al. Prognostic significance of blood lactate and lactate clearance in trauma patients. Anesthesiology 2012; 117: 1276-88.
12. Mitra B, Fitzgerald M, Chan J. The utility of a shock index > = 1 as an indication for pre-hospital oxygen carrier administration in major trauma. Injury-International Journal of the Care of the Injured 2014; 45: 61-5.
13. Cortés-Samacá CA, Meléndez-Flórez HJ, Álvarez Robles S, Meléndez-Gómez EA, Puche-Cogollo CA, Mayorga-Anaya HJ. Base deficit, lactate clearance, and shock index as predictors of morbidity and mortality in multiple-trauma patients. Revista Colombiana de Anestesiología 2018; 46: 208-15.
14. Sloan EP, Koenigsberg M, Clark JM, Weir WB, Philbin N. Shock index and prediction of traumatic hemorrhagic shock 28-day mortality: data from the DCLHb resuscitation clinical trials. The western journal of emergency medicine 2014; 15: 795-802.
15. Charry JD, Bermeo JM, Montoya KF, Calle-Toro JS, Núñez LR, Poveda G. Shock index as predictor of mortality in patients with penetrating trauma of the thorax Índice de shock como factor predictor de mortalidad en el paciente con trauma penetrante de tórax. Revista Colombiana de Cirugía 2015; 30: 24-8.
16. Claridge JA, Crabtree TD, Pelletier SJ, Butler K, Sawyer RG, Young JS. Persistent occult hypoperfusion is associated with a significant increase in infection rate and mortality in major trauma patients. J Trauma 2000; 48: 8-14
17. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg.1996; 171: 221-6
18. Rixen D, Raum M, Holzgraefe B, Sauerland S, Nagelschmidt M, Neugebauer EA. Shock and Trauma Study Group. A pig hemorrhagic shock model: Oxygen debt and metabolic acidemia as indicators of severity. Shock 2001; 16: 239-44

19. Hobbs TR, O'Malley JP, Khouangsathiene S, Dubay CJ. Comparison of lactate, base excess, bicarbonate, and pH as predictors of mortality after severe trauma in rhesus macaques (Macaca mulatta). Comp Med 2010; 60: 233-9

20. Revelly JP, Tappy L, Martinez A, et al. Lactate and glucose metabolism in severe sepsis and cardiogenic shock. Crit Care Med 2005; 33: 2235-40

21. Dunne JR, Tracy JK, Scalea TM, Napolitano LM. Lactate and base deficit in trauma: Does alcohol or drug use impair their predictive accuracy? J Trauma 2005; 58: 959-66

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Evaluation of arterial blood gases of patients with type 1-2 respiratory failure diagnosed in intensive care using the quantitative Stewart method

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ABSTRACT

Introduction: Arterial blood gases are tests that provide reliable information about the metabolic and respiratory status of patients. In traditional methods, arterial blood gases are evaluated by calculating the bicarbonate concentration and anion gap in the plasma. Since ICU patients almost always have protein and electrolyte disorders, a different method has been suggested instead of the traditional method that neglects electrolyte and protein in the evaluation. In the mathematical model described by Stewart and modified by Figge et al., 4 types of respiratory failure were defined according to their pathophysiology: hypoxemic (type 1), hypercapnic (type 2), perioperative (type 3), and hypoperfusion-induced respiratory failure in shock patients (type 4). The study aims to evaluate the arterial blood gases of intensive care patients with type 1 and type 2 respiratory failure with the Stewart method and compare them with the traditional method.

Material and Method: In the study, serum BUN (blood urea nitrogen), creatinine, glucose, sodium, chlorine, serum BUN (blood urea nitrogen) of 106 patients diagnosed with type 1-2 respiratory failure. Together with potassium, magnesium, albumin values, pH, pCO_2, pO_2, HCO_3, base deficit, and lactate values studied in arterial blood gas sample were determined and evaluated according to the Stewart method.

Results: The length of stay of the patients in the intensive care unit was determined as 17.48±10.58 (minimum 6-maximum 68) days. It was determined that 74 (69.8%) of the patients were discharged and 32 (30.2%) died. When the blood gases and laboratory values of the patients were compared according to the clinical outcomes of the patients, no statistically significant correlation was found between the patients' mean pH, pCO_2, HCO_3, base deficit, pO_2, albumin, lactate, creatinine, glucose, potassium, and chlorine values and the patients' discharge or death. BUN values of patients who died were found to be higher than those who were discharged. A statistically significant difference was found between the development of hypoalbuminemia and the length of stay in the intensive care unit. It has been determined that the treatment costs of patients with severe hypoalbuminemia are higher than other patients. The length of stay in the intensive care unit of the patients who did not develop acidosis was found to be statistically significantly lower than the patients who developed metabolic and respiratory acidosis.

Conclusion: While a significant relationship was found between albumin levels, which has an important place in the Stewart method, and the length of stay in the intensive care unit, no relationship was found between albumin levels or lactate levels and mortality. However, increased BUN values were associated with mortality. As the albumin value decreases in patients with hypoalbuminemia, treatment costs increase. There is a need for larger multicenter studies with a larger sample group that will evaluate metabolic status with the Stewart method and investigate its relationship with mortality.

Keywords: Arterial blood gas, respiratory failure, Stewart method

INTRODUCTION

Respiratory failure is a syndrome characterized by the deterioration in the ability of the respiratory system to maintain its functions. and the inability of the tissues to provide oxygen (O_2) or to remove carbon dioxide (CO_2) to meet their needs (1). Many diseases can cause respiratory failure with different physio pathological mechanisms. Most of the patients who develop respiratory failure require treatment in the intensive care unit (2,3).

Units. where unstable patients who require intensive treatment and observation are accepted. are intensive care units. Most of the patients followed in the intensive care unit (ICU) have respiratory failure due to infection or inflammation such as pneumonia, acute respiratory

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distress syndrome (ARDS) (2,3). In most cases of respiratory failure, hypercapnia, hypoxia, apnea, and related complications are observed. Therefore, respiratory support treatments are needed and used (4).

Data on the incidence of respiratory failure in the ICU are insufficient. According to the results of studies conducted in Europe, the frequency of patients treated with mechanical ventilation for more than 24 hours in ICUs is estimated to be 77.6-88.6/100000 years (5). In the USA, the prevalence of respiratory failure was found to be 137/100000 years, and its incidence was 360000/year (6).

Respiratory failures can be classified under three headings according to their clinic, onset time, and pathophysiology. According to his clinic; It can be subdivided into hypoxemic, hypercapnic, and combined respiratory failure. According to the onset time, acute respiratory failure can be grouped as acute, chronic, and chronic. According to its pathophysiology, four types of respiratory failure can be defined, Type 1; hypoxemic respiratory failure, Type 2; hypercapnic respiratory failure, Type 3; perioperative respiratory failure, and Type 4 is defined as respiratory failure due to hypoperfusion developing in patients in shock (1).

Arterial blood gas is one of the important laboratory methods that provide reliable information about the metabolic and respiratory status of patients. Arterial blood gas analysis is performed using blood gas measurement devices. With these devices, pH, partial carbon dioxide pressure, partial oxygen pressure is measured using electrodes; bicarbonate, oxygen saturation, and base deficit are calculated. Metabolic acidosis is one of the acid-base disorders that we see frequently in intensive care units (7).

Patients with severe sepsis or septic shock admitted to the intensive care unit present a wide spectrum of acid-base disturbances, the most common being metabolic acidosis. The presence of metabolic acidosis is associated with higher morbidity and mortality in the intensive care unit (8).

In general, acid-base disturbances are analyzed according to conventional methods that include the determination of base excess, bicarbonate concentration in plasma, and anion gap. When an only simple acid-base disturbance is present. the conventional method is sufficient. However, it does not give detailed information about the source of the problem. The calculation of base deficiency is a calculated figure that assumes normal plasma protein and electrolyte contents and ignores the role of non-bicarbonate buffers in the blood. Therefore, the conventional interpretation can be clinically misleading, as electrolyte or protein abnormalities are almost always present in ICU patients. An alternative to this traditional model is the mathematical model based on physicochemical principles described by Stewart and modified by Figge et al. (8,9).

This study aims to create a different perspective in the follow-up and treatment of patients by evaluating acid-base disorders with Stewart analysis in the patient population with respiratory failure hospitalized in the intensive care unit.

MATERIAL AND METHOD

Ethical approved this study by Ethics Committee of Atatürk Sanatoryum Training and Research Hospital (Date: 13.09.2019, Decision No: 1953). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration. This study was conducted by evaluating the arterial blood gases of 106 patients diagnosed with type 1-2 respiratory failure between January 2019 and August 2019. Serum BUN, creatinine, glucose, sodium, chlorine, potassium, magnesium, albumin values of the patients as well as pH, pCO_2, pO_2, HCO_3, base deficit, and lactate levels studied in arterial blood samples were evaluated. ABG evaluation was made using the Stewart method on the website www.acidbase.org, and an interface that was standardized and turned into a 'calculator' was used.

In our study, patients' arterial blood gases, lactate, BUN, creatinine, glucose, sodium, chlorine, potassium, magnesium, albumin values, additional diseases, length of stay in the intensive care unit, treatment costs were recorded retrospectively, and those who were discharged from the intensive care unit and those who died while in the intensive care unit, was also recorded. The relationship between arterial blood gases evaluated by the Stewart method and other parameters was evaluated.

Inclusion criteria in the study;

- Intensive care patients diagnosed with type 1-2 respiratory failure
- Patients with respiratory failure hospitalized directly from the emergency department
- Patients who were transferred to chest intensive care from any service or a higher-level intensive care unit

Exclusion criteria from the study;

- Patients with missing data
- Intensive care patients other than respiratory failure

Statistical Analysis

In our study, the data were evaluated in the IBM SPSS Statistics 22.0 statistical package program. As descriptive statistics. the number of units (n), percent (%), mean±standard deviation (x±ss), and median values are

given. The normal distribution of the data of numerical variables was evaluated with Shapiro Wilk. normality test. and Q-Q charts. Mann-Whitney U and Kruskal Wallis analyses were used to compare the groups. Spearman correlation analysis was used to determine the relationship between two numerical values. A $p<0.05$ value will be considered significant in statistical analysis.

RESULTS

The patients included in the study, 63 (59.4%) were male and 43 (40.6%) were female. The mean age of the patients was 70.36±10.5 (minimum 49- maximum 90) years. The mean age of women was 73.60±9.94 years, and the mean age of men was 68.14±10.37 years; the mean age of women was statistically significant and higher than the mean age of men (**Table 1**).

Table 1. Age distribution by gender

	Mean±Standard Deviation	Median	z	p
Female	73.60±9.94	74.00	-2.476	0.013
Male	68.14±10.37	67.00		
Age (total)	70.36±10.5	69.50		

The mean values of arterial blood gases (pH, pCO_2, HCO_3, BE, pO_2, Lactate), BUN, creatinine, glucose, albumin, sodium, potassium, magnesium, chlorine of the patients is given in **Table 2**.

Table 2. Mean blood gas and blood biochemistry values of the patients

	Mean±Standard Deviation	Median	Min.-Max.
pH	7.40±0.61	7.40	(7.29-7.57)
pCO_2	57.2±14.62	56.10	s(29.4-94)
HCO_3	33.95±7.59	33.65	(15.9-60.7)
BE	7.78±6.23	7.20	(-5.4-30.7)
pO_2	61.99±24.72	57.15	(25.7-192.8)
Lactate	1.2±0.66	1.01	(0.02-3.56)
BUN	24.68±15.49	20.50	(8-86)
Creatinin	0.9±0.44	.80	(0.43-3.78)
Glucose	132.76±67.08	113.00	(54-446)
Albumin	29.86±4.68	29.60	(18.3-40.8)
Sodium	139.91±4.36	141.00	(123-152)
Potassium	4.23±0.67	4.26	(2.7-6.19)
Magnesium	1.92±0.31	1.90	(1.2-2.6)
Chlorine	96.03±5.73	97.00	(80-111)

Min: minimum. Max: maximum BUN: Blood Urea Nitrogen

It was determined that 74 (69.8%) of the patients were discharged and 32 (30.2%) died. A statistically significant difference was found between BUN values according to the clinical outcome (death-discharge). The BUN value of the group that died was found to be higher than the group that survived (**Table 3**).

Table 3. Mean blood gas values according to the clinical outcome of the patients

	Discharged		Death		
	Mean±std deviation	Median	Mean±std deviation	Median	P
pH	7.4±0.1	7.4	250.9±1.333.8	7.4	0.647
pCO_2	57.2±15.8	55.1	57.1±11.7	57.1	0.915
HCO_3	34±8.1	33.7	33.9±6.4	33.9	0.736
BE	7.6±6.6	7.2	8.3±5.4	8.0	0.384
pO_2	62.1±25.1	57.4	61.7±24.2	53.5	0.836
Lactate	1.2±0.7	1.0	1.1±0.5	1.1	0.818
BUN	22.9±14.1	19.0	28.8±17.8	24.5	0.035
Creatinine	0.9±0.5	0.8	0.9±0.4	0.9	0.318
Glucose	127.3±50.2	114.5	145.4±95.2	105.5	0.853
Albumin	30.2±4.5	30.1	29±5.1	29.1	0.224
Sodium	139.7±4.3	141.0	140.4±4.6	141.0	0.174
Potassium	4.2±0.6	4.2	4.3±0.8	4.3	0.445
Magnesium	1.9±0.3	1.9	1.9±0.3	1.9	0.718
Chlorine	95.9±6	97.0	96.3±5.1	97.0	0.548

The comorbidities of the patients were examined. it was determined that 96 (89.7%) of them were COPD, 48 (44.8%) were hypertension, 28 (26.1%) were heart failure. Other additional diseases are given in **Table 4**.

Table 4. Additional Diseases of the Patients

		n(%)
Additional Disease	Chronic obstructive pulmonary disease	96 (89.7)
	Hypertension	48 (44.8)
	Heart failure	28 (26.1)
	Diabetes mellitus	27 (25.2)
	Coronary artery disease	16 (14.9)
	Pulmonary thromboembolism	9 (8.4)
	Pneumonia	9 (8.4)
	Chronic kidney disease	5(4.6)

A moderate and negative correlation was found between pH value and pCO_2 and potassium ($p=-0.557$ $p=-0.409$, respectively). A weak and negative correlation was found between pCO_2 and lactate, creatinine and chlorine ($p=-0.391$ $p=-0.201$ $p=-0.328$, respectively). There was a weak positive correlation between pCO_2 and sodium ($p=0.336$). and a good and positive correlation between pCO_2 and bicarbonate ($p=0.773$). A weak and negative correlation was found between pO_2, albumin, and potassium ($p=0.277$. $p=0.279$. respectively). There was a weak and negative correlation between HCO_3, lactate, and creatinine ($p=-0.394$. $p=-0.270$, respectively), and a moderate negative correlation between HCO_3 and chlorine ($p=-0.565$). There was a weak and negative correlation between albumin and BUN ($p=-0.232$), and a weak and positive correlation between albumin and potassium ($p=0.293$) (**Table 5**).

Table 5. Correlations of pH. pCO_2. pO_2. HCO_3. Lactate. Albumin values

	Ph	pCO_2	pO_2	HCO_3	Lactate	Albumin
pH	-					
pCO_2	-0.557**	-				
pO_2	-0.081	-0.031	-			
HCO_3	-0.173	0.773**	-0.150	-		
Lactate	0.209*	-0.391**	0.057	-0.394**	-	
Albumin	-0.110	-0.184	0.277**	-0.212*	0.187	-
BUN	-0.102	-0.005	-0.068	-0.116	0.054	-0.232*
Creatinine	0.013	-0.201*	-0.052	-0.270**	-0.016	-0.014
Na	-0.090	0.336**	0.037	0.342**	-0.179	-0.123
K	-0.409**	0.095	0.279**	-0.184	0.139	0.293**
Mg	-0.012	0.020	0.165	-0.041	0.031	-0.005
Cl	-0.083	-0.328**	0.020	-0.565**	0.089	-0.022

*p<0.005, **p<0.01

A statistically significant difference was found between the development of acidosis in the patients and the treatment costs (p=0.038). The cost of treatment of patients who did not develop acidosis was found to be statistically significant and lower than patients who developed metabolic and respiratory acidosis. A statistically significant correlation was found between hypoalbuminemia in patients and treatment costs (p=0.005). The patients with hypoalbuminemia were evaluated as mild-moderate-severe, a statistically significant relationship was found between the severity of hypoalbuminemia and the cost of treatment, In the post-hoc test performed to find the group that made the significant difference, the patient group with severe hypoalbuminemia (serum albumin value < 15 g/L) was found to have higher treatment costs than the other groups (p=0.005). Treatment costs increase significantly as albumin levels decrease in patients with hypoalbuminemia (**Table 6**).

The mean length of stay of the patients in the intensive care unit was determined as 17.48±10.58 (minimum 6-maximum 68) days.

Table 6. Comparison of metabolic status and treatment costs

	Mean	Median	p*	p**	
Acidosis	None	10119.08± 8.587.21	5.428.00	0.691	0.038
	Metabolic	15089.47± 9.515.71	12.760.00		
	Respiratory	15840.21± 9.146.63	13.196.00		
Alkalosis	None	13874.2± 15.015.89	8.216.00	0.443	0.459
	Metabolic	15050.12± 9.198.01	12.641.50		
	Respiratory	15548.4± 2.469.89	15.668.00		
Albumin	None	18.985.00± 11.646.83	15.346.00	0.005	<0.001
	mild hypoalbuminemia	13.034.43± 8.571.62	10.424.00		
	moderate hypoalbuminemia	16.530.50± 8.003.92	15.120.00		
	severe hypoalbuminemia	37.912.00± 2.081.72	37.912.00		

*Mann Whitney U. **Kruskall Wallis

A statistically significant difference was found between the development of acidosis and the length of stay in the intensive care unit. A statistically significant difference was found between the development of hypoalbuminemia and the length of stay in the intensive care unit (p=0.009). The patients who developed hypoalbuminemia were evaluated within themselves, a statistically significant relationship was found between the severity of hypoalbuminemia and the length of stay in the intensive care unit. In the post-hoc test performed to find the group that made the significant difference, it was determined that the patient group with severe hypoalbuminemia (serum albumin value < 15 g/L) had longer intensive care unit stays than the other groups (p=0.009) (**Table 7**).

Table 7. Comparison of metabolic status and length of stay in intensive care unit

	Mean	Median	p*	p**	
Acidosis	None	12.08±11841	10.00	0.357	0.040
	Metabolic	16.59±15980	14.00		
	Respiratory	18.61±36434	15.00		
Alkalosis	None	16.6±12359	15.00	0.962	0.919
	Metabolic	17.65±30956	15.00		
	Respiratory	15.2±30376	16.00		
Albumin	None	17.43±9.96	16.00	0.009	<0.001
	mild hypoalbuminemia	15.44±8.9	12.00		
	moderate hypoalbuminemia	19.21±9.47	19.50		
	severe hypoalbuminemia	52.5±21.92	52.50		

*Mann Whitney U. **Kruskall Wallis

No statistically significant correlation was found between the metabolic status of the patients (acidosis, alkalosis, hypoalbuminemia) and their clinical outcomes (**Table 8**).

Table 8. Comparison of metabolic status and clinical outcome

		Discharged n(%)	Deathn(%)	p
Acidosis	None	9(69.23)	4(30.77)	0.843*
	Metabolic	13(76.47)	4(23.53)	
	Respiratory	52(68.42)	24(31.58)	
Alkalosis	None	4(80)	1(20)	0.237**
	Metabolic	65(67.71)	31(32.29)	
	Respiratory	5(100)	0(0)	
Albumin	None	5(71.43)	2(28.57)	0.458**
	mild hypoalbuminemia	47(74.6)	16(25.4)	
	moderate hypoalbuminemia	21(61.76)	13(38.24)	
	severe hypoalbuminemia	1(50)	1(50)	

*Chi-square test. **Fisher's Exact Test

DISCUSSION

A change in patients' pH indicates that there must be a change in one of the independent variables (strong anion and cation) and cannot simply be explained by the influx of hydrogen ions or bicarbonate into body fluids (10). An

analysis of the complex acid/base disturbances commonly seen in critically ill patients can be performed using the approach that includes weak acids (10). The moderate-negative correlation between pH value and pCO_2 and potassium in our study supports this approach.

In a study conducted in respiratory intensive care patients at Trakya University, it was reported that 43% of the patients had COPD, 36% had severe pneumonia/sepsis + multi-organ failure, 7% had a massive pulmonary embolism, and 5% had acute respiratory distress syndrome. In this study, mortality rates were reported as 32% (11). In Çanakkale in 2014, 19% of the primary care intensive care patients had COPD, 8% had diabetes mellitus, 23% had hypertension, 9% had coronary artery disease, 14% had congestive heart failure, and 9% had chronic kidney disease co-diagnoses (12). Between 2014 and 2016, the diagnosis of hypertension (61%), coronary artery disease (27%), diabetes mellitus (27%). Alzheimer's 25%, 23% congestive heart failure, 20% previous CVA in the intensive care unit patients of sepsis patients in Ankara was available (13). In our study, 89% of the patients had COPD, 45% had hypertension, 26% had heart failure, 25% had diabetes mellitus, 15% had coronary artery disease, and 8% had pulmonary thromboembolism. Although the general rates vary, comorbid conditions are similar in the admission of patients to the intensive care unit or among the patients admitted to the intensive care unit.

In the study of Uçgun et al. (14), it was emphasized that there was no significant difference between the mean pH values of patients who survived in the intensive care unit (pH=7.2±0.6) and the pH values of patients who lost their lives. In another study, it was reported that there was no statistically significant relationship between pH values of patients who died and survived (11). In our study, the mean pH value was found to be 7.4±0.1 in patients who survived and died. The difference between the pH values found in the study of Uçgun et al. and our study may be due to the effect of differences in patient profiles on metabolic conditions (such as cancer cases). The fact that the pH values of the deceased and surviving patients were the same suggested that metabolic disorders may not be the main cause. even if metabolic processes were effective in the death of the patients.

In a study conducted in intensive care patients in China (n: 1003), it was emphasized that the albumin value was statistically higher in surviving intensive care patients (15). In a study examining the relationship between albumin values and mortality in intensive care trauma patients (n:200), a significant relationship was found between albumin and mortality. It was reported that the albumin values of the patients who died were found to be lower (16). In a study conducted in the respiratory intensive care unit of Trakya University, it was reported that albumin values were found to be lower in deceased patients than in surviving patients (11). In our study, the mean albumin value of the surviving patients was 30.2±4.5, while the mean albumin value of the deceased patients was 29±5.1. No statistically significant difference was found between the two groups. While albumin values were associated with mortality in trauma patients, it was thought not to be associated with mortality in respiratory intensive care patients. In our study, no relationship was found between albumin value and clinical outcome. In our study, a statistically significant relationship was found between albumin and the length of stay in the intensive care unit. Patients with severe hypoalbuminemia were found to have longer intensive care unit stays. Due to albumin being a negative acute phase reactant, as the amount of inflammation in the patient increases, the albumin value may decrease and the length of stay in the intensive care unit may be prolonged. Or, depending on the severity of the metabolic events in the patient, the albumin value may have decreased and these metabolic events may have prolonged the intensive care unit stay of the patient.

In a study examining the relationship between lactate levels and mortality in 200 trauma patients in the intensive care unit, a significant relationship was found between lactate and mortality. It was reported that the lactate values of patients who died were found to be higher (14). In our study, no significant difference was found between the lactate values of the patients who survived and those who died. The reason why lactate values, which were not included in the Hasselbach calculation method and were included in the SID calculation, were not found to be statistically significant in our study may be due to the fact that patients with metabolic problems. such as kidney failure and severe traumas, were not included in our study. Conditions and diseases in which lactate is elevated are well known. In the foreground, sepsis is one of the most important causes of lactic acidosis. Apart from this, inotropic infusion, metformin toxication, diseases causing peripheral circulatory disorders, etc. conditions such as can increase lactate. Since all of these conditions require 3rd level intensive care treatment, it may be natural that lactate does not make a significant difference in terms of mortality in the 2nd level respiratory intensive care unit where the study was conducted.

In a study by Uçgun et al. (14) it was stated that there was no significant difference between the mean PO_2 and PCO_2 values of surviving patients when compared to the values of deceased patients. In a study conducted in the respiratory intensive care unit, it was reported that no significant correlation was found between PaO_2 and $PaCO_2$ values in patients who died and survived (11). Similar to the literature, in our study, no significant

difference was found between the mean $PaCO_2$ and PaO_2 values of the discharged and deceased patients.

In a study by Uçgun et al. (14), it was stated that there was no significant difference between the mean leukocyte, hematocrit, thrombocyte, glucose, Na, K, albumin values of the patients who survived in the intensive care unit and the laboratory values of the patients who died. In the same study, it was emphasized that the mean pH and HCO_3 values of surviving patients were statistically lower than those of deceased patients. It was emphasized that the mean BUN and LDH values of the surviving patients were statistically lower than those of the deceased patients. In our study, no difference was found between discharged and deceased patients in the HCO_3, BE, lactate, creatinine, glucose, albumin, sodium, potassium, magnesium, chlorine values of the patients. BUN values of the patients who died were found to be significantly higher than those of the patients who survived. BUN values were thought to be more successful than other laboratory values in predicting the probability of mortality in patients.

In our study. the average length of stay in the intensive care unit was found to be 17 days.

In the study of Bıyıklı et al. (13), the 30-day mortality rate of intensive care patients was reported as 45%. In this study, it was reported that age, lactate, and SpO_2 did not affect 30-day mortality.

Mortality rates were found to be 40% in male patients and 45% in females in patients with acute respiratory failure followed in the intensive care unit (n:508) in Berlin (17). In our study, mortality rates in patients with respiratory failure followed in the intensive care unit were found to be 35% in male patients and 25% in female patients. These data show that the mortality rate is close to each other in both genders.

In a study conducted in Shanghai, the 30-day mortality of intensive care patients diagnosed with sepsis-associated pneumonia was reported as 33%(18). The rate of patients followed up with pneumonia in our study was 9% of the patients included in the study, and all of the patients were discharged, no mortality was detected. Due to the insufficient number of patients with pneumonia, it may be misleading to state the mortality rate in patients with pneumonia.

It was emphasized that the mortality rate of patients with lung injury was found to be 36% in patients with acute respiratory failure in Berlin (17). All patients participating in our study had acute or chronic lung disease and the mortality rate was found to be 30%.

CONCLUSION

While a significant relationship was found between albumin levels, which has an important place in the Stewart method, and the length of stay in the intensive care unit, no relationship was found between albumin or lactate levels and mortality. However, increased BUN values were associated with mortality. As the albumin value decreases in patients with hypoalbuminemia, treatment costs increase. There is a need for larger multicenter studies with a larger sample group that will evaluate metabolic status with the Stewart method and investigate its relationship with mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Atatürk Sanatoryum Training and Research Hospital Ethics Commitee (Date:13.09.2019, Decision No: 1953)

Informed Consent: Because the study was designed retrospectively. no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design. execution. and analysis of the paper. and that they have approved the final version.

REFERENCES

1. Yarkın T. Solunum Yetmezliği: Fizyopatoloji ve Klinik Yaklaşım. Toraks Derg 2000; 2: 76-84.
2. Frutos-Vivar F, Nin N, Esteban A. Epidemiology of acute lung injury and acute respiratory distress syndrome. Current Opinion in Critical Care 2004; 10: 1-6.
3. Esteban A, Anzueto A, Frutos F, et al. Mechanical Ventilation International Study Group: Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002; 287: 345-55.
4. Donlan M, Fontela PS, Puligandla PS. Use of continuous positive airway pressure (CPAP) in acute viral bronchiolitis: a systematic review. Pediatr Pulmonol 2011; 46: 736-46.
5. Lewandowski K. Contributions to the epidemiology of acute respiratory failure. Critical Care 2003; 7: 1-4.
6. Behrendt CE. Acute respiratory failure in the United States: incidence and 31-day survival. Chest. 2000; 118: 1100-5.
7. Aygencel G. Arter kan gazlarının yorumlanması. Türk Kardiyol Dern Arş 2014; 42: 195.
8. Szrama J. Smuszkiewicz P. An acid-base disorders analysis with the use of the Stewart approach in patients with sepsis treated in an intensive care unit. Anaesthesiology Intensive Therapy 2016; 48: 180-4.

9. Fencl V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med 2000; 162: 2246-51.
10. Nemec M. Interpretation of arterial blood gas analysis. Praxis 2019; 108: 269-77.
11. Altıay G, Tabakoğlu E, Özdemir L, et al. Mortality rates and related factors in respiratory intensive care unit patients. Turk Thorac J 2007; 8: 79-84.
12. Doğu T, Karakuzu Z, Katı ŞD, et al. Birinci basamak yoğun bakım ünitesi hastalarının prognozu. Uluslararası Klinik Araştırmalar Derg 2014; 2: 143-8.
13. Bıyıklı E. 65 yaş üstü sepsis ve septik şok hastalarında acil serviste ilk bakılan platelet lenfosit oranı ve laktat düzeyinin mortalite üzerine etkisi. Ankara. 2017.
14. Uçgun İ, Metintaş M, Moral M, Alataş F, Bektaş Y, Yıldırım H. To identify mortality rate and high risk patients in non-malignant respiratory intensive care unit patients. [Article in Turkish]. Toraks Derg 2003; 4: 151-60.
15. Yap FHY, Joynt GM, Buckley TA, Wong ELY. Association of serum albumin concentration and mortality risk in critically ill patients. Anaesth Intens Care 2002; 30: 202-7.
16. Yılmaz E, Bor C, Uyar M, Demirağ K, Çankayalı İ. Travma hastalarının yoğun bakıma kabulündeki laktat. albumin. C-reaktif protein. PaO_2/FiO_2 ve glukoz düzeylerinin mortaliteye etkisi. J Turk Soc Intens Care/Türk Yogun Bak Dern Derg 2014; 12: 3.
17. Lewandowski K, Metz J, Deutschmann C, et al. Incidence, severity, and mortality of acute respiratory failure in Berlin, Germany. Am J Respir Crit Care Med 1995; 151: 1121-5.
18. Chen YX, Wang JY, Guo SB. Use of CRB-65 and quick sepsis-related organ failure assessment to predict site of care and mortality in pneumonia patients in the emergency department: a retrospective study. Crit Care 2016; 20: 1-10.

Original Article

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Prognostic significance of controlling nutritional status (CONUT) score in hemodialysis patients

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ABSTRACT

Introduction: Malnutrition is a common and important problem in HD Hemodialysis (HD) patients. Malnutrition occurs due to various factors increases the risk of morbidity and mortality in HD patients. The Controlling Nutritional Status (CONUT) score has been designed to assess the nutritional status in patients. In addition, the relationship between the CONUT score and mortality has been investigated. We aimed to investigate the effectiveness of the CONUT score in predicting mortality in HD patients.

Material and Method: The data of 110 patients who started HD between 2017-2021 were analyzed retrospectively. From the laboratory parameters were evaluated before starting the first hemodialysis treatment. The CONUT score was calculated based on lymphocyte count, total cholesterol levels, and serum albumin levels. The patients were divided into two groups as CONUT score ≤4 and CONUT score ≥5. The groups were compared regarding these parameters.

Results: The data of 110 hemodialysis patients were analyzed. 58 (52.7%) of these patients were male. The mean age of the patients was 53.18±17.10 years. There were 49 (44.5%) patients with a CONUT score of ≤4 and 61 (55.5%) patients with a CONUT score of ≥5. 35 patients (13.9%) died. Among 35 all-cause deaths, 4 (11.4%) were occurred in the low CONUT group, and 31 (88.6%) were occurred in the high CONUT group ($p<0.001$). According to Kaplan-Meier analysis, the high CONUT group had significantly higher all-cause mortality ($p<0.001$) than the low CONUT group. According to the correlation analysis, there was a positive correlation between the CONUT score and mortality ($p<0.001$). In the multivariate Cox regression analysis, all cause of mortality was independently correlated to age, gender (male) and CONUT score (p: 0.010, p: 0.038 and $p < 0.001$, respectively). According to the ROC curve analysis, the optimal cut-off value of CONUT score in Hemodialysis HD patients was found at 4.5.

Conclusion: We concluded that the higher the CONUT score, the worse the nutritional status in hemodialysis patients, and may be associated with worse clinical outcomes. It is extremely important to evaluate the nutritional status at regular intervals, to detect malnutrition early and to follow up the results in HD patients. We think that CONUT score can be useful in predicting mortality risk for HD patients in clinical practice.

Keywords: Malnutrition, hemodialysis, mortality, CONUT score

INTRODUCTION

Hemodialysis (HD) is the most preferred renal replacement therapy (RRT) method for patients with end-stage renal disease (ESRD). Worldwide, HD forms for 89% of RRTs (1). Nutrition is an important issue in patients undergoing HD. While malnutrition is detected in approximately one third of these patients, the probability of encountering malnutrition increases as the duration of hemodialysis increases (2). Malnutrition occurs due to various factors reduces the quality of life (3) and increases the risk of morbidity and mortality in HD patients. The guidelines recommend frequent assessment of nutritional status in patients with ESRD (4).

It is important to evaluate the nutritional status at regular intervals and to determine malnutrition in the early period in HD patients. To establish the risk of malnutrition, a simple, inexpensive, and rapid screening tool should be used. Controlling Nutritional Status (CONUT) score is a screening tool calculated with laboratory parameters. These parameters are serum albumin level, total cholesterol level and lymphocyte count. CONUT score has been used to detect malnutrition in many diseases. In addition,

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studies have shown that the CONUT score can be used as an independent predictor of mortality (5,6).

Malnutrition is a common and important problem in HD patients. Early screening of malnutrition and implementation of necessary nutritional interventions in this population are very important since reducing morbidity and mortality rates (2). To the best of our knowledge, no study has been performed on the prognostic significance of the CONUT score in HD patients. In our study, we aimed to investigate the effectiveness of the CONUT score in predicting mortality in HD patients.

MATERIAL AND METHOD

The data of patients with ESRD initially undergoing HD at two different hemodialysis units between January 2017 and December 2021 were analyzed retrospectively. Patients under the age of 18, with missing data, malignancy or hematological disease were excluded from the study. 110 patients over the age of 18 were included in the study, regardless of gender. Demographic characteristics of the patients (age, gender), laboratory parameters were collected from the hospital database. From the laboratory parameters before starting the first hemodialysis treatment; leukocyte count, lymphocyte count, hemoglobin, serum urea, creatinine, albumin, corrected calcium, phosphorus, uric acid, total cholesterol, HDL High Density Lipoprotein (HDL) cholesterol, LDL Low Density Lipoprotein (LDL) cholesterol, triglyceride, Parathormone parathormone, CRP C reactive protein (CRP) levels were evaluated. The CONUT score was calculated based on lymphocyte count, total cholesterol levels, and serum albumin levels (**Table 1**) (7). The optimal CONUT score cut-off value for the survival was determined by the Receiver operating characteristics (ROC) curve analysis to be 4. The patients were divided into two groups as CONUT score ≤4 and CONUT score ≥5. The groups were compared regarding these parameters. This study was approved by the Ethics Committee of Gazi Yaşargil Training and Research Hospital (Date:11.02.2022, Decision No: 19). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Table 1. Definition of CONUT score

Parameters	CONUT			
	Normal	Mild	Moderate	Severe
Serum albumin (g/dL)	≥3.5	3.00-3.49	2.50-2.99	<2.50
Albumin score	0	2	4	6
Lymphocyte (count/mm³)	≥1600	1200-1599	800-1199	<800
Lymphocyte score	0	1	2	3
Total Cholesterol (mg/dL)	≥180	140-179	100-139	<100
Total Cholesterol score	0	1	2	3
CONUT score (total)	0-1	2-4	5-8	9-12

Statistical Analysis

Statistical analysis of the results obtained in the study was performed using the SPSS (Statistical Package for Social Sciences) 28 program. Descriptive statistics were used for demographic data. The normal distribution suitability of the variables was examined using visual (histogram and probability plots) and analytical methods (Kolmogrov-Simirnov/Shapiro-Wilk tests). Results are given as numbers and percentages for categorical variables and as mean±standard deviations for continuous variables. Spearman rank correlation analysis was performed to analyze the correlation between CONUT score and selected characteristics or parameters. The Kaplan-Meier method was used for survival analysis and compared using log rank analysis. Univariate and multivariate Cox Regression analysis was used for the analysis of variables related to mortality. The cut-off value of the CONUT score was analyzed with the ROC curve. A p value of less than 0.05 was considered statistically significant.

RESULTS

The data of 110 hemodialysis patients were analyzed. 58 (52.7%) of these patients were male. The mean age of the patients was 53.18±17.10 years. During the median follow-up period of 15.50 (1-58) months, 35 patients (13.9%) died. 20 (57%) of the patients who died were female (p:0.157). The median CONUT score was 4 (0-11) and the mean CONUT score was 4.51±3.196.

According to the cut-off value of 4, the enrolled patients were divided into two groups: Low CONUT group (CONUT score ≤4; 49 patients, 44.5%) and high CONUT group (CONUT score ≥5; 61 patients, 55.5%). There was no statistical difference between the groups and gender (p:0.900). The demographic and baseline laboratory parameters of the study population are shown in **Table 2**. Among 35 all-cause deaths, 4 (11.4%) were occurred in the low CONUT group, and 31 (88.6%) were occurred in the high CONUT group (p<0.001). The Kaplan-Meier analysis of all-cause mortality in hemodialysis patients according to the cut-off CONUT score is shown in **Figure. 1**. The high CONUT group had significantly higher all-cause mortality (p<0.001) than the low CONUT group.

A correlation analysis between CONUT score and variables in the hemodialysis patients were carried out using the Spearman correlation test (**Table 3**). CONUT scores showed a significant positive correlation to age and mortality, and a significant negative correlation to hemoglobin level, lymphocyte count, serum albumin, total cholesterol, HDL cholesterol, LDL cholesterol and parathormone level (p<0.05). There was a significant negative correlation between mortality and serum albumin and lymphocyte count (r: -0.569, p<0.001 and r: -0.388,

p<0.001 respectively). Although there was a negative correlation between mortality and total cholesterol, it was not statistically significant (r: -0.146, p:0.127)

The univariate and multivariate Cox regression analyses were performed to confirm the independent predictors of all cause of mortality (**Table 4**). In the univariate Cox regression analysis, age and CONUT score were found to be correlated to all cause of mortality. In the multivariate Cox regression analysis, all cause of mortality was independently correlated to age, gender (male) and CONUT score (p: 0.010, p: 0.038 and p < 0.001, respectively).

According to the ROC curve analysis, the optimal cut-off value of CONUT score in Hemodialysis patients was found at 4.5. CONUT score had an AUC of 0.858 (95% CI, 0.788 -0.928, p < 0.001), with a sensitivity of 88.6% and a specificity of 76% (**Figure 2**).

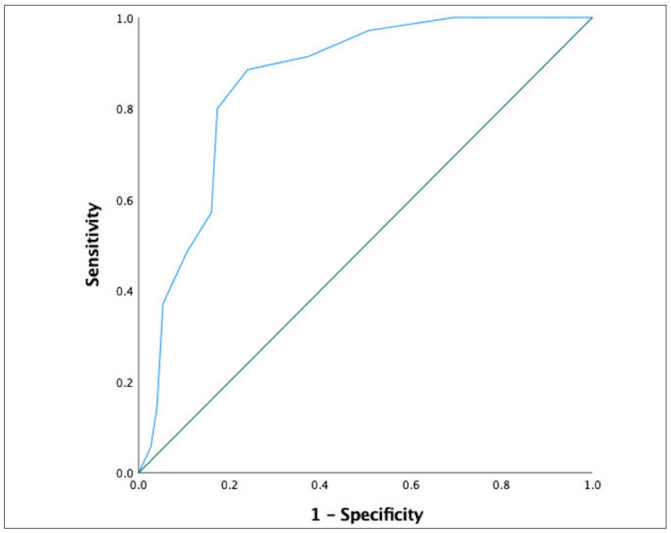

Figure 2. ROC analysis of CONUT score

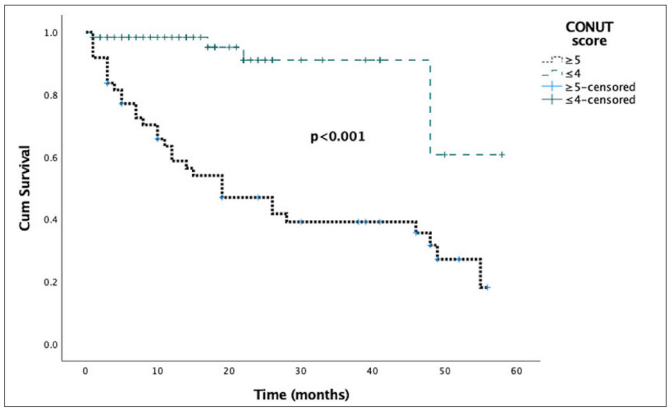

Figure 1. Kaplan-Meier analysis of all-cause mortality in Hemodialysis patients

Table 3. Spearman correlation between CONUT score and variables.

Variables	Correlation Coefficient	p
Age	0.189	0.048
Gender	-0.008	0.933
WBC	-0.121	0.209
Hemoglobin	-0.215	0.024
Lymphocyte	-0.639	<0.001
Urea	0.126	0.189
Creatinine	-0.072	0.452
Uric Acid	-0.002	0.984
Corrected Calcium	0.085	0.377
Phosphate	0.061	0.528
Albumin	-0.846	<0.001
Total Cholesterol	-0.432	<0.001
HDL Cholesterol	-0.305	0.001
LDL Cholesterol	-0.363	<0.001
Triglycerides	-0.148	0.124
CRP	0.075	0.436
Parathormone	-0.268	0.005
Mortality	0.581	<0.001

WBC: White Blood Cell, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, CRP: C Reactive Protein

Table 2. Demographic and baseline laboratory parameters of hemodialysis patients

Characteristics	All patients (n:110)	CONUT score ≤4 (n:61)	CONUT score ≥5 (n:49)	p
Age (years)	53.18±17.10	50.13±16.42	56.98±17.33	0.043
Gender				
Male	58 (52.7%)	29 (47.5%)	23 (46.9%)	0.900
Female	52 (47.3%)	32 (52.5%)	26 (53.1%)	
WBC (count/mm³)	7672.26±2442.20	7817.54±2326.88	7491.41 ±2591.50	0.975
Hemoglobin (g/dL)	9.09±1.85	9.44±1.94	8.65 ±1.65	0.290
Total Lymphocyte (count/mm³)	1534.00±573.43	1746.39±489.46	1269.59±564.40	0.563
Urea (mg/dL)	129.89±54.60	123.84±52.27	137.43 ±57.00	0.988
Creatinine (mg/dL)	6.47±2.64	6.61±2.57	6.14±2.73	0.829
Uric Acid (mg/dL)	6.36±1.52	6.36±1.60	6.37±1.44	0.499
Corrected Calcium (mg/dL)	8.91±0.90	8.89±0.76	8.92 ±1.06	0.019
Phosphate (mg/dL)	4.71±1.25	4.62±1.16	4.81±1.36	0.538
Albumin (g/dL)	3.10±0.61	3.56 ±0.31	2.53±0.38	0.042
Total Cholesterol (mg/dL)	163.69±46.05	169.87±38.38	156.00±53.52	0.112
HDL Cholesterol (mg/dL)	42.45±36.33	47.00±46.75	36.78±14.39	0.334
LDL Cholesterol (mg/dL)	98.51±36.80	102.44±31.39	93.61±42.42	0.106
Triglycerides (mg/dL)	127.98±63.50	131.84±59.29	123.18±68.70	0.987
CRP (mg/dL)	1.37±1.76	1.27±1.66	1.51±1.89	0.388
Parathormone (pg/mL)	441.91±311.258	495.30±338.04	375.45±262.73	0.244
CONUT Score				
Mean±std	4.51±3.196	2.03±1.32	7.59±1.87	0.002
Median (min-max)	4 (0-11)	2 (0-4)	8 (5-11)	

WBC: White Blood Cell, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, CRP: C Reactive Protein

Table 4. Univariate and multivariate Cox analysis of patient survival in hemodialysis dialysis patients

Characteristics	Univariate		Multivariate	
	HR (95%CI)	p	HR (95%CI)	p
Age	1.036 (1.014-1.059)	0.001	1.029 (1.007-1.051)	0.010
Gender (male)	0.536 (0.273-1.054)	0.071	0.480 (0.239-0.961)	0.038
Hemoglobin	0.959 (0.808-1.140)	0.636		
Urea	1.000 (0.994-1.007)	0.938		
Creatinine	0.944 (0.828-1.075)	0.383		
Uric Acid	0.963 (0.769-1.205)	0.740		
Corrected Calcium	1.068 (0.760-1.501)	0.703		
Phosphate	1.080 (0.859-1.358)	0.508		
HDL Cholesterol	0.971 (0.941-1.002)	0.065		
LDL Cholesterol	0.997 (0.987-1.006)	0.496		
Triglycerides	1.001 (0.996-1.006)	0.799		
CRP	0.930 (0.745-1.163)	0.525		
Parathormone	1.000 (0.999-1.001)	0.568		
CONUT score (≥5)	1.328 (1.177-1.500)	<0.001	1.313 (1.162-1.484)	<0.001

DISCUSSION

To the best our knowledge, there is no study comparing the CONUT score and prognosis in HD patients. In this study, we investigated the effectiveness of the CONUT score in predicting mortality. Our results show that malnutrition is associated with all-cause mortality in hemodialysis patients, and a high CONUT score at admission is an independent prognostic factor for mortality. We think that CONUT score can be useful in predicting mortality risk and diagnose malnutrition for HD patients in clinical practice.

Malnutrition has been shown to be associated with increased morbidity and mortality in patients with ESRD (8). Many scoring systems are used for the diagnosis of malnutrition. The CONUT score is one of the tests used to determine nutritional status and has been accepted as an important prognostic marker in many diseases. The CONUT score, calculated using total cholesterol level, serum albumin level and lymphocyte count, accurately reflects the patient's nutritional status by evaluating protein reserve, lipid metabolism and immune status (6,9). Albumin, lymphocytes, and total cholesterol are potential markers of malnutrition. Lower levels of these parameters represent a higher CONUT score (10). In the studies, in hemodialysis patients; It has been shown that low serum total cholesterol level, low lymphocyte count and low albumin level, are associated with malnutrition and are independent predictors of mortality (11,12). In the HEMO study, low serum albumin and low serum total cholesterol levels have been shown to have a relatively higher risk of mortality (13). In our study, there was a significant negative correlation between serum albumin and lymphocyte count and mortality, although there was a negative correlation with total cholesterol, it was not statistically significant.

In the literature, the relationship between the CONUT score and mortality in many diseases has been compared. Especially in cancer patients, there are many studies on the CONUT score. The results of these studies have been shown that the CONUT score is significantly associated with outcomes, including overall survival, in cancer patients, and that a high CONUT score adversely affects overall survival (14-16). It has been reported that a high CONUT score may be an independent prognostic factor for morbidity and overall survival in hematological diseases such as lymphoma (17), multiple myeloma (18), and thalassemia (19). In another study, 2466 patients with a diagnosis of acute heart failure were evaluated and a higher mortality and infection rate was found in patients with a CONUT score ≥5 at the time of hospitalization (20). CONUT score was investigated in patients with contrast-related acute kidney injury, ANCA-related vasculitis, and hypertension, and it was found that an increased CONUT score was associated with all-cause mortality (21-23).

Malnutrition is common in dialysis patients. There are few studies evaluating the CONUT score in dialysis patients. All these studies were conducted in peritoneal dialysis patients. Yang et al. (10) showed in their study that a CONUT score of >3 is associated with technique failure in PD patients. In another study, nutritional indexes were evaluated in PD patients, and it was stated that a CONUT score >3 may be an independent predictor of all-cause mortality (5). Zhou et al. (24), on the other hand, analyzed the relationship of the CONUT score at the onset of PD with technique failure, cardiovascular disease and mortality and reported that a CONUT score of >3 may be a prognostic marker. In our study, we found that a CONUT score of ≥5 increased all-cause mortality 1.3 times. When we reviewed the studies, different cut-off values were used for the CONUT score to predict mortality. This may be due to the fact that since it has been used to in different diseases and in different populations. In our study, we found the cut-off value of the CONUT score of 4.5 according to the ROC curve analysis and divided our patients into 2 groups as CONUT score ≤4 and ≥5. We found high mortality in the group with a CONUT score of ≥5. Similar to previous studies, our findings suggest that a high CONUT score may be an independent predictor of mortality.

Our study had several limitations. First, it is a retrospective study. Second, the number of patients was limited since there were only two centers. Third, we did not investigate how the CONUT score changes over time after dialysis and its relationship to outcomes.

CONCLUSION

It is extremely important to follow up the nutritional status at regular intervals, to detect malnutrition early and to follow up the results in HD patients. Our study includes important clinical findings as it evaluated the relationship between the CONUT score, which indicates nutritional status, and mortality in HD patients. In our study, we concluded that higher CONUT score is associated with worse nutritional status in HD patients and may lead to worse clinical outcomes. CONUT score is a simple and inexpensive scoring system, and we think that it can be useful in predicting mortality risk for HD patients in clinical practice. However, prospective studies with larger population are necessary.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the ethics committee of Gazi Yaşargil Training and Research Hospital (Date: 11.02.2022, Decision No: 19).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer- reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Sahathevan S, Khor BH, Ng HM, et al. Understanding development of malnutrition in hemodialysis patients: a narrative review. Nutrients 2020; 12: 3147.
2. Altıparmak MR. Nutrition in Hemodialysis. Turkiye Klinikleri J Nephrol-Special Topics 2015; 8: 53-60.
3. Yuksel E, Aydin E. The relationship between serum vitamin D levels and health-related quality of life in peritoneal dialysis patients. Int Urol Nephrol 2021 Jul 22. doi: 10.1007/s11255-021-02951-2.
4. Ikizler TA, Burrowes JD, Byham-Gray LD, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. Am J Kidney Dis 2020; 76: S1-S107.
5. Yang Y, Zhou H, Zhang P, Chao W, Zou Y, Yang M. Evaluation of objective nutritional indexes as predictors of worse outcomes in peritoneal dialysis patients. Nutrition 2020; 79-80: 110963.
6. Mineoka Y, Ishii M, Hashimoto Y, Nakamura N, Fukui M. Malnutrition assessed by controlling nutritional status is correlated to carotid atherosclerosis in patients with type 2 diabetes. Endocr J 2019; 66: 1073-82.
7. Spoletini G, Ferri F, Mauro A, et al. CONUT score predicts early morbidity after liver transplantation: a collaborative study. Front Nutr 2022; 8: 793885.
8. Cohen SD, Kimmel PL. Nutritional status, psychological issues and survival in hemodialysis patients. Contrib Nephrol 2007; 155: 1-17.
9. Kokura Y, Kimoto K, Okada Y, Kawakita S. The Controlling Nutritional Status score as a functional prognostic marker in patients with acute stroke: a multicenter retrospective cohort study. Nutrition 2020; 110889: 79-80.
10. Yang Y, Xu Y, Zhang P, Zhou H, Yang M, Xiang L. Predictive value of objective nutritional indexes in technique failure in peritoneal dialysis patients. J Ren Nutr 2021: S1051-2276(21)00232-6.
11. Reddan DN, Klassen PS, Szczech LA, et al. White blood cells as a novel mortality predictor in haemodialysis patients. Nephrol Dial Transplant 2003; 18: 1167-73.
12. Obialo CI, Okonofua EC, Nzerue MC, Tayade AS, Riley LJ. Role of hypoalbuminemia and hypocholesterolemia as copredictors of mortality in acute renal failure. Kidney Int. 1999; 56: 1058-63.
13. Dwyer JT, Larive B, Leung J, et al. HEMO Study Group. Are nutritional status indicators associated with mortality in the Hemodialysis (HEMO) Study? Kidney Int 2005; 68: 1766-76.
14. Takagi K, Buettner S, Ijzermans JNM, Wijnhoven BPL. Systematic review on the controlling nutritional status (CONUT) score in patients undergoing esophagectomy for esophageal cancer. Anticancer Res 2020; 40: 5343-9.
15. Peng L, Meng C, Li J, et al. The prognostic significance of controlling nutritional status (CONUT) score for surgically treated renal cell cancer and upper urinary tract urothelial cancer: a systematic review and meta-analysis. Eur J Clin Nutr 2021 Nov 23. doi: 10.1038/s41430-021-01014-0.
16. Kheirouri S, Alizadeh M. Prognostic potential of the preoperative controlling nutritional status (CONUT) score in predicting survival of patients with cancer: a systematic review. Adv Nutr 2021; 12: 234-50.
17. Baysal M, Bas V, Demirci U, et al. The utility of CONUT score in diffuse large B cell lymphoma patients. Niger J Clin Pract 2021; 24: 1194-9.
18. Kamiya T, Ito C, Fujita Y, et al. The prognostic value of the controlling nutritional status score in patients with multiple myeloma. Leuk Lymphoma 2020; 61: 1894-900.
19. Akgun Cagliyan G. Is CONUT score a predictor of morbidity in patients with adult transfusion dependent beta thalassemia? Transfus Apher Sci 2021; 60: 103126.
20. Kato T, Yaku H, Morimoto T, et al. Association with controlling nutritional status (CONUT) score and in-hospital mortality and infection in acute heart failure. Sci Rep 2020; 10: 3320.
21. Wei X, Chen H, You Z, et al. Nutritional status and risk of contrast-associated acute kidney injury in elderly patients undergoing percutaneous coronary intervention. Clin Exp Nephrol 2021; 25: 953-62.
22. Ahn SS, Jung SM, Song JJ, Park YB, Lee SW. Controlling nutritional status score is associated with all-cause mortality in patients with antineutrophil cytoplasmic antibody-associated vasculitis. Yonsei Med J 2019; 60: 1164-73.
23. Sun X, Luo L, Zhao X, et al. Controlling Nutritional Status (CONUT) score as a predictor of all-cause mortality in elderly hypertensive patients: a prospective follow-up study. BMJ Open 2017; 7: e015649.
24. Zhou H, Chao W, Cui L, Li M, Zou Y, Yang M. Controlling Nutritional Status (CONUT) score as immune-nutritional predictor of outcomes in patients undergoing peritoneal dialysis. Clin Nutr 2020; 39: 2564-70.

Original Article

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Rubella, cytomegalovirus and toxoplasmosis seroprevalence in pregnants in Çorum province

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ABSTRACT

Aim: *Toxoplasma gondii (T. gondii)*, rubella virus and cytomegalovirus (CMV) are important factors that can be transmitted from mother to baby and cause clinical findings in fetus or newborn. In our study, it was aimed to determine the seroprevalence of *T. gondii*, rubella virus and cytomegalovirus in pregnant women who applied to our hospital.

Material and Method: In our study, the serological test results of the blood samples of pregnant women used in the diagnosis of *T. gondii*, rubella virus and CMV infections in Microbiology Laboratory of Hitit University Erol Olçok Training and Research Hospital, were retrospectively analyzed in a five years period between 2016 and 2021.

Results: In our study, when *T. gondii*, rubella virus and CMV test results were examined in pregnant women who applied to our hospital, 18.9% positivity for anti-*T. gondii* IgG, 88.7% for anti-rubella virus IgG and 99.7% for anti-CMV IgG rates have been determined. The positivity of IgM tests of the same agents was determined as 1%, 0.85% and 1.08%, respectively.

Conclusion: Regional epidemiological data are important in terms of determining which of the routine screening approach or the risk of infection factors on the baby will be more important. We think that our study, which includes regional data, will contribute to the literature on this subject.

Keywords: *Toxoplasma gondii*, rubella, cytomegalovirus, pregnancy

INTRODUCTION

While *Toxoplasma gondii (T. gondii)*, rubella virus and cytomegalavirus (CMV) cause mostly asymptomatic or mild symptoms in pregnant women, they can cause serious clinical pictures by passing to the fetus. In order to prevent serious consequences such as fetal anomalies, premature birth, stillbirth and postnatal chronic infections, it is important to diagnose the disease quickly and accurately and to monitor the fetus (1). In addition, awareness of these diseases will enable clinicians to counsel the mother to protect her from these factors, and it will be useful to tell the family about negative fetal outcomes when infection occurs (2).

T. gondii is a protozoan that infects about a third of the world's population. *T. gondii* can be transmitted to humans through food contaminated with oocysts excreted in the feces of infected cats (3). When diagnosing toxoplasmosis, it is important to distinguish between primary and congenital infections correctly. The first approach in screening for infection is to look for IgG and IgM in serum every three weeks. Afterwards, an avidity test should be performed to distinguish between primary infection and congenital infection. Obtaining high avidity shows us that the infection has not been cured in the last four months, while in cases where low avidity is detected, investigating the agent with polymerase chain reaction (PCR) in amniocentesis sample seems to be a method with higher sensitivity (4).

CMV, a human-specific DNA virus from the herpesvirus family, is the most common cause of congenital infections worldwide (5). The rate of CMV congenital infection in newborns varies between 0.2-2.5% (6). It is an important non-genetic leading cause of sensorineural hearing loss and delay in nervous system development in children in developed countries (5). Unlike rubella infection and toxoplasmosis, CMV can produce both primary and post-reactivation/reinfection fetal infection. The rate of transmission varies between 30-40% after primary infection and 1% after secondary infection (7).

Rubella or German measles, caused by the rubella

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virus, is characterized by a clinical picture, usually mild, with fever and rash. Rubella, a teratogenic virus, is an important cause of birth defects and fetal death when transmitted during pregnancy. More than 100,000 cases of congenital rubella syndrome (CRS) each year indicate that this infection is an important public health problem (8). If rubella infection occurs in the first 16 weeks of pregnancy, up to 85% of newborns are born with growth retardation and major birth defects known as CRS (9). Serious complications such as blindness, deafness, congenital heart disease, mental retardation, and neurological disorders occur in CRS (8). Since there are no symptoms in half of rubella infections and can mimic many rash diseases, rubella seropositivity cannot be determined based on the patient's history (7).

However, the importance of screening for these factors during pregnancy is a controversial issue. There is no consensus among countries on this issue. In our country, studies have been carried out on the necessity of routine screening of pregnant women, but a consensus has not been reached (10,11).

Inclusion of these factors in prenatal screening programs in a certain geographical region can be determined according to seroprevalence studies and cost analysis studies conducted in this region (12). In our study, we investigated the seropositivity rates of *T. gondii*, rubella virus and CMV in pregnant women and those with suspected pregnancy who applied to our hospital in order to contribute to the seroprevalence in our country.

MATERIAL AND METHOD

Our study was approved by the Hitit University Faculty of Medicine Non-invasive Clinical Researches Ethics Committee (Date: 02.12.2021, Decision No: 2021-85). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study, the blood samples of pregnant women who were sent to the T.C. Ministry of Health Çorum Hitit University Erol Olçok Training and Research Hospital Microbiology Laboratory between 2016-2021 were evaluated. Anti-*T. gondii* IgM and IgG, anti-CMV IgM and IgG, anti-rubella virus IgM and IgG were evaluated retrospectively. The blood sample taken into EDTA tubes was separated into the serum part and studied in accordance with the instructions of the manufacturer for the detection of antibodies using Elecsys® (Roche, Penzberg, Germany) Electrochemiluminescence immunoassay (ECLIA) between 2016-2017 and ARCHITECT® (Abbott, USA) Chemiluminescent Microparticle Immunoassay (CMIA) technique in 2021 studies were performed in accordance with the manufacturer's instructions for the detection of antibodies using the technique. Repeat blood samples sent from the same patient were not included in the study.

RESULTS

In our study, antibody positivity in the blood of pregnant women and women with suspected pregnancy who applied to our hospital, anti- *T. gondii* IgM 1%, anti-rubella virus IgM 0.85%, anti-CMV IgM 1.08%; anti-*T. gondii* IgG 18.9%, anti-rubella virus IgG 88.7%, anti-CMV IgG 99.7% positive (**Table 1**).

Table 1. Antibody distributions of *Toxoplasma gondii*, Rubella virus and citomegalovirus

Toxoplasma gondii	**Positive**	**Intermediate value**	**Negative**
IgM	89/8649 (1%)	29/8649 (0.3%)	8531/8649 (98.6%)
IgG	1739/9199 (18.9%)	101/9199 (1.09%)	7359/9199 (81.9%)
Rubella virus	Positive	Intermediate value	Negative
IgM	76/8921 (0.85%)	70/8921 (0.78%)	8775/8921 (98.3%)
IgG	8176/9210 (88.7%)	194/9210 (2.1%)	840/9210 (9.1%)
Citomegalovirus	Positive	Intermediate value	Negative
IgM	89/8222 (1.08%)	30/8222 (0.36%)	8103/8222 (98.5%)
IgG	410/411 (99.7%)	0/411 (0%)	1/411 (0.24%)

DISCUSSION

It is important to detect *T. gondii*, rubella and CMV infections in the prenatal period because of their serious teratogenic consequences in pregnancy. Today, serological tests take the first place in the identification of these factors in pregnancy follow-up. Detection of specific IgM antibodies in these infections is guiding in the early diagnosis. However, there is no consensus on the routine screening of these infectious agents in pregnant women (13).

T. gondii can be transmitted by eating food that has come into contact with cat feces without washing it well, drinking water, consuming raw and undercooked meat, vertically, blood and organ transplants (14). In vertical transitions, with the progression of the pregnancy period, the risk of developing infection in the fetus increases, while the severity of the disease decreases (4). While screening for *T. gondii* is mandatory in some countries, it is recommended in some countries such as the United States and Canada. Among the factors affecting seroprevalence, there are factors such as gender,

age, immune status, feeding behaviors, keeping cats at home, geographical region differences (15).

In studies conducted in different regions of our country, anti-*T. gondii* IgM positivity rate ranged from 0.4% to 1.1%, while anti-*T. gondii* IgG positivity rate was reported to be between 28.9% and 52.1% (13,16-20). In a meta-analysis examined in pregnant women, the rate of anti-*T. gondii* IgG positivity was 32.9% worldwide, 45.2% in the Americas, 39.7% in the Eastern Mediterranean, 36.5% in Africa, 30% in Europe, 24.6% in Southeast Asia and 11.2% in the Western Pacific. Anti-*T. gondii* IgM positivity was reported at a rate of 1.9% worldwide, with the highest 4.1% in the Eastern Mediterranean, and the minimum 1.1% in the Americas (21). In our study, anti-*T. gondii* IgG positivity rate was found to be 18.9%, lower than other studies. In accordance with these studies in the world and in our country, anti-*T. gondii* IgM positivity was found to be 1%. Anti-*T. gondii* IgM and IgG positivity rate is low, it can be concluded that women should act consciously in contact with animals before and during pregnancy and be careful in consuming raw meat. In addition, we think that institutional and social good practices can be effective in the follow-up, vaccination and shelter services of stray animals.

German measles or rubella; It is a generally self-limiting infectious disease accompanied by fever, lymphadenopathy, maculopapular rash. However, rubella infection in the first trimester of pregnancy can cause fetal death or a condition called congenital rubella syndrome (22).

In studies conducted in Turkey, it has been reported that anti-rubella virus IgM positivity varies between 0.0% and 1.9% (16). In our study, anti-rubella virus IgM positivity was found to be 0.85% similar to other studies. In studies conducted in our country, anti-rubella virus IgG positivity has been reported between 76.5% and 97.3% (16, 18, 19, 23, 24). In our study, anti-rubella virus IgG positivity was similar to the data obtained with a rate of 88.7%.

Rubella vaccine is a live attenuated vaccine that can be administered as a monovalent Rubella vaccine or Measles-mumps-rubella (MMR) and can provide lifelong immunity. Rubella vaccine has been added to the routine vaccination program in Turkey since 2006. Vaccination programs were also thought to have an effect on the high seroprevalence values found in this study and in the literature (25). As seen in our study and other studies conducted in our country, it is thought that the vaccination program contributed to the low anti-rubella virus IgM positivity and the high anti-rubella virus IgG positivity. For this reason, routine vaccination program should be applied completely in order to prevent the risk of congenital rubella syndrome in seronegative girls and expectant mothers of childbearing age.

CMV is a common virus with an approximate seroprevalence of 45% to 100% worldwide (26). Since CMV can remain latent after primary infection, it can be reactivated during pregnancy or transmitted after contact with body fluids (27). Worldwide, congenital CMV infection is the leading cause of neurological damage in children and is associated with growth retardation, hearing loss, permanent disabilities, and microcephaly (28, 29). In studies conducted in our country, anti-CMV IgG positivity ranges between 92.6% and 99.5%. Anti-CMV IgM positivity varies between 1.7% and 2.6% (6, 30-33). In our study, anti-CMV IgG positivity was 99.7%, and anti-CMV IgM positivity was 1.08%, which is similar to other studies conducted in our country.

In conclusion, early diagnosis is important due to the high risk of congenital infections during pregnancy. Serological tests, which are an inexpensive and easy method in the follow-up of pregnant women and who are planning pregnancy, should be performed according to the seroprevalence rates and risk levels of the regions.

ETHICAL DECLARATIONS

Ethics Committee Approval: Our study was approved by the Hitit University Faculty of Medicine Non-invasive Clinical Research Ethics Committee (Date: 02.12.2021, Decision No: 2021-85).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Fuchs FE, Pauly M, Black AP, et al. Seroprevalence of ToRCH Pathogens in Southeast Asia. Microorganisms 2021; 9: 574.
2. Singh L, Mishra S, Prasanna S, et al. Seroprevalence of TORCH infections in antenatal and HIV positive patient populations. Med J Armed Forces India 2015; 71: 135-38.
3. Pleyer U, Gross U, Schluter D, et al. Toxoplasmosis in Germany. Dtsch Arztebl Int 2019; 116: 435-44.
4. Beder D, Esenkaya Tasbent F. General Features and Laboratory Diagnosis of *Toxoplasma gondii* Infection. Turkiye Parazitol Derg 2020; 44: 94-101.

5. Marsico C, Kimberlin DW. Congenital Cytomegalovirus infection: advances and challenges in diagnosis, prevention and treatment. Ital J Pediatr 2017; 43: 38.
6. Çeltek NY, Tetikçok R, Günal Ö, et al. Türkiye'nin Orta Karadeniz Bölgesi'nde Gebelerde Rubella, CMV ve Toksoplazmozis Seroprevalansı (Seroprevalence for Rubella, CMV and Toxoplasmosis Among Pregnant Women in Central Black Sea Region of Turkey). Gaziosmanpaşa Üniversitesi Tıp Fakültesi Dergisi 2014; 6: 54-62.
7. Karabulut A, Polat Y, Türk M, et al. Evaluation of rubella, *Toxoplasma gondii*, and cytomegalovirus seroprevalences among pregnant women in Denizli province. Turk J Med Sci 2011; 41: 159-64.
8. George S, Viswanathan R, Sapkal GN. Molecular aspects of the teratogenesis of rubella virus. Biol Res 2019; 52
9. Mawson AR, Croft AM. Rubella Virus Infection, the Congenital Rubella Syndrome, and the Link to Autism. Int J Environ Res Public Health 2019; 16 : 3543.
10. Karacan M, Batukan M, Çebi Z, et al. Screening cytomegalovirus, rubella and toxoplasma infections in pregnant women with unknown pre-pregnancy serological status. Archives of Gynecology and Obstetrics 2014; 290: 1115-20.
11. Duran B, Toktamış A, Erden Ö, et al. Doğum öncesi bakımda tartışmalı bir konu: TORCH taraması. CÜ Tıp Fakültesi Dergisi 2002; 24 :185-90.
12. Numan O, Vural F, Aka N, et al. TORCH seroprevalence among patients attending Obstetric Care Clinic of Haydarpasa Training and Research Hospital affiliated to Association of Istanbul Northern Anatolia Public Hospitals. North Clin Istanb 2015; 2: 203-09.
13. Mehmet O, Doğan Y, Bademkiran MH, et al. Diyarbakır ilindeki gebe kadınlarda toksoplazma, rubella ve sitomegalovirus seroprevalansı. Dicle Tıp Dergisi 46 :189-94.
14. Saricaoğlu EM, Memikoğlu KO. Gebelik ve toksoplazmoz. Ankara Üniversitesi Tıp Fakültesi Mecmuası 2018; 71 :17-22.
15. Rahmanian V, Rahmanian K, Jahromi AS, et al. Seroprevalence of *Toxoplasma gondii* infection: An umbrella review of updated systematic reviews and meta-analyses. J Family Med Prim Care 2020; 9: 3848-55.
16. Cinar Tanriverdi E, Goktug Kadioglu B, et al. Retrospective evaluation of anti-*Toxoplasma gondii* antibody among first trimester pregnant women admitted to Nenehatun Maternity Hospital between 2013-2017 in Erzurum. Turkiye Parazitol Derg 2018; 42: 101-05.
17. Alver O, Payaslioglu M, Ener B. Investigation of *Toxoplasma gondii* Seropositivity in Uludag University Hospital between 2009-2016. Turkiye Parazitol Derg 2019; 43 :8-12.
18. Madendağ Y, Erarslan Şahin M, et al. Hastanemize başvuran gebelerde toksoplazma, sitomegalovirus ve rubella seroprevalansının araştırılması. Perinatoloji Dergisi. 2018; 26: 7-10.
19. Tamer GS, Dundar D, Caliskan E. Seroprevalence of *Toxoplasma gondii*, rubella and cytomegalovirus among pregnant women in western region of Turkey. Clin Invest Med 2009 ;32 :43-47.
20. Ocak S, Zeteroglu S, Ozer C, at al. Seroprevalence of *Toxoplasma gondii*, rubella and cytomegalovirus among pregnant women in southern Turkey. Scand J Infect Dis 2007; 39: 231-34.
21. Bigna JJ, Tochie JN, Tounouga DN, et al. Global, regional, and country seroprevalence of *Toxoplasma gondii* in pregnant women: a systematic review, modelling and meta-analysis. Sci Rep 2020; 10 :12102.
22. Leung AKC, Hon KL, Leong KF. Rubella (German measles) revisited. Hong Kong Med J 2019; 25: 134-41.
23. Tekin A, Deveci Ö, Yula E. The seroprevalence of antibodies against *Toxoplasma gondii* and Rubella virus among childbearing age women in Mardin province. J Clin Exp Invest 2010; 1: 2.
24. Toklu GD. Antibodies frequency against toxoplasmosis, rubella virus and cytomegalovirus in pregnant women. J Clin Anal Med 2013; 4: 38-40.
25. Şener K, Kılıç A, Güney Ç, et al. Genişletilmiş bağışıklama programı öncesi rubella (kızamıkçık) seroprevalansı. TAF Prev Med Bull 2007; 6: 1-6.
26. Lachmann R, Loenenbach A, Waterboer T, et al. Cytomegalovirus (CMV) seroprevalence in the adult population of Germany. PLoS One 2018; 13 :e0200267.
27. Griffiths PD. Burden of disease associated with human cytomegalovirus and prospects for elimination by universal immunisation. Lancet Infect Dis. 2012; 12 :790-98.
28. Ludwig A, Hengel H. Epidemiological impact and disease burden of congenital cytomegalovirus infection in Europe. Euro Surveill. 2009; 14: 26-32.
29. Manicklal S, Emery VC, Lazzarotto T, et al. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev. 2013; 26: 86-102.
30. Efe Ş, Kurdoğlu Z, Korkmaz G. Van yöresindeki gebelerde Sitomegalovirus, Rubella ve Toksoplazma antikorlarının seroprevalansı. Van Tıp Derg. 2009;16: 6-9.
31. Kılınç Ç, Guckan R, Idil O, et al. Amasya Bölgesindeki Gebelerde Toksoplazma ve Sitomegalovirus Seroprevelansı Toxoplasma and Cytomegalovirus seroprevalence in pregnant women in Amasya district. Eur J Health Sci 2015; 72-5.
32. Şentürk Ş, Balik G, Şahin FK, et al. Rize Yöresindeki Gebe Kadınlarda Sitomegalovirus Seroprevalansı. Bozok Tıp Derg 2015; 5: 22-6.
33. Yilmazer M, Altindiş M, Cevrioğlu S, et al. Afyon Bölgesinde Yaşayan Gebe Kadınlarda Toksoplazma, Sitomegalovirus, Rubella, Hepatit B, Hepatit C Seropozitiflik Oranları. Kocatepe Tıp Derg 2004; 5.

Original Article

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Assessment of failed spinal anesthesia for cesarean section during COVID-19 pandemic

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ABSTRACT

Objective: 1490 pregnant women with confirmed COVID 19 were admitted to the hospital between April 2020 and February 2021. In Ankara City Hospital, Ankara, Turkey, 416 pregnant women gave birth spontaneously and 251 underwent cesarian section. We attempted spinal anesthesia for cesarian sections because all regional anesthesia organizations advised regional anesthesia for obstetric surgery. However, spinal anesthesia for cesarean delivery is not a foolproof method.

Material and Method: We used a retrospective analysis of 251 COVID 19 cesarean section anesthesia to determine the incidence of failed spinal anesthesia, management strategies, and risk variables that contribute to failure.

Results: The total number of failed spinal anesthesia instances was 14 (5.58%), with 1% of complete failures and 4% of partial failures. One patient was given spinal anesthesia for the 2nd attempt (0.4%), while the other two were given general anesthesia (0.79%). In failed spinal cases, sedation was utilized. Patients received varied dosages of midazolam, fentanyl, ketamine, and propofol.

Conclusion: The rate of failed spinal anesthesia among COVID 19 pregnant women was similar to, even lower than, the rate of failed spinal anesthesia in the general population. Despite all the negative consequences, such as wearing PPE and moving around, vision and hearing problems due to PPE, anesthesiologist fear about being infected by the patient or patient anxiety about infection, the future and babies' health is the reason for this result.

Keywords: SARS-CoV-2 (COVID-19), spinal anesthesia, obstetrical anesthesia

INTRODUCTION

All anesthesiologists face a challenge when it comes to the anesthesia of patients with coronavirus disease who are going to have a cesarian section. Patients' and healthcare personnel' safety should be prioritized. Non-emergent procedures in patients with respiratory infections, such as COVID-19, should be postponed and rescheduled once the infection has been treated. However, some emergency treatments, such as cesarian section, cannot be postponed.

Furthermore, general anesthesia, which requires aerosol-generating procedures such as ventilating and intubating patients, has a higher risk of respiratory problems during or after surgery than regional anesthesia. (1, 2, 3) Another important point is that, when compared to those who are not exposed to tracheal intubation, the transfer of acute respiratory infection to a health care professional during tracheal intubation is 6.6 times higher (4).

For such reasons, the European and American Societies of Regional Anesthesia jointly issued COVID 19 recommendations stating that regional anesthesia should be preferred over general anesthesia whenever possible, and practice recommendations for regional anesthesia during the pandemic have already been published (5).

In many facilities, single-shot spinal anesthesia is the preferred method for cesarian section. It delivers great anesthesia because of its ease of use, rapid onset of sensory and motor blockage, reliability, ease of mastering, and capacity to provide optimal surgical circumstances; it also minimizes the hazards of general anesthetic while enhancing partition satisfaction (6,7). In addition, when compared to general anesthesia, the risk of complications such intraoperative bleeding, surgical site infection, and postoperative pain is lower with spinal anesthesia (8).

Failed spinal anesthesia can be partial or complete. If anesthesia and analgesia are not achieved within ten minutes after successful intrathecal injection, the

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bupivacaine spinal anesthetic is regarded to have failed. Partial failure was defined as insufficient extent, quality, or duration of pharmacological action for that procedure, while complete failure was described as no sensory or motor blockage (9).

The failure rate of spinal anesthesia is widely distributed, according to researches, ranging from 1 to 17 percent. During spinal anesthesia, the Royal College of Anesthetics proposes a failure rate of 3% in emergencies and 1% for elective procedures (10,11,12).

The goal of this study was to determine our failure rate for spinal anesthesia in the context of a COVID 19 pandemic.

MATERIAL AND METHOD

The study was initiated with the approval of the Ankara City Hospital Ethics Committee (Date: 17.11.2021, Decision No: E1-21-2116). All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

Study Design

After receiving approval from the local ethics committee and permission to use the hospital archives, we included records of spinal anesthesia performed on confirmed COVID 19 patients in the Ankara City Hospital between April 2020 and February 2021, as well as related data, in our study. Patients who did not have their data gathered, or whose operation took more than 3 hours due to any reason, were excluded from the study.

The absence of block formation despite delivery of the anesthetic agent, the requirement for sedation to complete the surgery, converting to general anesthesia, or re-performing spinal anesthesia were all defined as spinal anesthesia failure using data from patient files and anesthesia records. So, we invented the term "failed block" to describe spinal anesthesia that was attempted but failed to produce a block (full failed block) or a block that was insufficient (partial failed block). The age of the patients, ASA status, gestational week, surgical emergency, co-morbidities, COVID 19 infection symptoms, and the amount of medicine utilized during spinal or sedation, Bromage scales of lower extremity of the patients were all documented.

Cesarian delivery urgency was classified as "emergent," indicating a threat to the mother or fetus that necessitates immediate delivery; "urgent," indicating a need for delivery within 30 minutes in situations where there is no immediate threat to the mother or fetus, but maternal or fetal compromise may be expected if spontaneous delivery is delayed; "Elective," suggesting that an early cesarean delivery is required, that no maternal or fetal compromise exists, and that the cesarean delivery should take place at a time that is convenient for the patient and labor and delivery staff (13,14,15).

RESULTS

The study included 251 patients. The overall number of failed spinal anesthetic cases was 14 (5,58%). One patient had spinal anesthesia again (0,4 %), while the other two received general anesthesia (0,79 %). Resting 11 patients were sedated with analgesic and hypnotic agents. Patients in the successful and unsuccessful spinal block groups had similar demographic data and used the same bupivacaine dose (**Table 1**). All the women were in their third trimester of pregnancy.

Table. Properties of patients with succesful and failed spinal block

	Successful Spinals	Failed Spinals	p
Age (years)	29,35±5,13 (16-45)	29,86±6,76 (18-41)	0,72
Height (cms)	162,87±7,64 (150-180)	167,33±8,03 (158-172)	0,34
Weight (kgs)	82,83±17,01 (52-161)	88,00±4,46 (85-93)	0,60
Gestational age (weeks)	37,13±2,62 (27-41)	38,14±1,17 (36-40)	0,14
Bupivacaine dose (mgs)	12,59±1.02 (10-15)	12,93±1,37 (12-15)	0,24
Data expressed mean±SD, and (min-max)			

Sedation was used in unsuccessful spinal cases. Midazolam, fentanyl, ketamine, and propofol were combined in varying amounts in 11 of 14 patients.

All the patients who had failed spinal anesthesia were emergent cesarean sections.

DISCUSSIONS

Our study is the first one in the literature which was conducted to determine the incidence and associated factors of failed spinal anesthesia among COVID 19 positive women who underwent a cesarean section. In this retrospective analysis, we used a failed term to describe spinal anesthesia that was attempted but failed to produce a complete block or a partial block. Our findings revealed that 14 out of 251 pregnant women treated by obstetric-specialized anesthesiologists had failed spinal anesthesia. The incidence rate was 5,8 %. And midazolam, propofol, fentanyl, and ketamine were used to sedate 4,4 percent of unsuccessful instances. 2 of the patients were converted to general anesthesia with endotracheal intubation (0,79 %), and 1 was treated with repeated spinal (0,4 %). According to the Royal College of Anesthesiologists (RCOA), the acceptable conversion rate from spinal to general anesthesia in obstetric anesthetic treatment should be less than 1% for elective CS and less than 3% for emergency CS (16). Our findings

suggest conversion rates that are similar to or even lower than the RCOA's target.

The failure rate of spinal anesthesia for elective procedures was 8.7%, and 9.3% for emergency sections, according to Rukewe et al (17). All of our cases were emergencies, and our failure spinal anesthetic rate was 5.8%. Our result, on the other hand, is outside the acceptable range of 0-4 % stated by previous researchers. (6,12, 17-19).

In our study, we found that patients who need supplemental analgesia to complete the surgery begin with a spinal block rate was 4,4 % and was comparable with the 5,7 % reported by Rukewe et al. (17) and % 4,1 reported by Sngb et al. (20). And our result was nearly half of the Gary and Davies (21) study results (10,9 %).

All spinal anesthesia in our study was performed by obstetric anesthesiologists with at least 5 years of full-time obstetric clinic experience and common sense about complications; our failure rate (5.8%) was comparable to the RCOA's predictions. Despite stringent precautions, there is a high chance of contamination and becoming a possible patient or infector during the COVID 19 pandemic. Anxiety and fear are the results of feelings (22). Regardless of how senior the obstetrician anesthesiologist was, this worry, or anxiety may have contributed to the failed spinal anesthesia. Since there was no resident anesthesiologists' group to compare the outcomes with, this may be a disadvantage of our study.

The operation rooms in our hospital are positive-pressure rooms. We use Level III PPE for infection control, which includes a disposable surgical cap, medical protection mask, goggles or face shields, surgical scrubs, gowns, disposable surgical gloves, and disposable foot rubbers. The most common problems associated with using PPE kits were excessive sweating (100%), fogging of goggles, spectacles, or face shields (88%), suffocation (83%), breathlessness (61%), fatigue (75%), headache due to prolonged use (28%), and pressure marks on the skin in one or more areas of repeated use (19%) (23). Although we use PPE to prevent infection, it has a negative impact on our lives. Limitation of movement due to foot rubbers, loss of vision because of the fogging over the surface of goggles or sheets, and most importantly communication problems with the patient because of the masks, cap and rubbers especially positioning during spinal anesthesia could be other factors for the failed spinal anesthesia procedures.

In some studies, they discovered that injecting less than 2 ml of local anesthetics was linked to failed spinal anesthesia without the use of adjuvants (24). However, because we administered at least 12,5 mg of bupivacaine in our investigation, this reason could not be the source of our failed anesthesia rates.

Intraabdominal pressure increases with gestational age, which may increase intrathecal medication dissemination throughout pregnancy, Henos et al. (24) and Adesope et al. (25) discovered that the spinal failure rate dropped as gestational age increased. All the failed spinal anesthesia patients in our study were in their third trimester. Only one of the patients was 36 weeks pregnant, and the others were bigger.

We use a 26-gauge atraucon spinal needle in our clinic because it has a greater rate of successfully identifying the subarachnoid space on the first attempt, faster CSF backflow, less postdural puncture headaches, and less paresthesia than other spinal needles (26,27) Smaller spinal needles, according to some studies, may lead to more spinal attempts and increase the probability of failure (19, 24). However, we did not repeat the spinal attempts to create failure in our work.

Furthermore, studies have shown that parturients who were operated by the resident obstetricians had a higher risk of spinal anesthesia failure during surgery than those who were operated on by senior surgeons (24). Inexperienced hands may manipulate the upper sites of adjacent structures to the uterus, as well as take a long time to operate, allowing the block to resolve. Unfortunately, we did not identify the surgeon's seniority in our research, although there were no changes in surgery times.

The drug's action on the spinal nerve root is one of the failure mechanisms of spinal anesthesia. However, because failure did not occur with just one batch of the drug, our failure was random. If one batch of the drug was defective, all patients who received that batch should have failed at the same time.

In a single patient, we repeated spinal anesthesia for a failed spinal block and no complications were seen. But the studies suggest that repeat injection after a failed spinal can be potentially unsafe (28,29).

CONCLUSION

Although spinal anesthesia is the preferred method for COVID 19 confirmed cases, failed anesthesia can occur for a variety of reasons. The reason could be technical, but we should also consider other factors during COVID 19 pandemic, such as the patient's and anesthesiologist's anxiety, as well as personal equipment issues. Despite these disadvantages, the team's most senior anesthesiologist must be the one in charge, because quick response in difficulties or emergencies requires clinical experience and common sense, and in this way failure rates are comparable to those of normal pregnant women. Resident anesthesiologists, like senior anesthesiologists, must adapt to these new normals and

medical conditions as we become accustomed to living with COVID 19 disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Ankara City Hospital Ethics Committee (Date: 17.11.2021, Decision No: E1-21-2116).

Informed Consent: The study was designed retrospectively; no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer- reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Warren J, Sundaram K, Anis H, et al. Spinal anesthesia is associated with decreased complications after total knee and hip arthroplasty. J Am Acad Orthop Surg 2020; 28: e213-e221.
2. Neuman MD, Silber JH, Elkassabany NM, Ludwig JM, Fleisher LA. Comparative effectiveness of regional versus general anesthesia for hip fracture surgery in adults. Anesthesiology 2012; 117: 72-92.
3. Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000; 321: 1493.
4. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: A systematic review. PLoS One 2012; 7: e35797.
5. Uppal V, Sondekoppam RV, Lobo CA, Kolli S, Kalagara HKP. Practice recommendations on neuraxial anesthesia and peripheral nerve blocks during the COVID-19 pandemic. https://www.asra.com/page/2905/practicerecommendations-on-neuraxial-anesthesia-andperip heral-nerve-blocks-dur. [Accessed 10 May 2020]
6. Sng BL, Lim Y, Sia ATH. An observational prospective cohort study of incidence and characteristics of failed spinal anaesthesia for caesarean section. Int J Obstet Anesth 2009; 18: 237e41.
7. Shrestha AB, Shrestha CK, Sharma KR, Neupane B. Failure of subarachnoid block in caesarean section. Anesth Analg 2009; 11: 50e1.
8. Jairo J, Paez L, Ricardo J. Revista Colombiana de Anestesiología Regional versus general anesthesia for cesarean section delivery. Colomb J Anesthesiol 2012; 40: 203e6
9. Agrawal J, Rajput A, Mittal R. Failed spinal anaesthesia- a review. Anaesth Critic Care Med J 2019; 4: 000145.
10. Purva M, Russell IF, Kinsella M. Caesarean section anaesthesia: technique and failure rate. In: Colvin JR, Peden CJ, eds. Raising the Standard: A Compendium of Audit Recipes for Continuous Quality Improvement in Anaesthesia. 3rd ed. London, UK: The Royal College of Anaesthetists, 2012: 221-222.
11. Levy JH, Islas JA, Ghia JN, Turnbull CA. Retrospective study of the incidence and caues of failed spinal anesthetics in a university hospital. Anesth Analg 1985; 64: 705-10.
12. Fuzier R, Bataille B, Fuzier V, et al. Spinal anesthesia failure after local anesthetic injection into cerebrospinal fluid: a multicenter prospective analysis of its incidence and related risk factors in 1214 patients. Reg Anesth Pain Med 2011; 36: 322-6.
13. Van Dillen J, Diesch M, Schutte J, Zwart J, Wolterbeek R, van Roosmalen J. Comparing grades of urgency for classification of cesarean delivery. Int J Gynaecol Obstet 2009; 107: 16-8.
14. Yentis SM, Richards NA. Classification of urgency of caesarean section. Obstet Gynaecol Reprod Med 2008; 18:139-40.
15. Lucas DN, Yentis SM, Kinsella SM, et al. Urgency of caesarean section: A new classification. J R Soc Med 2000; 93: 346-50
16. Kinsella M. Royal College of Anaesthetists / Raising the Standard: a compendium of audit recipes, 3rd Edition, Year 2012.
17. Rukewe A, Adebayo OK, Fatiregun AA. Failed Obstetric Spinal Anesthesia in a Nigerian Teaching Hospital: Incidence and Risk Factors. Anesth Analg 2015; 121: 1301-5.
18. Kinsella SM. A prospective audit of regional anaesthesia failure in 5080 Caesarean sections. Anaesthesia 2008; 63: 822-32.
19. Partani S, Yogendra S, Gupta S A prospective, observational audit of failed regional anaesthesia in 4085 caesarean sections at a tertiary care hospital. Indian J Clin Anaesthesia, 2018; 5: 50-5.
20. Sng BL, Lim Y, Sia AT. An observational prospective cohort study of incidence and characteristics of failed spinal anaesthesia for caesarean section. Int J Obstet Anesth 2009; 18: 237-41.
21. Garry M, Davies S. Failure of regional blockade for caesarean section. Int J Obstet Anesth 2002; 11: 9-12
22. Wu J, Chen X, Yao S, Liu R. Anxiety persists after recovery from acquired COVID-19 in anaesthesiologists. J Clin Anesth 2020; 67: 109984.
23. Agarwal A, Agarwal S, Motiani P. Difficulties encountered while using PPE kits and how to overcome them: an Indian perspective. Cureus 2020; 12: e11652.
24. Henos EA, Seid AA, Debas YM. The incidence and factors associated with failed spinal anesthesia among parturients underwent cesarean section, 2019: A prospective observational study, International Journal of Surgery Open, Volume 24, 2020, 47-51.
25. Adesope OA, Einhorn LM, Olufolabi AJ, Cooter M, Habib AS. The impact of gestational age and fetal weight on the risk of failure of spinal anesthesia for cesarean delivery. Int J Obstet Anesth 2016; 26: 8e14.
26. Sharma SK, Gambling DR, Joshi GP, Sidawi JE, Herrera ER. Comparison of 26-gauge Atraucan and 25-gauge Whitacre needles: insertion characteristics and complications. Can J Anaesth 1995; 42: 706-10.
27. Arevalo-Rodriguez I, Muñoz L, Godoy-Casasbuenas N, et al. Needle gauge and tip designs for preventing post-dural puncture headache (PDPH). Cochrane Database Syst Rev 2017; 4: CD010807.
28. Drasner K, Ringler ML. Repeat injection after a failed spinal: at times, a potentially unsafe practice. Anaesthesiology 1991; 75: 713-4.
29. Steiner LA, Hauenstein L. Ruppen W, Hampl KF, Seeberger MD. Bupivacaine concentrations in lumbar cerebrospinal fluid in patients with failed spinal anaesthesia. Br. J. Anaesth 2009; 102: 839-44.

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