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Original Article

Predictive role of neutrophil-to-lymphocyte ratio (NLR) in the progression of COVID-19 patients in intensive care unit

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ABSTRACT

Aims: The aim of this study was to evaluate the neutrophil-to-lymphocyte ratio (NLR) as a predictive marker for the prognosis of COVID-19 patients, in order to provide an easy, accessible, and cost-effective way to measure inflammation.

Methods: A total of 365 patients, aged over 18 years and admitted to the intensive care unit (ICU) between 01.08.2020 and 31.03.2021 with a positive RT-PCR test for COVID-19, were included. This was a single-center, retrospective study. Demographic data and laboratory results of the patients at the time of the first admission and ICU admission were analyzed. The relationship between NLR values at initial presentation and ICU admission with patient prognosis was statistically investigated.

Results: In our study, we found that NLR and d-NLR values at the time of initial hospital admission and ICU admission had a predictive role in forecasting 30-day mortality in COVID-19 patients admitted to the ICU. An NLR cutoff value of>0.48 at first presentation predicted mortality with a sensitivity of 72.2% and a specificity of 46.0%. An NLR cutoff value of 11.7 at ICU admission predicted mortality with a sensitivity of 64.7% and a specificity of 60.9%. Additionally, procalcitonin, CRP, IL-6, D-Dimer, and ferritin levels at both initial admission and ICU admission were found to have a predictive role in mortality.

Conclusion: The NLR is a predictive marker for mortality in ICU patients. The lower sensitivity and specificity values compared to those in the literature are attributed to differences in the age, comorbidities, and clinical severity of the patient population included in this study.

Keywords: COVID-19, neutrophil-to-lymphocyte ratio, mortality, intensive care, prognosis

INTRODUCTION

In December 2019, pneumonia cases caused by a novel coronavirus leading to acute respiratory distress syndrome were reported in humans in Wuhan, Hubei Province, China. Due to the increasing number of cases, the World Health Organization declared a pandemic in March 2020.[1,2] One of the major issues arising from the pandemic was the significant strain placed on national healthcare systems worldwide and the increased number of patients requiring intensive care unit (ICU) support within a very limited timeframe. Many hospitals made adjustments to inpatient services and ICUs due to the increased hospital admissions caused by the pandemic.[3-5] The importance of the effective use of resources in ICUs became even more critical as hospitals received patient admissions exceeding their capacities.[6,7] Early diagnosis and treatment in critically ill patients can impact disease prognosis and reduce mortality rates.[8] Particularly, hyperinflammatory response and cytokine storm, associated with elevated levels of inflammatory markers, has been shown to significantly increase mortality.[6]

The neutrophil-to-lymphocyte ratio (NLR) is used as a marker of systemic inflammation. The inflammatory response stimulates the release of inflammatory cytokines such as TNF-alpha and IL-6, leading to an increase in neutrophil levels. Proinflammatory mediators such as catecholamines and cortisol bind to the lymphocyte surface, initiating lymphocytic apoptosis, which results in lymphopenia.[6,9] In addition to being an indicator of inflammation, NLR

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has been studied in various fields to determine its potential associations.[10,11] The clinical course of COVID-19 correlates with the inflammatory response, and NLR, reflecting changes in both neutrophil and lymphocyte counts, is considered a reliable inflammatory marker.[12]

This study aims to investigate the effect of NLR values on the prognosis and length of ICU stay in patients admitted to the ICU. Additionally, other inflammatory markers that influence the prognosis of COVID-19 were also analyzed.

METHODS

The study protocol was approved by the Clinical Researches Ethics Committee of University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 08.03.2021, Decision No: 106/12). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This was a single-center, retrospective study conducted between 01.08.2020 and 31.03.2021 at the COVID-19 ICU of University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital. The study included patients aged 18 years and older, who were admitted to the ICU for the first time with a positive SARS-CoV-2 RT-PCR result.

Patients with a history of previous hospitalization in different hospitals, those under 18 years of age, patients with a negative SARS-CoV-2 RT-PCR test result or no PCR test result, patients with respiratory distress due to non-COVID-19 causes, patients with long-standing COVID-19-like symptoms who tested positive for SARS-CoV-2 RT-PCR during hospitalization with a different diagnosis, and patients with repeated ICU admissions were excluded. In the case of repeated ICU admissions, only the first admission data were included in the study.

Demographic and clinical data of the patients were obtained through analysis of the hospital's electronic automation system and ICU monitoring forms. Laboratory parameters during the first hospital admission and the first ICU admission were included in the study. The parameters evaluated included leukocyte count, neutrophil count, lymphocyte count, ferritin, D-Dimer, procalcitonin (PCT), CRP, BNP, IL-6, NLR, and derived neutrophil-to-lymphocyte ratio (d-NLR) [d-NLR is calculated by dividing the difference between the total leukocyte count and the neutrophil count by the neutrophil count].

The onset dates of symptoms and signs, age, gender, comorbidities, dates of first hospital admission and ICU admission, ICU and hospital length of stay, SOFA and APACHE scores were recorded. Mortality was assessed based on the patiaent's status on the 30th day of ICU admission.

Statistical Analysis

Data analysis was performed using SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) version 22.0. Descriptive statistics for continuous variables were presented as mean±standard deviation and median (minimum-maximum), while categorical variables were presented as frequency and percentage. The distribution of continuous variables was evaluated for normality using the Shapiro-Wilk test. When parametric conditions were met, the differences between two groups for continuous variables were assessed using the Independent t-test, and when parametric conditions were not met, the Mann-Whitney U test was used. For comparisons involving more than two groups, continuous variables were evaluated using the Kruskal-Wallis test. In cases where significant differences were found, pairwise analysis was performed to identify the source of the differences. For categorical variables, the chi-square test or Fisher's exact test was used. Survival analysis was conducted using Kaplan-Meier analysis and the Log-Rank test. Regression analysis was performed to evaluate factors affecting mortality. In the ROC analysis, predictive factors for mortality were assessed, and cut-off values were determined. Sensitivity and specificity values corresponding to the identified cut-off values were calculated. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 365 patients were included in the study. The mean age of the patients was 69.94 (12.57). Of the patients, 153 (41.9%) were female and 212 (58.1%) were male (Table 1).

Mortality occurred in 199 patients (54.5%) within 30 days (Table 1). The mean age of survivors was 66.82 (13.33), and the mean age of deceased patients was 72.41 (11.38). The mean age of deceased patients was significantly higher than that of survivors ($p<0.001$). The gender distribution between deceased and surviving patients was similar ($p=0.913$) (Table 2).

The time from symptom onset to hospital admission was 3.27 (3.21) days for deceased patients and 4.42 (3.97) days for survivors ($p=0.003$). The time from symptom onset to ICU admission was similar for both groups ($p=0.053$) (Table 2).

The length of ICU stay and total hospital stay were significantly longer in survivors ($p<0.001$) (Table 2).

The APACHE II and SOFA scores were significantly higher in deceased patients compared to survivors ($p<0.001$) (Table 2).

There was no significant difference between deceased and surviving patients in terms of the prevalence of hypertension ($p=0.074$), diabetes mellitus ($p=0.776$), pulmonary diseases ($p=0.685$), and rheumatologic diseases ($p=0.965$). However, the prevalence of cardiac diseases ($p=0.003$), neurological diseases ($p=0.011$), kidney diseases ($p=0.015$), and malignancies ($p=0.025$) were significantly higher in deceased patients (Table 2).

There was no significant difference between deceased and surviving patients regarding the presenting symptoms ($p>0.05$). The prevalence of myalgia and loss of taste and smell was significantly higher in survivors than in deceased patients ($p=0.040$, $p=0.026$) (Table 2).

The NLR value at the time of first admission and ICU admission was significantly higher in deceased patients compared to survivors ($p=0.001$ and $p<0.001$, respectively). The d-NLR value calculated at first admission and ICU

Table 1. Demographic data and basic characteristics of all patients

Variable	
Age (years)	69.94±12.57
Gender	
Female	153 (41.9%)
Male	212 (58.1%)
Comorbidities	
Hypertension	227 (67.2%)
Diabetes mellitus	139 (38.1%)
Cardiac disease	119 (32.6%)
Pulmonary disease	76 (20.8%)
Neurological disease	49 (13.4%)
Kidney disease	32 (8.8%)
Malignancy	25 (6.8%)
Rheumatological disease	20 (5.5%)
Presenting symptoms	
Dyspnea	198 (54.2%)
Cough	137 (37.5%)
Fever	114 (31.2%)
Fatigue	95(26.0%)
Myalgia	53 (14.5%)
Nausea-vomiting	33 (19.0%)
Loss of appetite	27 (7.4%)
Headache	24 (6.6%)
Sputum production	22 (6.0%)
Loss of taste-smell	10 (2.7%)
Chest pain	7 (1.9%)
Time from symptom onset to presentation (days)	3.79±3.62
Time from symptom onset to ICU admission (days)	7.89±5.02
ICU length of stay (days)	9 (1-56)
Hospital length of stay (days)	14 (0-79)
SOFA score	3 (1-15)
APACHE II score	17 (6-53)
Mortality	199 (54.5%)

The data are presented as mean±standard deviation, median (minimum-maximum), and number (%). Abbreviations: ICU: Intencive care unit, SOFA: Sequential organ failure assessment, APACHE: Acute physiology and chronic health evaluation

Table 2. Distribution of demographic data and basic characteristics in deceased and surviving patients

	Deceased (n=166)	**Survived (n=199)**	**p**
Age (years)	66.82±13.33	72.41±11.38	<0.001*
Gender			
Female	70 (42.2%)	83 (41.7%)	0.913**
Male	96 (57.8%)	116 (58.3%)	
Comorbidities			
Hypertension	95 (57.1%)	132 (66.3%)	0.074**
Diabetes mellitus	60 (37.3%)	79 (38.7%)	0.776**
Cardiac disease	41 (24.7%)	78 (39.2%)	0.003**
Pulmonary disease	33 (19.9%)	43 (21.6%)	0.685**
Neurological disease	14 (8.4%)	35(17.6%)	0.011**
Kidney disease	8 (4.8%)	24 (12.1%)	0.015**
Malignancy	6(3.6%)	19 (9.5%)	0.025**
Rheumatological disease	9 (5.4%)	11 (5.5%)	0.965**
Presenting symptoms			
Dyspnea	85 (51.2%)	113 (56.8%)	0.287**
Cough	63 (38.0%)	74 (37.2%)	0.880**
Fever	45 (27.1%)	69 (34.7%)	0.120**
Fatigue	38 (23.6%)	57 (27.9%)	0.348**
Myalgia	31(18.7%)	22 (11.1%)	0.040**
Nausea-vomiting	12 (7.2%)	21 (10.6%)	0.270**
Loss of appetite	12 (7.2%)	15 (7.5%)	0.911**
Headache	8 (4.8%)	16 (8.0%)	0.216**
Sputum production	8 (4.8%)	14 (7.0%)	0.376**
Loss of taste-smell	8 (4.8%)	2 (1.0%)	0.026**
Chest pain	2 (1.2%)	5 (2.52%)	0.332**
Time from symptom onset to presentation (days)	4.42±3.97	3.27±3.21	0.003*
Time from symptom onset to ICU admission (days)	11.22±28.81	6.99±4.49	0.053*
ICU length of stay (days)	12 (1-52)	7 (1-56)	<0.001***
Hospital length of stay (days)	19 (0-79)	11 (1-41)	<0.001***
SOFA score	2 (1-13)	4(2-15)	<0.001***
APACHE II score	13 (6-29)	19 (8-53)	<0.001***

The data are presented as mean±standard deviation, median (minimum-maximum), and number (%); *Independent Simple T test, ** Chi-square test, *** Mann-Whitney U test, Abbreviations: ICU: Intencive care unit, SOFA: Sequential organ failure assessment, APACHE: Acute physiology and chronic health evaluation

admission was also significantly higher in deceased patients compared to survivors (p<0.001 and p=0.017, respectively) (Table 3).

Procalcitonin, CRP, and BNP levels at first admission and ICU admission were significantly higher in deceased patients compared to survivors (p<0.001) (Table 3).

The D-Dimer values measured at first admission and ICU admission were significantly higher in deceased patients compared to survivors (p=0.002 and p<0.001, respectively). IL-6 levels measured at first admission and ICU admission were also significantly higher in deceased patients compared to survivors (p<0.001). There was no significant difference in ferritin levels at first admission, but levels at ICU admission were significantly higher in deceased patients (p=0.251 and p=0.001, respectively) (Table 3).

In ROC analysis, the role of laboratory test results at first admission and ICU admission in predicting mortality was analyzed. Elevated procalcitonin (AUC=0.679, p<0.001), elevated NLR (AUC=0.604, p=0.001), elevated d-NLR (AUC=0.579, p=0.009), elevated D-Dimer (AUC=0.607, p=0.001), elevated CRP (AUC=0.619, p<0.001), and elevated IL-6 (AUC=0.750, p<0.001) all had significant predictive value for mortality. Elevated WBC and ferritin levels at ICU admission also had predictive value for mortality (<0.05) (Table 4, Figure 1, Figure 2).

For NLR at first admission, the cut-off value of >4.38 predicted 30-day mortality with 72.2% sensitivity and 46.0% specificity. For NLR at ICU admission, the cut-off value of 11.17 predicted mortality with 64.7% sensitivity and 60.9% specificity (Table 5). Table 5 shows the cut-off values, sensitivity, and specificity for tests predicting mortality at first admission and ICU admission.

In univariate analysis of risk factors associated with mortality, advanced age was found to be a significant risk factor for increased mortality (OR: 1.03, p<0.001). Gender (OR: 0.97, p=0.913), history of diabetes mellitus (OR: 1.06,

Table 3. Laboratory tests at initial admission and ICU admission in deceased and surviving patients

	Initial admission			ICU admission		
	Deceased	Survived	p	Deceased	Survived	*p
Procalcitonin (µg/L)	0.1 (0.0-0.3)	0.2 (0.1-.7)	<0.001	0.1 (0-0.3)	0.5 (0.2-1.8)	<0.001
Aspartate transaminase (U/L)	34.5 (24.0-50.0)	33.0 (23.0-54.0)	0.753	32.0 (22.0-45.0)	41.0 (29.0-58.0)	<0.001
Alanine transaminase (U/L)	23.5 (16.0-40.0)	20.0 (14.0-32.5)	0.017	27.5 (17.0-48.0)	24.0 (16.0-39.0)	0.274
Laktat dehidrogenaz (U/L)	329.0 (235.0-439.0)	368.5 (275.0-516.0)	0.015	375.5 (296.0-470.0)	540.0 (419.0-681.0)	<0.001
Creatinine kinase (U/L)	102.5 (56.0-217.0)	137.0 (70.0-321.0)	0.022	71.0 (39.5-143.5)	135.0 (71.0-416.0)	<0.001
Creatinine kinase-MB (U/L)	19.0 (15.2-26.0)	21.5 (15.0-29.9)	0.125	22.0 (16.5-28.8)	29.0 (22.0-44.0)	<0.001
White blood cell ($\times10^3$/µL)	6.4 (4.9-8.2)	6.6 (4.94-9.3)	0.290	7.5 (5.8-9.9)	8.8 (6.2-12.7)	0.009
Platelet ($\times10^3$/µL)	195.5 (162.0-259.0)	184.0 (143.0-232.0)	0.016	247.5(198.0-317.0	201.0 (149.0-270.0)	<0.001
Neutrophil ($\times10^3$/µL)	4.8 (3.4-6.4)	5.0 (3.5-7.7)	0.141	6.4 (4.7-8.76)	7.9 (5.3-11.6)	0.001
Lymphocyte ($\times10^3$/µL)	0.9 (0.7-1.3)	0.8 (0.5-1.1)	0.005	0.6 (0.4-1.0)	0.5 (0.3-0.7)	<0.001
NLR	4.8 (2.8-8.4)	6.0 (3.8-11.1)	0.001	9.2 (5.6-15.3)	14.3 (8.3-24.9)	<0.001
d-NLR	3.3 (1.9-5.2)	3.8 (2.4-5.8)	<0.001	5.9 (4.0-9.5)	8.24 (5.5-13.5)	0.017
PLR	206.4 (147.2-289.3)	214.7 (141.2-326.7)	0.622	384.5 (239.0-371.0)	371.0 (239.2-560.7)	0.556
Ferritin (µg/L)	453.5 (229.0-894.0)	549.5 (232.0-1030.0)	0.251	574.0 (314.0-1004.0)	853.0 (485.0-1483.0)	<0.001
PaO_2/FiO_2	164.8 (128.8-207.8)	155.5 (121.4-204.0)	0.261	113.1 (87.7-153.3)	86.9 (63.6-120.0)	<0.001
Troponin (ng/ml)	0.1 (0.1-0.11)	0.1 (0.1-0.13)	0.018	0.1 (0.1-0.1)	0.1 (0.1-0.3)	<0.001
BNP (ng/L)	359.6 (120.5-906.7)	822.1 (288.4-3807.0)	<0.001	508.2 (271.8-1250.0)	1791.0 (517.0-5607.0)	<0.001
Fibrinojen (mg/dl)	543.0 (451.0-635.0)	529.0 (428.0-647.0)	0.333	554.5 (454.0-645.0)	562.0 (460-650.0)	0.383
D-Dimer (µg/l)	0.7 (0.4-1.2)	0.9 (0.5-2.0)	0.002	0.9 (0.5-1.7)	1.4 (0.8-3.0)	<0.001
C-reactive protein (mg/L)	85.5 (42.7-135.6)	115.0 (60.9-206.4)	<0.001	64.5 (35.8-128.3)	134.5 (77.0-201.0)	<0.001
Interleukin-6 (pg/ml)	17.2 (11.8-50.6)	56.9 (28.8-93.7)	<0.001	17.9 (10.9-43.40)	45.9 (23.4-81.2)	<0.001

Mann Whitney U Test. The data are presented as median and IQR (interquartile range, 25th-75th percentiles). Abbreviations: NLR: Neutrophil-to-lymphocyte ratio, d-NLR: Derived neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PaO_2: Arterial oxygen partial pressure, FiO_2: Fractional inspired oxygen, BNP: Brain natriuretic peptide

Table 4. Predictive value of test results at initial admission and ICU admission for predicting mortality

	Parameter	AUC	SE	95 CI%		p
				Minimum	Maximum	
Initial admission	Procalcitonin	0.679	0.029	0.622	0.735	<0.001
	White blood count	0.531	0.030	0.472	0.590	0.305
	NLR	0.604	0.030	0.545	0.662	0.001
	d-NLR	0.579	0.009	0.555	0.670	<0.001
	Ferritin	0.536	0.036	0.466	0.607	0.317
	PaO_2/FiO_2	0.463	0.035	0.394	0.532	0.299
	Fibrinojen	0.472	0.033	0.408	0.537	0.401
	D-Dimer	0.607	0.030	0.548	0.666	0.001
	C-reaktive protein	0.619	0.033	0.555	0.683	<0.001
	Interleukin-6	0.750	0.045	0.662	0.838	<0.001
ICU admission	Procalcitonin	0.771	0.025	0.722	0.820	<0.001
	White blood count	0.588	0.030	0.530	0.647	0.004
	NLR	0.662	0.028	0.606	0.717	<0.001
	d-NLR	0.652	0.029	0.595	0.708	<0.001
	Ferritin	0.602	0.030	0.543	0.661	0.001
	PaO_2/FiO_2	0.327	0.028	0.271	0.383	<0.001
	Fibrinojen	0.531	0.030	0.472	0.591	0.306
	D-Dimer	0.647	0.029	0.591	0.704	<0.001
	C-reactive protein	0.701	0.027	0.647	0.755	<0.001
	Interleukin-6	0.706	0.033	0.642	0.770	<0.001
	SOFA	0.756	0.025	0.707	0.805	<0.001
	APACHE II	0.851	0.020	0.811	0.890	<0.001

Abbreviations: AUC: Area under the curve, S.E: Standard error, CI: Confidence ınterval, NLR: Neutrophil-to-lymphocyte ratio, d-NLR: Derived neutrophil-to-lymphocyte ratio, ICU: Intencive care unit, PaO_2: Arterial oxygen partial pressure, FiO_2: Fractional inspired oxygen, SOFA: Sequential organ failure assessment, APACHE: Acute physiology and chronic health evaluation

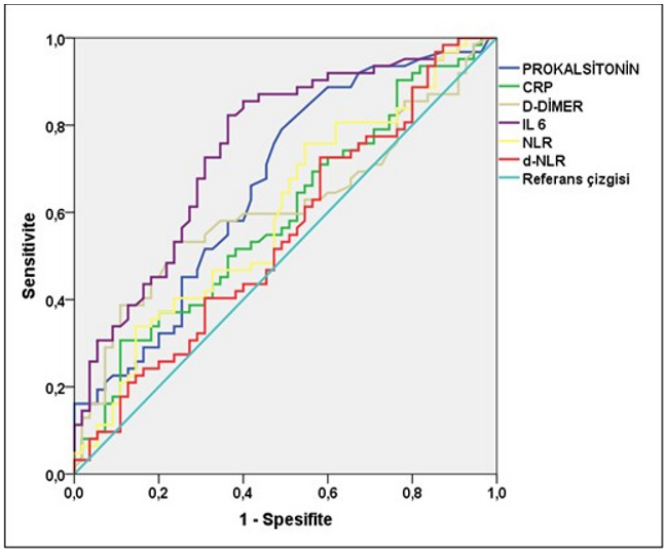

Figure 1. ROC analysis of initial assessment laboratory results and mortality
ROC: Receiver operating characteristic, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, d-NLR: Derived neutrophil-to-lymphocyte ratio

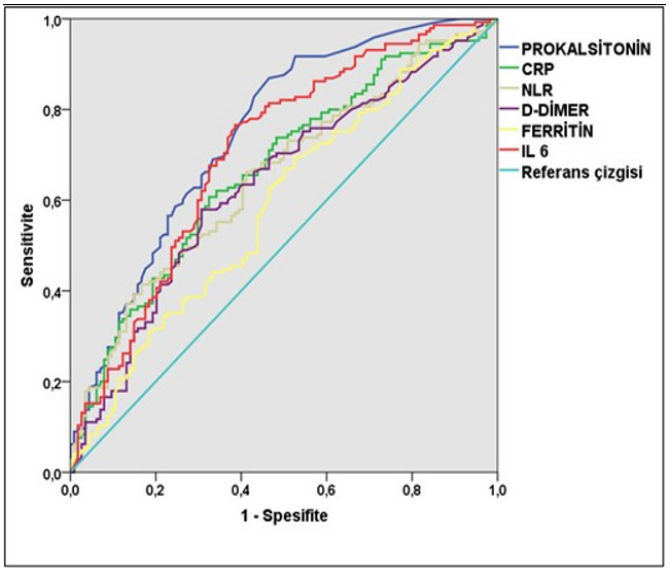

Figure 2. ROC analysis of ICU admission laboratory results and mortality
ROC: Receiver operating characteristic, ICU: Intencive care unit, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio

p=0.776), history of hypertension (OR: 1.46, p=0.078), history of pulmonary diseases (OR: 1.10, p=0.693), and history of rheumatologic diseases (OR: 0.96, p=0.934) were not significant risk factors for increased mortality. History of cardiac diseases (OR: 2.13, p=0.001) and renal diseases (OR: 2.55, p=0.027) were identified as risk factors associated with increased mortality (Table 6).

Table 6. Mortality-related risk factors

	OR	95 CI%		p
		Mimimum	Maximum	
Age	1.03	1.01	1.05	<0.001
Gender	0.97	0.64	1.48	0.913
Diabetes mellitus	1.06	0.69	1.62	0.776
Hypertension	1.46	0.95	2.24	0.078
Cardiac disease	2.13	1.34	3.37	0.001
Pulmonary disease	1.10	0.66	1.84	0.693
Rheumatologic disease	0.96	0.38	2.38	0.934
Renal disease	2.55	1.11	5.84	0.027
Neurological disease	2.31	1.20	4.74	0.012
Malignancy	2.81	1.09	7.22	0.031

Abbreviations: OR: Odds ratio, CI: Confidence interval

In the univariate analysis of mortality-related risk factors, NLR, d-NLR, and IL-6 levels at first admission, and NLR and CRP levels at ICU admission were identified as significant independent risk factors for mortality (Table 7).

For patients with NLR values>4.38 at first admission, the survival rate during hospitalization was significantly lower (p<0.001). For patients with NLR values >4.38 at ICU admission, the survival rate during hospitalization was also significantly lower (p<0.001). For patients with d-NLR values >3.03 at first admission, the survival rate during hospitalization was significantly lower (p<0.001). For patients with d-NLR values >5.64 at ICU admission, the 30-day survival rate during hospitalization was significantly lower (p<0.001) (Table 5).

Table 5. Cut-off values for laboratory results with diagnostic value in predicting mortality and their sensitivity and specificity levels

Time	Parameter	Cut-off	AUC	p	Sensitivity (%)	Specificity (%)
Initial admission	Procalcitonin	0.12	0.670	<0.001	82.9%	47.4%
	NLR	4.38	0.604	0.001	72.2%	46.0%
	d-NLR	3.03	0.579	0.009	67.2%	49.0%
	D-dimer	0.93	0.607	0.001	53.6%	68.6%
	C-reactive protein	143	0.619	<0.001	42.1%	78.9%
	Interleukin-6	23.2	0.750	<0.001	82.5%	63.2%
ICU admission	Procalcitonin	0.13	0.771	<0.001	88.7%	54.7%
	White blood cell	9.6	0.588	0.004	45.1%	73.9%
	NLR	11.17	0.662	<0.001	64.7%	60.9%
	d-NLR	5.64	0.652	<0.001	78.4%	49.1%
	Ferritin	575	0.602	0.001	67.3%	50.3%
	D-dimer	1.95	0.647	<0.001	58.7%	67.1%
	C-reactive protein	76	0.701	<0.001	74.4%	57.8%
	Interleukin-6	23.5	0.750	<0.001	76.0%	61.4%

Abbreviations: AUC: Area under the curve, NLR: Neutrophil-to-lymphocyte ratio, d-NLR: Derived neutrophil-to-lymphocyte ratio

Table 7. Univariate analysis of the relationship between initial assessment and ICU admission tests and mortality

	Parameter	OR	95 CI%		p
			Minimum	Maximum	
Initial admission	Procalcitonin	1.83	1.26	2.67	0.002
	White blood cell	1.04	0.99	1.10	0.105
	NLR	1.04	1.01	1.08	0.009
	d-NLR	3.06	1.65	5.67	0.000
	Ferritin	1.00	1.00	1.00	0.208
	Fibrinojen	0.99	0.99	1.00	0.345
	D-dimer	1.10	1.01	1.20	0.021
	C-reactive protein	1.00	1.00	1.00	<0.001
	Interleukin-6	1.02	1.00	1.03	0.001
ICU admission	Procalcitonin	1.11	1.02	1.20	0.013
	White blood cell	1.05	1.00	1.10	0.021
	NLR	1.04	1.02	1.06	<0.001
	d-NLR	2.02	1.24	3.30	0.005
	Ferritin	1.00	1.00	1.00	0.013
	Fibrinojen	1.00	0.99	1.00	0.328
	D-dimer	0.99	0.99	1.00	0.514
	C-reactive protein	1.00	1.00	1.01	<0.001
	Interleukin-6	1.00	1.00	1.00	0.035

Abbreviations: OR: Odds ratio, CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, d-NLR: Derived neutrophil-to-lymphocyte ratio, ICU: Intencive care unit

DISCUSSION

In our study, which investigated the relationship between NLR and mortality in patients admitted to the ICU with COVID-19 infection, we found that deceased patients had higher NLR, procalcitonin, CRP, IL-6, D-Dimer, and BNP levels. We also observed that deceased patients had a higher mean age, as well as higher APACHE II and SOFA scores. Additionally, in the multivariate analysis of risk factors associated with mortality, NLR, d-NLR, and IL-6 levels at the time of initial hospital admission, and NLR and CRP levels at ICU admission, were found to be significant independent risk factors for mortality.

The literature suggests that different NLR values have a predictive role in mortality and patient prognosis.[13-15] NLR values may vary due to systemic inflammatory conditions such as race, socioeconomic status, smoking, obesity, diabetes, age, cardiovascular diseases, and cancer.[16] In a study by Meng et al.[17], higher NLR values were found in males and patients over the age of 65. We believe that differences in NLR values across studies may be due to variations in clinical severity of the disease, as well as different characteristics of the included patients, such as age, gender, and comorbidities. In our study, NLR values at both initial hospital admission and ICU admission were consistent with the literature and were found to be risk factors for mortality. Furthermore, although the neutrophil count at initial admission was not associated with mortality, lymphocyte levels at both initial admission and ICU admission were significantly associated with mortality. An increase in systemic inflammatory response due to COVID-19 is believed to play a role in these findings. While an increase in neutrophil levels is observed due to heightened inflammatory responses, lymphocyte levels decrease due to apoptosis. The use of NLR, a combined parameter of neutrophils and lymphocytes, has been shown to be a more effective and reliable indicator of systemic inflammation.[18] Therefore, we believe that using NLR values rather than just neutrophil and/or lymphocyte counts may be more effective.

Studies in the literature have reported hospital mortality rates in COVID-19 patients ranging from 18.8% to 49.6%. Additionally, mortality rates have been reported to be over 60% in older and critically ill patients.[13,19] In our study, the mortality rate was found to be 54.5%. We believe that the higher mortality rate in our study can be attributed to the fact that our study only included ICU patients and the mean age of deceased patients was above 60 years.

Viral infections respond primarily through T lymphocytes and cytotoxic lymphocytes, such as natural killer cells. In patients with low lymphocyte counts, viral infections may progress more rapidly. SARS-CoV-2 directly reduces lymphocyte levels through ACE-2 receptors present on lymphocytes. Despite an increase in neutrophil counts, studies have shown that their phagocytic ability is partially impaired. The decrease in T lymphocytes and the increase in neutrophils may increase the risk of bacterial infections. Secondary bacterial infections may contribute to the deterioration of the disease. NLR, PCT, and CRP are parameters that can be used to assess the severity of bacterial infections.[13,14,17] In accordance with the literature, we observed lower lymphocyte counts and higher neutrophil, CRP, and PCT levels in deceased patients. When comparing the results of initial admission and ICU admission, neutrophil levels increased in both groups, while lymphocyte levels decreased. In deceased patients, higher PCT and CRP levels

were observed. This finding may be explained by an increase in inflammatory response due to the progression of COVID-19, as well as secondary bacterial infections.

Ferritin, an acute-phase reactant, is known to be prognostic in acute infections and tissue damage. It is also used in the prognosis of COVID-19 patients. In a study by Chen et al.[13], ferritin levels in deceased patients were found to be twice as high as in surviving patients. Tural et al.[20] also reported that ferritin levels were associated with mortality. In our study, ferritin levels at the time of hospital admission were similar in both surviving and deceased patients. However, in line with the literature, ferritin levels at ICU admission were significantly higher in deceased patients. Therefore, we believe that ferritin could be a valuable parameter for assessing patient prognosis in COVID-19 patients in the ICU.

One of the important causes of mortality in COVID-19 patients is the cytokine storm caused by the excessive release of proinflammatory cytokines such as IL-6.[21,22] Chen et al.[13] reported that IL-6 levels were higher in deceased patients compared to survivors. In our study, in accordance with the literature, we found higher IL-6 levels in deceased patients at hospital admission. Additionally, we observed that IL-6 levels at hospital admission were associated with mortality. The lack of a difference in IL-6 levels at ICU admission could be due to the already severe clinical condition of ICU patients.

D-Dimer and BNP levels also have prognostic significance in COVID-19 patients regarding mortality and the clinical course of the disease. Elevated D-Dimer and BNP levels have been reported as predictive factors for mortality.[23,24] In line with the literature, we observed higher D-Dimer and BNP levels in deceased patients. We believe that D-Dimer and BNP levels are valuable indicators for assessing patient prognosis.

Limitations

The limitations of our study include that it is a retrospective study, and therefore only data recorded in the files were analyzed. Additionally, due to the presence of multiple comorbidities and medications in patients in the ICU, the impact of these factors on the evaluated parameters could not be clearly assessed.

CONCLUSION

In our study, we found that NLR and d-NLR values at the time of initial hospital admission and ICU admission had a predictive role in forecasting 30-day mortality in COVID-19 patients admitted to the ICU. Additionally, procalcitonin, CRP, IL-6, D-Dimer, and ferritin levels at both initial admission and ICU admission were found to have a predictive role in mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was approved by the Clinical Researches Ethics Committee of University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 08.03.2021, Decision No: 106/12).

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.

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Impact of consecutive earthquakes on pediatric anesthesia and analgesia practices in Turkiye

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ABSTRACT

Aims: The study aims to describe anesthesia and analgesia techniques, accompanying crush syndrome or complex conditions like dialysis, along with perioperative management, for 78 pediatric earthquake victims ranging from 10 days old to 18 years, who underwent multiple consecutive surgeries.

Methods: Following approval from the ethics committee, this study was conducted retrospectively using the medical records of all pediatric patients—ranging in age from 10 days to 18. Between February 6 and March 6, 2023, the demographic data, surgical procedures, anesthesia method and anesthesia duration of 78 patients who underwent 216 surgical procedures were recorded from the medical records and subjected to statistical analysis.

Results: The number of surgeries for children started on the second day of the earthquakes and continued until the first month, with a gradually decreasing number. The average age of patients is 10.45±4.59 and commonly performed orthopedic surgeries include debridement (121%, n=55.8%), fasciotomy (17.1%, n=37) for compartment syndrome, multiple fractures (6.5%, n=14), and limb amputations at different levels (17%, n=7.8). Patients who were included in the hemodialysis program (5.1%, n=11) also underwent consecutive surgical procedures during this process. Intraoperative blood transfusion was performed on 20 patients (9.2%). There were no intraoperative morbidities or perioperative mortality. The most commonly used method in the analgesia approach was the administration of intravenous opioids (50.46%).

Conclusion: Centers with well-structured multidisciplinary system, intensive care units, dialysis units, and blood banks are likely to have lower rates of morbidity and mortality during natural disasters like earthquakes, particularly for pediatric patients.

Keywords: Earthquake, disaster, anesthesia, pediatric anesthesia, Crush syndrome

INTRODUCTION

In 2023, two devastating earthquakes struck Turkiye, causing over 60.000 deaths and widespread injuries, overwhelming local healthcare facilities. These potent seismic events occurred consecutively on February 6th, with magnitudes of 7.8 and 7.5, respectively (Figure 1). Rescue efforts were hampered by infrastructure damage, making transportation of supplies and personnel difficult. The focus was immediate trauma care and surgical interventions. Pediatric surgical care readiness requires careful planning, specialized training, and established protocols for rapid response, triage, and integrated care.[1] Children's distinct physiological and psychological needs necessitate individualized anesthesia and analgesia.[2] Successful pediatric post-earthquake management requires a multidisciplinary approach integrating surgical care with effective anesthetic and perioperative protocols. Appropriate anesthesia minimizes patient stress.[3] Following devastating earthquakes, numerous children have tragically lost their parents and urgently need medical care. When these children arrive at the hospital for surgery or other procedures, getting informed consent becomes particularly complicated. Medical staff must consider both legal and ethical implications in order to protect the wellbeing and rights of these vulnerable children. If parents are not present, consent may be needed from a legal guardian or through judicial approval. It is important for healthcare professionals to explain the procedures in terms that are clear and

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appropriate for the child's age and emotional condition.[4] Procedures must be explained clearly, age-appropriately, and with sensitivity. Both general and regional anesthesia are applicable.

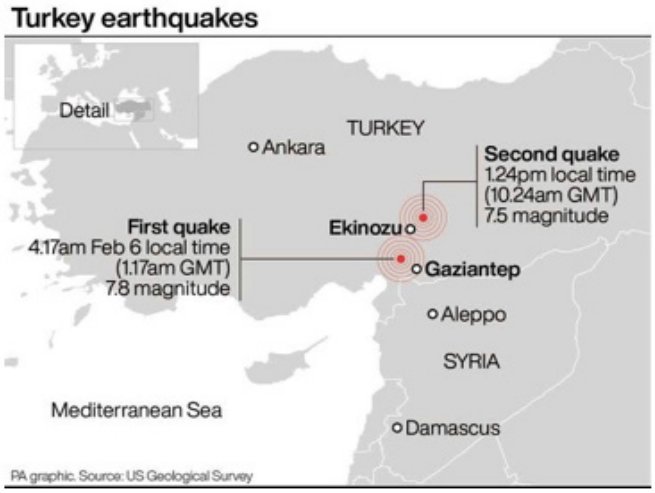

Figure 1. 2023 Feb 6th, Turkiye earthquakes and impact strength

The 2015 Nepal earthquake saw extensive regional anesthesia use due to resource limitations. Advantages include safety for patients with unknown histories, reduced recovery time, and less ICU resource use.[5] The 2018 Indonesia earthquake, with better resources, saw more general anesthesia, especially in pediatric and multiple extremity injuries, though the difference wasn't significant.[6] Safe pediatric transfer from the disaster area to hospitals requires careful management. Healthcare professional involvement, especially anesthesiologists and surgeons, is crucial in the first hour after an earthquake.[7] Anesthesia is vital for pain management. Crush syndrome highlights the need for prompt identification and management of acute conditions. Pediatric anesthesia and analgesia in disasters present unique challenges requiring careful consideration.

The primary objective of this study was to determine the anesthesia and analgesia methods applied to 78 pediatric patients who underwent trauma surgeries, including fasciotomy, debridement, amputation, grafting, flap procedures, and fracture repair, following the 2023 earthquake.

The secondary objective was to determine the factors affecting morbidity and mortality in these patients.

METHODS

The study was conducted with the permission of Ankara Etlik City Hospital Clinical Researches Ethics Committee (Date: 22.03.2023, Decision No: AEH-EKI-2023-022). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. 78 children aged 0 to 18 years were recruited for the study during the period from February 6th to March 6th, 2023, retrospectively (Figure 2).

The data for all patients was gathered from the anesthesia forms completed by the anesthesiologists on duty and from the medical registration system of the hospital.

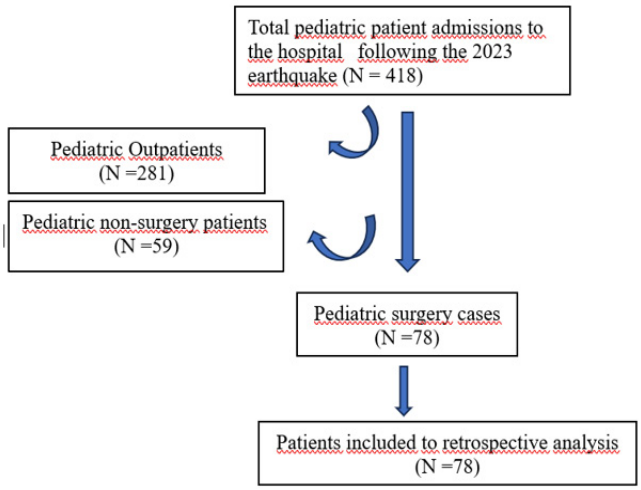

Figure 2. The flowchart illustrating the clinical protocol for pediatric patients at hospital admission

The study focused on the following aspects: demographic data (including age, gender, and other background information of the pediatric patients), surgical procedures (the types and frequency of surgeries performed), anesthesia and analgesia methods (details concerning the anesthetic agents utilized, techniques employed—such as general, regional, or local anesthesia—and pain management strategies), consecutive surgical procedures (the number and types of surgeries each patient underwent and the intervals between procedures), intensive care requirements, and medical conditions, specifically crush syndrome, including the need for hemodialysis and the associated mortality and morbidity rates.

Upon admission to the emergency department, photographs were taken of all children and recorded in the system. Unidentified children were initially assigned a temporary identification starting with the 'G' code, which was utilized from the moment they were rescued from the devastation caused by the earthquake. Patients were assigned new Turkish ID numbers, marked with a 'G' code on their wrists, and admitted to our hospital under this designation.

Informed consent was obtained from accompanying first-degree relatives for those children, and from legal guardians for children who had lost their parents, prior to their operations.

This description outlines the anesthetic procedure for pediatric patients undergoing surgery, particularly those with anxiety, pain, or bilateral lower extremity injuries. For children who are anxious or in pain, sedation is administered while still on the stretcher. This step uses midazolam at a dose of 0.1 mg/kg intravenous (IV) to help calm the patient before moving them to the operating table. In emergency situations or when rapid admission to the operating room is necessary, general anesthesia is typically used. Propofol is used at a dose of 2 mg/kg IV for inducing anesthesia. Rocuronium at 0.5 mg/kg is administered if muscle relaxation is required. Anesthesia is maintained with inhalation of sevoflurane at 1.5 MAC (Minimum Alveolar Concentration) along with an initial IV infusion of remifentanil at 0.01 mcg/kg to provide additional anesthesia and analgesia. If stronger pain relief is needed, fentanyl is administered at a dose of 0.5-1 mcg/kg IV. After the surgical procedure, based on clinical evaluation

and the patient's condition, they are transferred to either an inpatient unit or an intensive care unit for recovery and further monitoring.

Statistical Analysis

While frequency (n) and percentages (%) are used to represent categorical variables, descriptive statistics for continuous variables include mean, standard deviation, median, and interquartile range. The Kolmogorov-Smirnov test was used to verify that the variables were normal. Two groups' non-normally distributed continuous variables were compared using the Mann-Whitney U test. Using Fisher's exact or Chi-square tests, relationships between categorical variables were investigated. IBM SPSS version 25 was used for all analyses, and a significance level of $p<0.05$ was taken into account.

RESULTS

Anesthesia and analgesia data were retrospectively analyzed for 216 procedures performed on 78 pediatric patients who were admitted to our hospital beginning one day after the earthquakes.

The accompanying table (Table 1) provides comprehensive details regarding the demographic parameters, location of injury, types of surgery and operations performed, need of dialysis and transfusion. The number of patients having 1 operation was n=34 (43.5%). The number of patients having >1 operation n=44 (56.4%).

The most commonly performed surgeries were orthopedic, which included fasciotomies for compartment syndrome (n=37, 17.1%), treatment of multiple fractures (n=61, 28,1%), and limb amputations at various levels (n=11, 5.1%).

A subset of patients with renal complications who required hemodialysis also underwent other surgical procedures, highlighting the need for integrated perioperative and dialysis care.

The renal parameters (blood urea nitrogen [BUN] and creatinine levels) and liver function tests (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels) were regularly monitored. These parameters were crucial in managing patients with crush syndrome, as they are indicative of kidney and liver stress or damage.

Hemoglobin and hematocrit levels were tracked to assess the patients' anemic status and overall blood volume, which were critically important due to potential blood loss from injuries and surgeries (Table 2).

Crush syndrome occurred in a significant number of patients, requiring all-encompassing care that included fluid therapy and, in certain situations, renal replacement therapy such as hemodialysis (Table 3).

Crush injury and dialysis status were found to be significantly correlated; patients with crush injuries had a significantly higher percentage of dialysis patients (45.5%) than those without (2.9%) ($p<.001$). Amputation and crush injury were also found to be significantly correlated, with patients with crush injuries having a significantly higher amputation rate (27.3%) than those without ($p=.013$). Crush injury and transfusion status, however, did not significantly correlate ($p>.05$).

Table 1. The sociodemographic and medical characteristics of the patients

Total admission	**n**	**Percentage (%)**	
Gender	78	100.0	
Male/female	48/30	61.54/38.46	
	n (%)	**Male, n (%)**	**Female, n (%)**
Age (y)	78		
0-2	5 (6.4)	2 (4.1)	3 (10)
2-5	11 (14.1)	9 (18.7)	2 (6.6)
5-10	23 (29.4)	10 (20.8)	13 (43.3)
10-15	26 (33.3)	12 (25)	14 (46.6)
15-18	12 (15.3)	9 (18.7)	3 (10.0)
Weight (kg)	78	46.07±25.63	40.00 (30.00-70.00)
ASA physical status			
ASA II	119 (55.09)	65 (30.1)	54 (25.0)
ASA III	83 (38.42)	43 (19.9)	40 (18.5)
ASA IV	14 (6.48)	8 (3.7)	6 (2.7)
Location of injury			
Head and neck	5 (6.4)	3 (6.2)	2 (6.6)
Upper limb	28 (35.8)	16 (33.3)	12 (40.0)
Lower limb	42 (53.8)	22 (45.8)	20 (66.6)
Trunk	3 (3.8)	1 (2.0)	2 (6.6)
Primary surgery			
Orthopedic surgery	65 (83.3)	37 (77.0)	28 (93.3)
Plastic surgery	4 (5.1)	2 (4.1)	2 (6.6)
Neurosurgery	6 (7.6)	2 (4.1)	4 (13.3)
Other	3 (3.8)	2 (4.1)	1(3.3)
Operation duration (min)	216	108.53±56.72	95.00 (75.00-120.00)
Dialysis			
-	67 (85.89)		
+	11 (14.1)	7 (8.97)	4 (5.13)
Transfusion			
-	57 (73.08)		
+	21 (26.92)	11 (14.1)	10 (12.82)
Amputation			
-	67 (85.89)		
+	11 (14.1)	6 (7.7)	5 (6.4)

Table 2. Preoperative renal, hepatic, and hematological monitoring parameters

	n	**Mean±SD**	**Median (Min-Max)**
Hematocrit (%)	216	30.13±4.92	30.00 (27.10-32.90)
Hemoglobin (g/dl)	216	9.98±2.53	9.70 (8.90-10.70)
BUN (mg/dl)	216	29.71±27.27	19.90 (12.00-34.15)
Creatinin (mg/dl)	216	.72±.90	.39 (.25-.60)
AST (IU/L)	216	211.57±367.63	52.00 (25.00-172.00)
ALT (IU/L)	216	96.52±139.19	46.50 (19.75-105.25)

SD: Standard deviation, Min: Minimum, Max: Maximum, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 3. Comparison of the values of certain parameters according to Crush condition and relation between dialysis, transfusion and amputation

	Crush syndrome (-)		Crush syndrome (+)		
	Mean±SD	**Median (Min-Max)**	**Mean±SD**	**Median (Min-Max)**	**p**
Age (y)*	10.41±4.63	11.00 (7.00-14.00)	11.18±4.00	12.00 (8.00-14.00)	.697
Weight (kg)*	45.69±25.34	40.00 (25.00-70.00)	53.27±30.99	40.00 (30.00-85.00)	.379
Hematocrit (%) **	30.14±4.95	30.05 (27.10-32.85)	29.90±4.49	29.70 (26.80-34.70)	.876
Hemoglobin (g/dl) *	9.98±2.58	9.70 (8.90-10.58)	9.95±1.37	9.80 (8.90-10.90)	.617
BUN (mg/dl) *	27.35±23.93	19.30 (11.70-30.10)	73.24±45.56	81.20 (25.50-102.00)	.001
Creatinin (mg/dl) *	.64±.75	.37 (.24-.55)	2.23±1.80	2.21 (.40-3.48)	.003
AST (IU/L) *	172.69±316.74	49.00 (25.00-128.50)	930.80±506.22	910.00 (546.50-1424.0)	<.001
ALT (IU/L) *	81.73±110.43	43.00 (19.00-91.00)	368.50±284.39	350.50 (136.00-510.25)	<.001
	n	**%**	**n**	**%**	
Dialysis***		5			<.001
+	5	6.9	6	7.2	
Transfusion***					.606
+	21	26.92	-	-	
Amputation***					.013
+	6	7.2	5	6.9	

*Mann-Whitney Test; **Independent Samples t-test, *** Fisher's Exact test, SD: Standard deviation, Min: Minimum, Max: Maximum, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

The following table provides an overview of analgesia techniques for pediatric earthquake victims (Table 4).

Table 4. Analgesia approaches in pediatric anesthesia procedures for pediatric earhquake victims

Analgesia (drugs/methods)	**n**	**Percentage (%)**
Intravenous drugs	196	96.1
Opioid (fentanyl/tramadol/morphine)	109	50.46
Paracetamol	87	40.27
Neuraxial/regional block	8	4
Infraclavikuler block	3	1.5
Caudal block	3	1.5
Spinal anesthesia	1	0.5
None (entubated/pre-arrest emergency) surgery)	1	0.5

DISCUSSION

Our research, which examines the two February 2023 earthquakes in Turkiye, stands apart from other studies by solely concentrating on pediatric patients. As a pediatric anesthesia unit, we present data from 216 procedures performed on 78 children aged 0-18 years, highlighting the specific challenges, distinctive approaches, and expert skills involved in anesthesia and analgesia. Anesthetic management of pediatric earthquake victims transferred to our hospital from a remote region with widespread damage has been challenging but effective. Due to being one of the largest and most organized pediatric hospitals in the region and our proximity, transfers were primarily made to our institution.

Given the complicated and varying nature of injuries sustained by children during disasters, it is highly recommended that these medical interventions are carried out in fully equipped and multidisciplinary hospitals. This ensures access to essential resources, expert teams, and comprehensive care, which are crucial for the successful management of multiple trauma and crush injury complications. Jacquet et al.[8] reviewed the literature on earthquake-related injuries in the pediatric population to provide recommendations for improving the reporting and classification of pediatric injuries in disasters. They found that crush injuries were reported at a rate of 6.3% to 18.7%. The results of our study support the similarity between our statistical data and this outcome (16.6%).

Similar to all major earthquakes in the past, particularly when they occur in the nighttime when people are asleep, as in our case, orthopedic injuries have been the most common, with orthopedic surgeries being the most frequently performed.[9-11] Consequent surgeries are widely anticipated as a consequence of devastating earthquakes in Turkiye explaining the multiextremity fractures and debridement for children. These data exhibit comparable outcomes to previous significant earthquakes.

Anesthesia management can be particularly challenging for vulnerable populations, such as children, due to constraints, difficulties in approaching the ideal method, and a lack of medications or medical equipment. Compared to adults, who also play a major role in anesthetic management, pediatric patients present unique challenges that clinicians must address to ensure safety and efficacy when administering anesthesia in such chaotic and resource-constrained environments. Several important factors must be considered when choosing anesthetic agents for pediatric patients in disaster situations, such as large earthquakes. First, the selection of agents needs to consider the restricted supply of medical supplies, which could limit the use of conventional anesthetics. Prioritizing agents with a broad therapeutic window, rapid onset, and brief duration of action is crucial in these settings because they enable flexibility in situations that change quickly. Given its rapid onset, swift recovery, and low emetogenic potential, propofol-based total IV anesthesia is frequently selected for pediatric patients, mirroring its use

in adults. Moreover, IV anesthetics like ketamine also may be favored due to their relative safety, rapid induction, and analgesic properties, which are beneficial when additional pain management resources are scarce. Additionally, inhalational agents, if available, can be useful due to their ease of administration and controllable effects.[14] These approaches support our findings as well.

Analgesia in all patients, owing to the repeated surgical procedures and the increasingly serious conditions associated with each procedure, has proven to be quite challenging. Because they are children with multiple traumas, the common practice has been the administration of IV opioids and/or paracetamol infusions in children undergoing general anesthesia. The analgesic approach in our clinic is like that described in the literature for other earthquakes.[15] However, previous studies on analgesia in earthquake victims have typically included a broad age range, often encompassing both pediatric and adult populations. Moreover, these studies have frequently lacked detailed information regarding regional anesthesia or advanced blocks in children. In contrast, our study specifically focuses on pediatric earthquake victims, providing valuable insights into the unique analgesic needs of this population. Almost all the implementation of postoperative analgesia in our patient group demonstrates our commitment to pain management in pediatric patients, even during periods of high workload. IV opioid agents were most commonly used as the analgesic modality; however, due to the high volume of patients, it was observed that pain assessment records for these patients were incomplete.

In the context of significant earthquakes, effective pain management is essential for optimizing pediatric patients recovery and minimizing trauma-related stress. Multimodal analgesia, which incorporates diverse analgesic agents and techniques, has the potential to be particularly advantageous. This approach may include the use of regional anesthesia, such as nerve blocks, in combination with systemic medications, such as opioids and non-opioid analgesics. Regional approaches offer the advantage of targeted pain relief with potentially fewer systemic side effects. Furthermore, incorporating non-pharmacological interventions, such as distraction, relaxation techniques, and psychological support, can greatly assist in managing pain and anxiety. A limited use of regional anesthesia and analgesia methods was noted in our patient population. This was due to the substantial increase in workload and time limitations.

Successful pediatric surgery, anesthesia, and critical care disciplines in a hospital during disaster conditions depend on efficient cooperation and communication between medical professionals and all facets of government. Optimizing the use of current medical resources and essential supplies is made possible by upholding open communication and solid partnerships. Additionally, good communication ensures that children who cannot receive the necessary care in the current disaster scenario can obtain the right care through a coordinated referral system.[16,20] The efficient management of the system and the comprehensive documentation of all protocols and decisions significantly contributed to the smooth operation of our work in the hospital during this period.

The second leading cause of death in earthquakes is crush syndrome resulting from muscle trauma. The importance of crush syndrome is rhabdomyolysis, which develops as a result of the release of intracellular components into the systemic circulation in striated muscle cells because of compression of the muscles. Acute kidney injury occurs as a result of impaired renal perfusion due to hypovolemia caused by compartment syndrome. It has been demonstrated that children who experienced crush syndrome following the Marmara earthquake had significantly longer entrapment times compared to adults.[17,18] This finding suggests that children may have been better protected from trauma in confined spaces. In a study by Oda et al.[19], the incidence of acute kidney injury (AKI) was found to be 50.5%, 74.5%, and 100% in children with one, two, and three extremity injuries, respectively. The authors also noted that AKI was present in 14.3% of children with a single extremity injury and in 85.7% of those with multiple extremity injuries, suggesting that the number of affected extremities is a crucial determinant of crush syndrome severity.[19] This underscores the importance of close monitoring and proactive measures in pediatric patients with multiple injuries to mitigate the risk of severe AKI, showing the same results of our analysis.

Limitations

There were limitations of this retrospective study. The success of the analgesia approach may be influenced by the specific skills and experience of the anesthesiologist. This introduces potential bias, as the results may not be replicable in settings with less experienced personnel. The study also didn't compare the combination of regional blocks (ultrasound-guided) with other anesthetic techniques regarding this severe emergency, the shortage of medical supplies was also effective in the decision to apply regional blocks the initiative.

CONCLUSION

To mitigate the impact of large-scale disasters like earthquakes, it is vital to recognize that children, being among the most vulnerable groups, require specialized anesthesia and analgesia practices. Pediatric anesthesia requires careful consideration and expertise, particularly in the context of the complex and severe injuries often seen in such scenarios.

The structured approach to analyzing and managing the surgical and anesthetic needs of pediatric earthquake victims provided valuable insight into how to handle large-scale medical emergencies. This study aims to contribute valuable data towards improving future disaster response protocols (While a comprehensive disaster preparedness protocol is not yet fully established in our country, it is currently under development. The preparation of protocols in such disasters will reduce morbidity and mortality rates, specifically in relation to pediatric care under emergency conditions.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Ankara Etlik City Hospital Clinical Researches Ethics Committee (Date: 22.03.2023, Decision No: AEH-EKI-2023-022).

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.

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Effects of smoking on postoperative pain and opioid consumption in patients with major abdominal oncological surgery

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ABSTRACT

Aims: Major abdominal oncologic surgeries cause serious postoperative pain because they contain extensive tissue damage and large skin incision. Therefore, major abdominal oncological surgeries require more opioid consumption. In addition, there is an association between smoking and opioid use. The objective of this study is to evaluate the potential relationships between smoking status and postoperative pain and opioid analgesic consumption in patients after major abdominal oncological surgery.

Methods: For the study, the approval was obtained from the ethics committee of our institution. 130 patients between 18-75 years of age who underwent elective major abdominal oncological surgery under general anesthesia, had ASA I-III score and was planned for intravenous morphine-controlled analgesia for postoperative analgesia were included in the study. The patients were divided into two groups as smoking (65 patients) and non-smoking (65 patients). ASA scores, age, gender, height, weight, and additional diseases were recorded. Fagerström Test for Nicotine Dependence was applied to patients who had been smoking for at least 1 year. In the postoperative care unit, heart rate, blood pressure, SpO2 values, blood pressure values, Ramsey sedation scores were recorded at 0 hours, 2 hours, 6 hours, 12 hours, 24 hours and 48 hours. At these measurement times, the pain intensity of the patients was evaluated by a visual pain scale. Patients' additional analgesic requirement, total morphine consumption, demand from patient-controlled analgesia device, nausea-vomiting, itching, gas release times, hypotension and dry mouth were recorded.

Results: In this study, postoperative 0-hour, 2nd hour, 6th hour, 12th hour, 24th hour and 48th hour VAS values and the amount of morphine consumed were significantly higher in the smokers compared to non-smokers. In terms of additional analgesic use, it was found that the use of additional analgesics was significantly higher in the group of smokers. Dry mouth and the incidence of nausea/vomiting were significantly higher in smoking patients than in non-smoking patients.

Conclusion: It has been found that smoking increases the severity of postoperative pain in patients who underwent major abdominal cancer surgery and these patients need more opioids. We are of the view that while planning postoperative analgesia, effective treatment strategies can be determined by considering that there may be more severe pain in smoking patients.

Keywords: Smoking, adverse effects, analgesia, postoperative pain, oncologic surgery

INTRODUCTION

Major abdominal oncologic surgeries consist of extensive tissue damage and large skin incision. Therefore, it can cause serious postoperative pain. Inadequate pain control may also delay the overall healing of cancer patients and their return to normal function and limiting their planned oncological treatments.[1] An effective treatment plan by determining patient-specific risks for postoperative pain can help to improve their outcomes.

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Experimental studies have shown that nicotine has analgesic efficacy.[2] The analgesic effect of nicotine is likely due to its effects on central and peripheral nicotinic acetylcholine receptors. Another possible explanation for the mechanism of nicotine's analgesic effect may be an increase in plasma endorphins after smoking.[3,4]

On the other hand, epidemiological studies have supported that smoking is a risk factor for acute and chronic pain. This paradox is of increasing clinical significance for smokers and smokers with chronic pain during the perioperative period.[5]

The nicotine in cigarettes affects many physiological systems including the peripheral nervous system, central nervous system, cardiovascular system, gastrointestinal tract, and exocrine glands.[6] In addition, nicotine regulates the natural neuroendocrine-opioid system, causing an increased perception of pain and decreasing the analgesic effect of applied opioid drugs.[7] According to a study by Hooten et al.[7]; smokers have a higher rate of opioid use compared to those with previous smokers and non-smokers. After surgical procedures, nicotine withdrawal in nicotine-dependent patients results in hyperalgesia or lower pain threshold.[8] Failure to manage postoperative pain results in effects on many systems such as an increased proinflammatory cytokine, a decreased anti-inflammatory cytokine, changes in the acute-phase proteins, and coagulation system.[9]

Several studies have shown a relationship between smoking and opioid use.[10] However, we could not find any study which evaluates the relationship between smoking status and opioid consumption in patients undergoing major abdominal oncological surgery.[11,12] It is not clear whether these patients need more analgesics in the postoperative period or not. If such a risk arises, smoking can be used as a marker when postoperative analgesia is planned for this patient population.

In this study, our hypothesis that we aim to observe, and test is: Is the postoperative pain level higher in smokers compared to non-smokers after major abdominal oncological surgery? Does this increase vary depending on the duration of smoking and the degree of nicotine dependence? Additionally, do smokers consume more opioids than non-smokers, and is this consumption positively correlated with the duration of smoking?

METHODS

This study was a prospective, observational study. This study was conducted after the approval of the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Health Practice and Research Centre (Date: 06.03.2019, Decision No: 2019-03/230). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The patients who underwent major abdominal oncological surgery and planned for PCA with intravenous morphine for postoperative analgesia in the postoperative care unit (PACU) were included in the study between March 2019 and October 2019. According to the power analysis calculated in G Power 3.1 program (alpha 0.05 1-beta 0.80). The patients were divided into two groups, and we planned to enroll patients in groups until 65 patients in each group and 130 patients in total.

Group 1: Smoker for at least 1 year.

Group 2: Never smoked before or no smoking for at least 6 months.

After all the patients to be operated on were informed in the preoperative anesthesia outpatient clinic, their written consents were obtained. The patients were informed about patient-controlled analgesia (morphine-PCA) and a 10 cm visual analog scale (VAS) before an operation. After being taken to the intensive care unit postoperatively, age, weight, gender, ASA score, comorbidities, previous operations, operation time, intraoperative crystalloid, colloid and blood products, and Fagerström Test for Nicotine Dependence (FTND) score values were recorded.

The FTND was applied to assess the level of nicotine dependence in smoking patients. FTND is a widely used 6-item questionnaire designed to determine the severity of nicotine addiction. The total score ranges from 0 to 10, and the levels of dependence are classified as follows:

- 0-2 points: Low dependence
- 3-4 points: Mild dependence
- 5-7 points: Moderate dependence
- 8-10 points: High dependence

In our study, preoperative FTND scores were recorded for all smoking patients. These scores were analyzed to investigate the relationship between nicotine dependence, postoperative pain intensity, and opioid consumption. The FTND scores were compared with the VAS values and total morphine consumption at different postoperative time points.

Additionally, smoking patients were categorized based on their nicotine dependence level, and we examined whether individuals with higher nicotine dependence had a different postoperative analgesic requirement. Spearman correlation analysis was used to evaluate the relationship between FTND scores and VAS scores at 24 and 48 hours, as well as total morphine consumption.

Inclusion criteria;
- 18 years and older
- ASA physical risk scores I-III
- Patients undergoing elective major abdominal oncological surgery under general anesthesia and PCA with intravenous morphine to be used for postoperative pain control.

Exclusion criteria ;
- Emergency operations
- Younger than 18 and older than 75 years
- Patients with body mass index ≥35
- Patients with an ASA IV and above
- Pregnant women, hemodynamically unstable patients
- Morphine allergy, chronic opioid use, alcohol or drug addictions
- Neurological and psychiatric illness, liver and kidney failure
- Illiterate and non-cooperative patients
- Cardiac rhythm disorder, diabetic neuropathy

• Patients who do not agree to participate in the study
• Epidural PCA for postoperative analgesia

Study Design

The patients who were included in the study was taken to the operation room on the morning of the operation and evaluated by an anesthesiologist who was independent of the study. Patients who underwent standard anesthesia after monitoring (electrocardiogram, noninvasive blood pressure, SpO_2) according to ASA criteria were included in the study (propofol 2 mg/kg, fentanyl 1.5 µg/kg, lidocaine 1.5 mg/kg and rocuronium 0.6 mg/kg in anesthesia induction, and 2% sevoflurane in 40% nitrogen oxide/oxygen mixture for maintenance of anesthesia). In our clinic, intraoperative acetaminophen and/or nonsteroidal anti-inflammatory analgesics and/or 0.05 mg/kg iv morphine is applied to all patients as standard procedure in major abdominal oncological surgeries. For postoperative analgesia, one of the PCA with iv opioid or epidural PCA methods is preferred. Among these patients, patients with PCA with iv morphine were included in the study. PCA was set as 1mg/h infusion, 1 mg bolus, 10-minute lock time.

After being taken to the PACU, the patients were visited at the 0, 2nd, 6th, 12th, 24th, and 48th hours. Heart rate (HR), blood pressure, SpO_2 values, and frequency of PCA demands, and total morphine consumption was recorded. Patients were evaluated in terms of Ramsey Sedation Score, nausea/vomiting, itching, hypotension, and dry mouth. Postoperative pain severity was evaluated by visual pain scale (VAS, 0=no pain, 10=most severe pain). Extra analgesic applications (patients with VAS values of 4 and above) in PACU were considered as additional analgesic requirements. Extra analgesic applications and its dosage was recorded.

Statistical Analysis

Research data was uploaded to the computer environment and evaluated via "SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL)". Descriptive statistics were presented as mean±standard deviation (minimum-maximum), frequency distribution and percentage. In the evaluation of categorical variables, Pearson Chi-square test and Fisher's Final test were used. The suitability of variables to normal distribution was examined using visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov test). Mann-Whitney U test was used as a statistical method for statistical significance between the two independent groups, and Friedman test was used as a statistical method between 3 and more dependent groups. When a significant difference was found between three and more groups, the Wilcoxon signed ranks test was used in post-hoc binary comparisons to determine the source of the significant difference. The relationship between the variables was evaluated with the Spearman correlation test. The statistical significance level was accepted as $p<0.05$.

RESULTS

Demographic characteristics and clinical data of patients are shown in Table 1. 15.4% of patients had ASA-I, 66.9% ASA-II and the remaining 17.7% had ASA-III risk scores. There was a statistically significant difference between the two groups in terms of ASA classification ($p<0.001$).

There was no statistically significant difference between smokers and non-smokers in terms of surgery branch, types of cancer, duration of operation, presence of comorbidity and all comorbidities present ($p>0.05$).

In terms of VAS values a significant difference was found between smoker and non-smoker groups at all postoperative measurement times ($p<0.001$) (Table 2). In addition, there was a statistically significant difference between smokers in comparison to VAS values over time ($p <0.001$). As a result of post-hoc binary comparisons; it was determined that only VAS value at the 12th hour showed a significant decrease compared to the 6th hour, there was not any significant decrease compared to the previous time, but there was a significant decrease compared to the 2nd or 3rd or 4th time.

When compared to VAS values in non-smokers group, there was not any significant decrease compared to the previous time, but there was a significant decrease compared to the 2nd or 3rd, or 4th time ($p<0.001$). Unlike smokers, there was no significant difference between the 12th hour and 48th hour in terms of VAS values in non-smokers.

The change in the amount of morphine given at different times according to the smoking status is presented in Figure 1. There was a statistically significant difference between the two groups in terms of the amount of morphine given at all measurement times ($p<0.001$).

Also, the percentage of those who needed additional analgesia among smokers was significantly higher than those who did not smoke ($p<0.001$) (Figure 2).

In the smoker group, while there was a positive, moderate statistically significant relationship between the VAS at the 24th hour ($r=0.33$) and the 48th hour ($r=0.28$) and the FTND (Fagerstöm Test for Nicotine Dependence) Score. There was no statistically significant relationship between the FTND test scores with the VAS values at other times ($p>0.05$) (Table 3).

The frequency of patient analgesic demand at all measurement times of smokers was significantly higher than non-smoker patients (Table 4).

A positive and mild relationship was found between the amount of morphine given at 48 hours and the Fagerström Test Score in smokers, which was statistically significant ($r=0.29$, $p=0.019$).

The average of FTND score for smoking patients was 5.1±1.4 (min: 2-max: 8). While only 1 (1.5%) of 65 patients were mildly (2 points) and only 1 (1.5%) was highly dependent (8 points), the remaining 63 patients (97.0%) were moderately dependent.

There was no significant difference between the two groups in terms of intraoperative parameters such as the amount of bleeding, intraoperative crystalloids, and colloids, blood transfusion requirements, and transfused blood product components ($p>0.05$).

There was no statistically significant difference between smokers and non-smokers in terms of HR, systolic artery

Table 1. Demographic characteristics and clinical data of patients

	Total (n=130)	Smoking (n=65)	Non-smoking (n=65)	p
Age (year)	58.2±10.4 (19-89)	57.3±9.6 (27-89)	59.2±11.2 (19-76)	0.097[a]
Gender				
Male	56 (43.1)	31 (47.7)	25 (38.5)	0.288[b]
Female	74 (56.9)	34 (52.3)	40 (61.5)	
Body weight (kg)	74.9±13.6 (40-125)	73.9±14.2 (40-125)	75.9±13.0 (50-115)	0.302[a]
ASA				
I	20 (15.4)	0	20 (30.8)	
II	87 (66.9)	54 (83.1)	33 (50.8)	<0.001[b**]
III	23 (17.7)	11 (16.9)	12 (18.5)	
Type of surgery				
General surgery	70 (53.8)	37 (56.9)	33 (50.8)	
Gynecological surgery	44 (33.8)	20 (30.8)	24 (36.9)	0.744[b]
Urological	16 (12.3)	8 (12.3)	8 (12.3)	
Cancer type				
Endometrium	36 (27.7)	16 (24.6)	20 (30.8)	
Stomach	24 (18.5)	13 (20.0)	11 (16.9)	
Colon	21 (16.2)	11 (16.9)	10 (16.9)	
Rectum	17 (13.1)	9 (13.8)	8 (12.3)	
Prostate	10 (7.7)	4 (6.2)	6 (9.2)	0.959[b]
Ovary	8 (6.2)	4 (6.2)	4 (6.2)	
Pancreas	6 (4.6)	4 (6.2)	2 (3.1)	
Bladder	4 (3.1)	2 (3.1)	2 (3.1)	
Klatskin tumor	3 (2.3)	1 (1.5)	2 (3.1)	
Renal cell tumor	1 (0.8)	1 (1.5)	0	
Operation time (min)	172.9±68.2 (50-480)	174.7±74.8 (50-480)	171.1±61.4 (75-350)	0.968[a]
Presence of comorbidity	79 (60.8)	37 (56.9)	42 (64.6)	0.369[b]
Comorbidities				
CAD	59 (45.4)	26 (40.0)	33 (50.8)	0.218[b]
Endocrine	45 (34.6)	20 (30.8)	25 (38.5)	0.357[b]
Respiratory	11 (8.5)	4 (6.2)	7 (10.8)	0.344[b]
Neurological	2 (1.5)	0	2 (3.1)	0.496[c]
Urinary	1 (0.8)	0	1 (1.5)	1.000[c]

* Continuous variables are presented as "mean±standard deviation (minimum-maximum)" and categorical variables as "number (percent of column)"; n: Number of patients, a: Mann-Whitney U test; b: Pearson Chi-square test; c: Fisher's exact test; **p<0.01; CAD: Coronary artery disease, Min: Minimum

Table 2. VAS scores at different times according to smoking status

	Total (n=130)	Smoking (n=65)	Non-smoking (n=65)	p[a]
	Mean±SD (min-max)	Mean±SD (min-max)	Mean±SD (min-max)	
VAS score				
0	5.0±1.8 (1-9)	5.7±1.8 (2-9)	4.3±1.7 (1-8)	<0.001**
2nd hour	4.0±1.6 (1-8)	4.7±1.5 (2-8)	3.4±1.3 (1-6)	<0.001**
6th hour	3.0±1.3 (0-8)	3.7±1.2 (2-8)	2.3±1.0 (0-4)	<0.001**
12th hour	2.5±1.1 (0-6)	3.0±1.0 (1-6)	1.9±1.0 (0-4)	<0.001**
24th hour	2.0±0.9 (1-4)	2.6±0.8 (1-4)	1.5±0.7 (1-4)	<0.001**
48th hour	1.8±0.8 (1-4)	2.2±0.7 (1-4)	1.4±0.6 (1.3-)	<0.001**

n: Number of patients; mean: Average; SD: Standard deviation, Min: Minimum, Max: Maximum, VAS: Visual pain scale, a: Mann-Whitney U test, **: p<0.01.

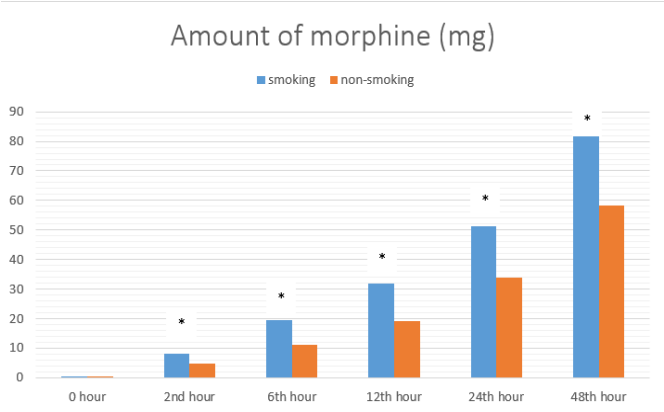

Figure 1. The distribution of the total amount of morphine between smokers and non-smokers

pressure (SAP), diastolic artery pressure (DAP), and oxygen saturation (SpO_2) at all postoperative measurement times (p>0.05).

When the two groups were compared in terms of the Ramsey sedation score, it was observed that there were similar sedation scores at all measurement times except for the 12th hour (Table 5).

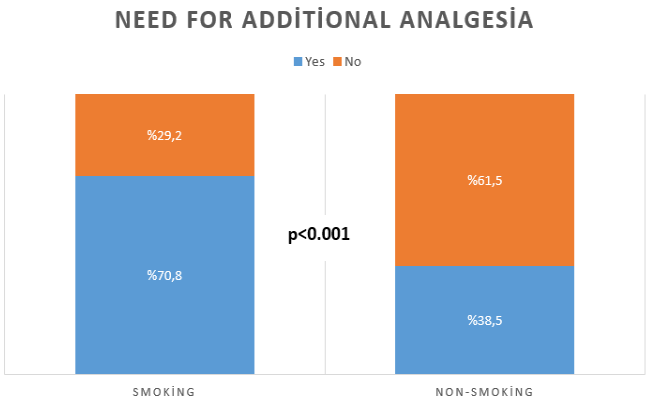

Figure 2. Distribution of the need for additional analgesia

Table 3. Relationship between FTND (Fagerström Test for Nicotine) scores and VAS values at different times and morphine amounts in smokers

	Test score of Fagerström Test for Nicotine Dependence (n=65)	
	r	p
VAS		
0	0.047	0.713
2nd hour	0.011	0.931
6th hour	0.209	0.094
12th hour	0.225	0.072
24th hour	0.327	0.008**
48th hour	0.282	0.023*

n: Number of patients, r: Spearman correlation coefficient, VAS: Visual analog scale, *: p<0.05, **: p<0.01

The most common side effect among the patients included in the study was nausea/vomiting and dry mouth. There was a statistically significant difference between the two groups in terms of the presence of nausea/vomiting (30 (46.2%) vs. 13 (20.0%)) and dry mouth (24 (36.9%) vs. 8 (12.3%)) (p=0.002; p=0.001, respectively). The percentage of patients with nausea/vomiting and dry mouth was significantly higher in smokers than in non-smokers. There was no statistically significant difference between the two groups in terms of urinary/fecal retention, hypotension, and itching (p>0.05) (Table 6).

Table 6. Side effects in both groups

	Total (n=130)	Smoking (n=65)	Non-smoking (n=65)	p[a]
	n (%)	n (%)	n (%)	
Nausea/vomiting	43 (33.1)	30 (46.2)	13 (20.0)	0.002**
Dry mouth	32 (24.6)	24 (36.9)	8 (12.3)	0.001**
Urinary/fecal retention	27 (20.8)	16 (24.6)	11 (16.9)	0.280
Hypotension	15 (11.5)	11 (16.9)	4 (6.2)	0.055
Itching	10 (7.7)	7 (10.8)	3 (4.6)	0.188

n: Number of patients, %: Percentage of column, a: Pearson Chi-square test, **: p<0.01

DISCUSSION

In our study, we found that VAS values were always significantly higher in the smoker group in the postoperative period. At the same time, it was observed that an additional analgesic requirement and morphine consumption were also higher in smoking patients at the end of 48 hours.

Nicotine affects many systems, especially the peripheral nervous system, central nervous system, cardiovascular system, and gastrointestinal tract. In addition, nicotine can provide an analgesic effect through the release of nicotine neurotransmitters and the activation of inhibitory pain pathways in the central nervous system. In a study, nicotine nasal spray was used after transabdominal uterine surgery and less postoperative pain was observed.[13]

Table 4. Change in frequency of patient analgesic demand measured at different times

	Total (n=130)	Smoking (n=65)	Non-smoking (n=65)	p[a]
	Mean±SD (min-max)	Mean±SD (min-max)	Mean±SD (min-max)	
Frequency of demand				
2nd hour	12.5±14.7 (0-86)	18.9±18.0 (0-86)	6.2±5.6 (0-21)	<0.001**
6th hour	20.6±20.4 (0-110)	31.6±22.8 (3-110)	9.6±8.7 (0-41)	<0.001**
12th hour	26.7±24.1 (0-122)	41.0±25.7 (6-122)	12.3±9.4 (0-43)	<0.001**
24th hour	33.4±29.2 (0-140)	51.3±30.9 (8-140)	15.4±11.0 (0-45)	<0.001**
48th hour	37.6±32.1 (0-150)	59.2±31.8 (8-150)	16.2±11.3 (0-52)	<0.001**

n: Number of patients, Mean: Average, SD: Standard deviation, Min: Minimum, Max: Maximum, a: Mann-Whitney U Test; **: p<0.01

Table 5. RAMSEY scores at different times according to smoking status

	Total (n=130)	Smoking (n=65)	Non-smoking (n=65)	p[a]
	Mean±SD (min-max)	Mean±SD (min-max)	Mean±SD (min-max)	
RAMSEY score				
0	2.6±0.7 (1-4)[6;12;24;48]	2.6±0.7 (1-4)[12;24;48]	2.7±0.7 (1-4)[6;12;24;48]	0.434
2nd hour	2.4±0.6 (1-4)[12;24;48]	2.4±0.6 (1-4)[48]	2.4±0.6 (2-4)[12;24;48]	0.959
6th hour	2.2±0.5 (1-4)	2.3±0.6 (1-4)	2.2±0.4 (2-3)	0.456
12th hour	2.1±0.3 (2-3)	2.2±0.4 (2-3)	2.0±0.2 (2-3)	0.004**
24th hour	2.1±0.3 (1-3)	2.1±0.4 (1-3)	2.0±0.2 (2-3)	0.222
48th hour	2.0±0.2 (1-3)	2.0±0.3 (1-3)	2.0±0 (2-2)	0.173

n: Number of patients, Mean: Average, SD: Standard deviation, Min: Minimum, Max: Maximum, a: Mann-Whitney U Test, **: p<0.01, 6 : Post-hoc binary comparison showed a significant difference at 6th hour, 12 : Post-hoc binary comparison showed a significant difference at 12th hour, 24: Post-hoc binary comparison showed a significant difference at 6th hour, 48: Post-hoc binary comparison showed a significant difference at 24th hour

Although nicotine has an analgesic effect, the pharmacological effects of nicotine-dependent patients lack nicotine during hospital stay should also be considered. Nicotine appears to suppress the perception of pain. When nicotine use is stopped suddenly, nicotine-dependent patients show some symptoms such as depressed mood, insomnia, irritability, anger, anxiety, difficulty concentrating, restlessness, decreased HR, and increased appetite. However, the sudden withdrawal of nicotine in these patients results in hyperalgesia or lower pain threshold after surgery or painful procedures. In our hospital as in other hospitals, patients cannot smoke 48 hours.

Creekmore et al.[6] conducted a retrospective study and examined 89 patients hospitalized for coronary artery bypass graft operation and showed that investigated whether the patients who suddenly quit smoking required more opioid analgesics than non-smokers. They demonstrated that smokers who were deprived of nicotine within the first 48 hours after surgery had a higher opioid requirement than non-smokers. In another study of 248 patients who underwent postoperative total hip arthroplasty, smokers showed significantly higher opioid consumption both in the early postoperative period (first 48 hours) and in the 90 days compared to non-smokers. Moreover, VAS values were higher in smokers than in non-smokers, but this was not statistically significant.[14]

Similarly, we found that the VAS values measured at all times were significantly higher in the smoker group than in the non-smoker group. Total morphine consumption was also higher. Zanaty[5] investigated the effect of smoking on perioperative pain and analgesic requirements in patients who had surgery due to lower limb fractures. In this study, patients with VAS higher than 3 were given NSAIDs, and those who were higher than 6 were given meperidine, and their analgesic needs were evaluated. While there was no difference in NSAID consumption of patients, meperidine consumption was found to be higher in favor of the smoker group. In addition, postoperative VAS values were significantly higher at the 8th hour and 24th hour in the smoker group compared to the non-smoker group.[5]

We also found that the need for additional analgesics was higher in the smoker group, and the VAS values were higher in the smoker group at all evaluation times. In our study, the reason for the high VAS in each follow-up interval may be that our patient group consists of patients who have undergone cancer surgery and cancer patients have a different pain character than orthopedic surgery patients. Woodside and Jack conducted a retrospective study on the relationship between smoking and postoperative opioid consumption in female patients following pelvic surgery. Patients were divided into 3 groups as "never smoked", "previous smoker" and "current smoker" according to smoking status. While previous smokers and current smokers used more opioids than patients who never smoked postoperatively, there was no difference between previous smokers and current smokers.[16]

In our study, both male and female patients were included and 56.9% of the patients were female and there was no statistically significant difference between groups.

FTND is a commonly used method to evaluate nicotine addiction levels. There are six questions in the test and the total score range in the test is 0-10. This test embodies addiction through physiological and behavioral symptoms, does not require an invasive procedure and can be applied easily. However, FTND is insufficient to control tobacco consumption and does not cover different aspects of addiction such as the failure of quitting attempts. Weingarten et al.[15] showed that the Brief pain inventory (FTND≥6) was higher in smokers with severe nicotine addiction. In our study, a positive correlation was found between the 24th and 48th-hour VAS values and the 48th-hour morphine consumption and FTND score in the smoker group. In patients with high nicotine dependence, the severity of pain and the morphine consumption were higher.

Opioid analgesics have side effects such as itching, urinary retention, ileus and bradycardia, especially nausea-vomiting. These side effects can delay the healing process and reduce patient satisfaction in the postoperative period. Morphine and synthetic opioids are assumed to increase vestibular sensitivity by activating μ receptors in the vestibular epithelium. In a previous study conducted by Ionescu[16], 71 patients were scheduled for elective laparoscopic cholecystectomy. They found that the incidence of postoperative nausea and vomiting was significantly lower in smokers than in non-smokers. In our study, the incidence of postoperative nausea and vomiting was significantly higher in the smoker group. We think that this result is due to the side effect of morphine consumed 1.4 times in the smoker group more than non-smokers at the end of 48 hours.

Limitations

Lack of standardization of intraoperative and postoperative use of additional analgesics due to the observational design of the study and not investigating the relationship between smoking duration and pain severity and opioid use may be the limitations of our study. In addition we think that it should be investigated whether the time of nicotine withdrawal affects analgesia and opioid use.

CONCLUSION

In this study, we found that smoking increased the severity of postoperative pain in patients undergoing major abdominal cancer surgery and that these patients needed more opioids. The relationship between smoking, perception of pain and opioid consumption, and increased pain severity due to nicotine withdrawal may be important for patients undergoing major oncological abdominal surgery. We think that effective treatment strategies should be determined by identifying the patients who are at risk for severe pain in the perioperative period.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted after the approval of the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Health Practice and Research Centre (Date: 06.03.2019, Decision No: 2019-03/230).

Informed Consent

All patients signed and free and informed consent form.

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.

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Perioperative SARS-CoV-2 screening and comparison of immunoglobin values: a retrospective study

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ABSTRACT

Aims: The SARS-CoV-2 pandemic has posed significant challenges to perioperative management, particularly in the context of preoperative screening and immune response evaluation. Various methods, including polymerase chain reaction (PCR) tests, immunoglobulin (Ig) level assessments, chest X-rays, and computerized tomographies, have been employed to mitigate risks. This study aims to explore the differences in immune responses, particularly Ig levels, between vaccinated and non-vaccinated individuals undergoing surgery during the pandemic.

Methods: During the study period, data from 656 patients who underwent elective or urgent surgery were collected. Among these, only 86 patients had complete and reliable data on vaccination status and immunoglobulin G (IgG) and immunoglobulin M (IgM) levels. Patients with missing or incomplete information were excluded. The final 86 patients were grouped as follows: non-vaccinated and non-infected (NVNI), non-vaccinated but previously infected (NVI), and individuals who received two doses of the Biontech mRNA vaccine (B). The study compared IgG and IgM levels among these three groups.

Results: Patients in group B were significantly older than those in groups NVNI and NVI (mean age: 43.5±13.0 years vs. 30.0±13.2 years and 38.0±18.8 years, respectively; $p<0.05$). Ig G levels were highest in group B (median: 4641.2 AU/ml, IQR: 13137±14502), followed by group NVI (median: 345.5 AU/ml, IQR: 3236±8082), and were lowest in group NVNI (median: 2.4 AU/ml, IQR: 4.1±5.5) ($p<0.05$ for all comparisons). Similarly, Ig M levels were significantly higher in group B (median: 0.38 AU/ml, IQR: 0.91±1.40) than in groups NVI (median: 0.28 AU/ml, IQR: 0.61±0.93) and NVNI (median: 0.05 AU/ml, IQR: 0.18±0.29) ($p<0.05$), while there was no significant difference in Ig M levels between groups NVI and NVNI ($p>0.05$).

Conclusion: Vaccination enhances the immune response, leading to significantly higher IgG levels compared to non-vaccinated individuals, regardless of prior infection. However, some vaccinated individuals did not achieve protective antibody levels. Further research is needed to assess the clinical implications of these findings.

Keywords: Perioperative screening, SARS-CoV-2, immunoglobulin levels, vaccination

INTRODUCTION

The emergence of SARS-CoV-2 in December 2019 marked a pivotal moment in global health, as the virus rapidly spread from Wuhan, China, to become a worldwide pandemic. By October 2021, COVID-19 had infected over 238 million people and caused nearly 4.9 million deaths globally, posing unprecedented challenges to healthcare systems and medical professionals.[1-3] Among the many challenges faced during the pandemic, the management of perioperative care, particularly for patients undergoing elective or urgent surgeries, became a critical issue. The lack of robust data on preoperative screening and the immune response to SARS-CoV-2 created significant dilemmas for anesthesiologists and surgeons, leading to the adoption of various diagnostic tools, including thoracic CT scans, lung X-rays, PCR testing, and laboratory markers such as lymphopenia, eosinopenia, and C-reactive protein (CRP) levels.[4-8]

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The rapid development and deployment of SARS-CoV-2 vaccines, including the Pfizer/BioNTech mRNA vaccine (BNT162b2), ushered in a new era in pandemic management. These vaccines were authorized under emergency use protocols, utilizing rolling review regulatory tools to expedite their assessment and distribution.[9] Despite the success of vaccination programs, questions remain regarding the durability and efficacy of immune responses, particularly in terms of immunoglobulin G (IgG) and immunoglobulin M (IgM) levels, which are critical indicators of antiviral immunity. While prior infection and vaccination have been shown to elicit antibody responses, the correlation between antibody levels and protective immunity remains a subject of ongoing research.[10-12]

Previous studies have provided valuable insights into the immune responses elicited by SARS-CoV-2 infection and vaccination. However, these studies often face limitations, such as small sample sizes, heterogeneity in vaccine types, and variability in the timing of antibody measurements.[13-15] Additionally, there is a lack of comprehensive data on the comparative immune responses in surgical patients, particularly in the context of perioperative care. This gap in the literature highlights the need for further research to better understand the relationship between vaccination status, prior infection, and perioperative immune responses.

In this retrospective study, we aimed to address these limitations by investigating the differences in IgG and IgM levels among patients with varying vaccination and infection histories. Our goal was to provide a clearer understanding of how these factors influence perioperative immune status, thereby contributing to improved preoperative risk assessment and management strategies for surgical patients during the COVID-19 pandemic.

METHODS

The Study Design And Oversight

This study is a retrospective analysis designed to evaluate perioperative SARS-CoV-2 screening and Ig levels in patients undergoing elective and urgent surgeries. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of a university-affiliated special hospital, and ethical approval was obtained from the Scientific Research Ethics Committee of Şehit Prof. Dr. İlhan Varank Training and Research Hospital. (Date: 18.09.2024, Decision No: 2024/279). Informed consent was obtained from each participant during the preoperative anesthetic evaluation. All data were collected, stored, and analyzed in accordance with the ethical guidelines and privacy policies of the IRB and the Declaration of Helsinki.

The Study Population

A total of 656 patients who underwent elective or urgent surgeries between July and December 2021 were initially included in this study. Various perioperative parameters were evaluated, including age, vaccine type, PCR results, IgG and IgM levels, American Society of Anesthesiologists (ASA) scores, operative time, postoperative complications, and prior COVID-19 infection history.

To ensure a homogeneous study population and enable meaningful statistical comparisons, we applied strict inclusion and exclusion criteria. Although data were initially collected from 656 patients who underwent elective or urgent surgery between July and December 2021, not all of them were eligible for the final analysis.

A large proportion of patients (n=540) had received vaccine types other than two doses of the Biontech mRNA vaccine. This group included patients who were vaccinated solely with non-Biontech vaccines (e.g., Sinovac or AstraZeneca), as well as those who had received mixed regimens involving Biontech and other brands (e.g., two doses of Sinovac followed by one dose of Biontech). These patients were excluded to avoid confounding effects from different vaccine combinations and to ensure a consistent immunological comparison.

Additionally, in some urgent surgical cases, patients were taken to the operating room without sufficient time to complete preoperative Ig testing. As a result, 20 patients with missing or incomplete data regarding vaccination status or antibody levels were excluded.

Another 10 patients who received mixed vaccine regimens (e.g., one dose of Biontech and one dose of another brand) were also excluded to preserve the clarity of group definitions. After applying these exclusion criteria, 86 patients remained eligible for analysis.

The final assessed patients was divided into three groups based on vaccination and infection history. The non-vaccinated, non-infected (NV-NI) group consisted of 22 patients who had never received a COVID-19 vaccine and had no prior SARS-CoV-2 infection. The non-vaccinated, infected (NV-I) group included 25 patients who had not been vaccinated but had a documented history of SARS-CoV-2 infection. The Biontech Vaccinated (B) group comprised 39 patients who had received two doses of the Biontech mRNA vaccine, regardless of their prior infection status.

This classification allowed for a comparative analysis of immune responses by assessing IgG and IgM levels across these distinct patient groups, providing valuable insights into the impact of vaccination and prior infection on perioperative immune status.

This research was carried out at a university-affiliated private hospital, which catered to a heterogeneous patient demographic during the COVID-19 pandemic. The healthcare facility delivered comprehensive medical services to both domestic and international patients, encompassing a wide range of surgical and perioperative interventions.

Analytical testing was performed using the ARCHITECT i1000 system (Abbott Laboratories), which utilizes a chemiluminescent microparticle immunoassay (CMIA) for the quantitative detection of antibodies in serum samples. The ARCHITECT system calculates the mean chemiluminescence value from triplicate measurements of the calibrator (C) and stores this value for subsequent calculations. Sample results (S) are determined by dividing the sample chemiluminescence by the calibrator value.

In this study, we quantitatively measured IgG antibodies targeting the S1 subunit of the viral spike (S) protein and IgM antibodies directed against the nucleocapsid (N) protein using a commercially available Abbott kit. Following the manufacturer's guidelines, IgG antibody levels were considered positive at concentrations ≥50.0 AU/ml (arbitrary units per milliliter). For IgM antibodies, results were classified as positive if the index value was ≥1.1 AU/ml.

Statistical Analysis

The data analyses were conducted using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as mean (±standard deviation), median (minimum–maximum), frequency (percentage), or ratio, as appropriate. The normality of the data distribution was evaluated using the Kolmogorov-Smirnov test. For comparisons involving independent quantitative variables, non-parametric tests such as the Kruskal-Wallis test and Mann-Whitney U test were employed. Categorical variables were analyzed using the chi-square test. A p-value of <0.05 was considered statistically significant.

In this study, the SPSS 28.0 program (IBM SPSS Statistics for Windows, Version 28.0; IBM Corp.) was utilized for all statistical analyses. Data were summarized using means, standard deviations, minimum and maximum values, medians, frequencies, and ratios, as appropriate. Continuous variables were presented as mean (±standard deviation), while categorical variables were expressed as numbers (percentages) or ratios. The Kolmogorov-Smirnov test was applied to assess the distribution of variables. For the analysis of quantitative independent data, the Kruskal-Wallis and Mann-Whitney U tests were used, whereas the chi-square test was applied for qualitative independent data. Statistical significance was defined as a p-value <0.05.

RESULTS

A total of 656 patients who underwent elective or urgent surgeries between July and December 2021 were initially included in this study. After applying exclusion criteria—such as incomplete data or vaccination with regimens other than two doses of the Biontech mRNA vaccine—the final analysis was conducted on 86 patients. These patients were categorized into three groups based on their vaccination and infection history: non-vaccinated and non-infected (NV-NI, n=22), non-vaccinated but previously infected (NV-I, n=25), and individuals who received two doses of the Biontech mRNA vaccine (group B, n=39). The demographic and immunological characteristics of these groups are presented in Table 1. An overview of the patients' demographic and immunological data across the study groups is provided in Table 2.

The overall mean age of the study population was 38.42±SD years, and the mean ASA score was 1.22±SD. Only two patients tested positive for SARS-CoV-2 via PCR and underwent emergency surgery due to life-threatening conditions. The mean operative time was 86.7±SD minutes.

In group B (n=39), the median IgG level was 4641.2 AU/ml, while the median IgM level was 0.38 AU/ml. The median age in this group was 43.0 years. Despite receiving two doses of the vaccine, five patients had IgG levels below the seropositivity threshold of 50 AU/ml.

A total of 47 patients (7%) had not received any vaccination. Among them, 25 patients had a documented history of SARS-CoV-2 infection (group NV-I), with a median IgG level of 345.5 AU/ml and a median IgM level of 0.28 AU/ml. The median age in this group was 38.0 years, and only one patient had an IgG level below 50 AU/ml.

The remaining 22 patients were neither vaccinated nor previously infected (group NV-NI). In this group, the median IgG level was 2.4 AU/ml, and the median IgM level was 0.05 AU/ml. All patients in this group had IgG levels below 50 AU/ml. The median age in group NV-NI was 30.0 years.

The age of patients in group B was significantly higher (p<0.05) compared to both the NVİ and NV-Nİ groups. Additionally, the age of patients in the NVİ group was significantly higher (p<0.05) than that of the NV-Nİ group (Table 1).

Regarding IgG levels, group B demonstrated significantly higher values (p<0.05) compared to both the NVİ and NV-Nİ groups. Furthermore, IgG levels in the NVİ group were significantly higher (p<0.05) than those in the NV-Nİ group (Table 1).

For IgM levels, group B exhibited significantly higher values (p<0.05) compared to the NVİ and NV-Nİ groups. However, no significant difference (p>0.05) in IgM levels was observed between the NVİ and NV-Nİ groups (Table 1).

A significant positive correlation (r=0.450) was observed between immunoglobulin M (IgM) and immunoglobulin G (IgG) levels (Figure 1).

A significant positive correlation (r=0.388) was observed between age and IgG levels. A significant positive correlation (r=0.105) was found between age and IgM levels (Figure 2). The correlation of IgG and IgM levels with age is detailed in Figure 3.

Among the study participants, seven patients (1%) had received two doses of the BioNTech vaccine and one dose of the Sinovac vaccine. Five patients (0.7%) had received two doses of BioNTech and two doses of Sinovac. Twenty-seven patients (4%) were administered two doses of Sinovac, while seven patients (1%) received three doses of Sinovac. Fifty-seven patients (8%) had been vaccinated with one dose of BioNTech. Additionally, thirty-nine patients had received two doses of Sinovac and one dose of BioNTech; within this group, one patient exhibited an IgG level below 50 AU/ml.

Other vaccination profiles included one patient with two doses of the Pfizer vaccine, one patient with one dose of the AstraZeneca vaccine, one patient with one dose of the Sputnik vaccine, and three patients with two doses of the Moderna vaccine. One patient had received the Janssen vaccine. Five patients were administered one dose of Sinovac, and within this group, one patient also had an IgG level below 50 AU/ml.

Table 1. Evaluation of age distribution and serum immunoglobulin G and M levels between the groups

			NV-NI	NV+INF	B	p
Age	Mean±SD		27.8±13.2	34.4±18.8	43.5±13.0	0.001[K]
	Median		30.0	38.0	43.0	
Age	0-18 age	n %	6 27.3%	5 20.0%	0 0.0%	0.003[X²]
	19-44 age	n %	14 63.6%	1 52.0%	21 53.8%	
	45≤ age	n %	2 9.1%	7 28.0%	18 46.2%	
IgG	Mean±SD		4.1±5.5	3236±8082	13137±14502	0.000[K]
	Median		2.4	345.5	4641.2	
IgM	Mean±SD		0.18±0.29	0.61±0.93	0.91±1.40	0.000[K]
	Median		0.05	0.28	0.38	

[K] Kruskal-wallis (Mann-whitney u test)/[X²] Chi-square test, NV-NI: Non-vaccinated and non-infected, B: Biontech vaccinated, IgG: Immunoglobulin G, IgM: Immunoglobulin M, SD: Standard deviation

Table 2. Evaluation of the age characteristics between the groups

		Min-max	Median	Mean±SD/n %
Age (years)		2.0-81.0	37.0	36.9±16.2
Age (years)	0-18 age			11 12.8%
	19-44 age			48 55.8%
	45≤ age			27 31.4%
IgG (Au/ml)		0.0-40000	595.2	6899.2±12106.6
IgM (Au/ml)		0.00-6.00	0.20	0.64±1.11
Non vaccinated-non infected				22 25.6%
Non vaccinated+infected				25 29.1%
2 doses of Biontech				39 45.3%

Min: Minimum, Max: Maximum, SD: Standard deviation, IgG: Immunoglobulin G, IgM: Immunoglobulin M

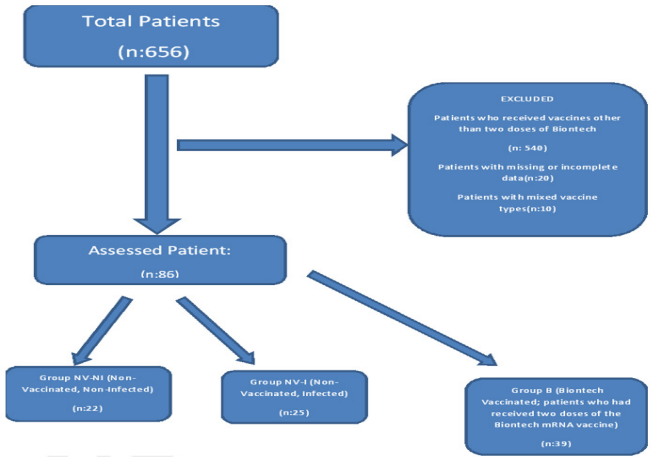

Figure 1. Flow diagram

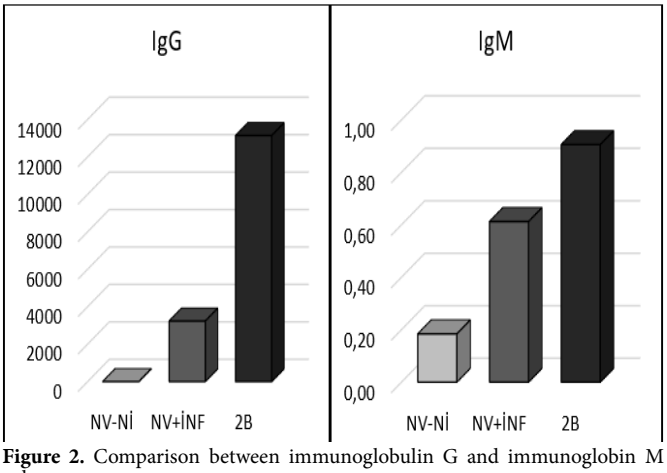

Figure 2. Comparison between immunoglobulin G and immunoglobin M values
NV-NI: Non-vaccinated and non-infected, B: Biontech vaccinated

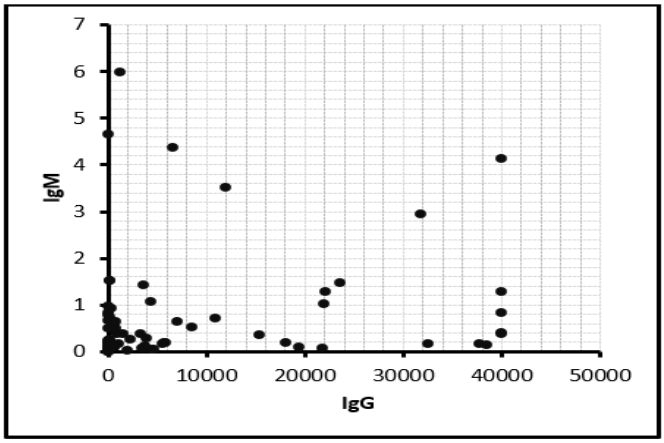

Figure 3. Correlation of immunoglobulin G and immunoglobulin M values with age

Overall, we identified seven patients (1% of the total study population) who did not achieve protective IgG levels (≥50 AU/ml) despite being vaccinated.

DISCUSSION

Our study aimed to evaluate differences in immune responses between vaccinated and non-vaccinated populations by measuring Ig levels. Identifying predictive immune response factors, such as Ig values which is critical for assessing various medical challenges and assisting physicians in anticipating clinical outcomes. We compared quantitative Ig levels across three groups admitted to the surgical residency unit between July and December 2021. Our findings demonstrated that vaccination elicits a stronger immune response, resulting in higher IgG levels compared to non-vaccinated individuals and non-vaccinated-infected groups.

One patient, who was PCR-positive and unvaccinated, was admitted for an emergency cesarean section under spinal anesthesia. Tragically, the patient passed away 43 days post-operation. Another patient, who had received two doses of Sinovac and one dose of BioNTech, contracted COVID-19 one month after surgery. Additionally, a patient with two doses of BioNTech and a negative PCR test was diagnosed with COVID-19 based on thoracic CT findings post-operation. Another patient, also vaccinated with two doses of BioNTech, was diagnosed with pulmonary tuberculosis two months after surgery.

An unvaccinated patient was diagnosed with COVID-19 after three months of her operation but recovered. Another

patient, who had received two doses of Sinovac and one dose of BioNTech, developed COVID-19 one month after surgery and required intensive care admission but eventually recovered.

While antibody levels alone are not the sole indicators of immunity, they correlate with antiviral immunity. However, numerous factors can influence this response, including ethnicity, age, body-mass index (BMI), vaccine type, sex, prior infection history, infection severity, time since vaccination, and profession. For instance, healthcare professionals tend to produce higher and more sustained Ig levels.[11-19]

In our study, IgG levels in group B were significantly higher ($p<0.05$) than in the NVİ and NV-Nİ groups. Furthermore, IgG levels in the NVİ group were significantly higher ($p<0.05$) than in the NV-Nİ group. These observations align with findings by Angyal et al.[21], who reported that individuals vaccinated after COVID-19 infection exhibited 6.8-fold higher antibody responses and 5.9-fold higher T-cell responses after the first dose of the BNT162b2 vaccine compared to those without prior infection.

The age of patients in group B was significantly higher ($p<0.05$) than in the NVİ and NV-Nİ groups, and the age of patients in the NVİ group was significantly higher ($p<0.05$) than in the NV-Nİ group. This age difference may contribute to the observed disparity in antibody responses between groups. Similar findings were reported by De Giorgi et al.[22] and Robbiani et al.[23], who noted that age enhances immune responses. In our study, a significant positive correlation was observed between IgG ($r=0.388$) and IgM ($r=0.105$) levels and age.

Rapid development of SARS-CoV-2-specific IgM has been associated with a milder disease course, whereas delayed IgM elevation is often observed in severe cases.[23] However, the data on IgM development remain inconsistent. Some studies report that a subset of patients never develop IgM, and in some cases, IgG production precedes IgM.[24] For instance, one study found that approximately 50% of inactivated vaccine recipients did not develop IgM after the first dose of the BNT162b2 vaccine.[25]

In our study, the IgM seroconversion rate was 28% in group B after two doses of the BioNTech vaccine. Wei et al.[27] identified 5.1% of participants as non-responders after one dose of BNT162b2, defined as those who did not produce sufficient Igs. In our study, the non-responder rate was 12.8% in group B.

Limitations

This study has several limitations. First, we only evaluated surgical patients or those undergoing diagnostic or therapeutic procedures under anesthesia. Second, the time since vaccination was not consistently recorded. Third, prior infection status in the vaccinated population was not accounted for. Finally, our sample size was limited. Despite these limitations, we believe our findings contribute valuable insights into understanding immune responses during the pandemic era.

CONCLUSION

In conclusion, the findings of this study demonstrate that vaccination elicits a stronger immune response, resulting in higher IgG levels compared to non-vaccinated individuals and non-vaccinated-infected groups. However, as medical professionals, we recognize the need for further research to better understand immune responses, factors influencing COVID-19 severity, and the underlying reasons for increased disease severity. Future studies should investigate additional variables that may impact clinical outcomes, such as pregnancy, vitamin deficiencies, and heavy metal toxicities. It is also important to note that, despite vaccination, some individuals may not achieve protective antibody levels, highlighting the complexity of immune responses and the need for personalized approaches to vaccination and disease management.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was obtained from the Scientific Research Ethics Committee of Şehit Prof. Dr. İlhan Varank Training and Research Hospital. (Date: 18.09.2024, Decision No: 2024/279).

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.

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Hyperbaric oxygen therapy in emergencies: approaches to mechanical ventilation and anesthesia

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ABSTRACT

Aims: The aim of this study is to evaluate the epidemiology, anesthesia management, mechanical ventilator (MV) modes, sedative agents, drug dosages, and complications in mechanically ventilated patients undergoing hyperbaric oxygen therapy (HBOT).

Methods: This study was conducted retrospectively and observationally in a tertiary care center. Intubated adult and pediatric patients who received anesthesia and sedation under emergency conditions for HBOT between February 10, 2023, and May 15, 2024, were included. Data were obtained from the hospital information system, patient discharge summaries, and anesthesia observation forms. Patients' demographic data, indications, comorbidities, respiratory parameters, intravenous agents and their dosages, MV parameters, and complications were analyzed.

Results: HBOT was applied to 560 patients, of whom 3.75% (21 patients) received anesthesia and sedation. Among these patients, 29.4% (5 patients) were children, and 70.6% (12 patients) were adults, with an age range of 2 to 93 years. The indications included carbon monoxide intoxication (COI) (75%), COI with burns (17.6%), COI with synthetic cannabinoid intoxication (5.9%), and purpura fulminans (5.9%). A total of 44 sessions were conducted, ranging from 1 to 8 sessions per patient. The drugs used included midazolam (35.3%), dexmedetomidine (29.4%), remifentanil (23.5%), propofol, ketamine, and rocuronium bromide (64.7%). The ventilation modes utilized were SIMV-VC, SIMV-PC, PRVC, and PC. Increased sedation dose requirement was observed in 88.2% of the cases due to MV asynchrony. Complications included bradycardia, nausea and vomiting, hypo/hypertension, self-extubation, desaturation, and session incompletion. The in-hospital mortality rate was 29.4%.

Conclusion: Anesthesia management in a hyperbaric environment requires a multidisciplinary approach due to the unique physical conditions of the procedure. In intubated patients, the increased need for sedation must be met, and asynchrony should be prevented. During HBOT, propofol, ketamine, dexmedetomidine, remifentanil, and midazolam can be safely used in combination to optimize sedation. Anesthesia management should be individualized to prevent complications.

Keywords: Hyperbaric oxygen therapy, anesthesia, complications, mechanical ventilation, emergency

INTRODUCTION

Hyperbaric oxygen therapy (HBOT) is a medical treatment method in which 100% oxygen is administered under special conditions at pressures higher than sea level (2-3 atmospheres absolute [ATA]) (Figure 1).[1] HBOT is utilized as an emergency treatment for conditions such as crush injuries, carbon monoxide intoxication (COI), acute smoke inhalation, compartment syndrome, air-gas embolism, decompression sickness, retinal artery occlusion, cyanide intoxication, anoxic-hypoxic encephalopathy, gas gangrene, and necrotizing soft tissue infections.[2] The fact that patients with these indications reach HBOT as soon as possible increases the success of treatment.

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Figure 1. The hyperbaric chamber used in our center

The general principles of HBOT are based on increasing the pressure and partial pressure of oxygen to enhance the level of oxygen delivered to tissues. The increase in dissolved oxygen improves oxygen delivery at the tissue level, compensating for defects in oxygen transport in related conditions.[3] Due to these effects, HBOT also exhibits bactericidal and bacteriostatic properties.[4]

HBOT is also administered to critically ill patients with conditions such as acute respiratory failure and sepsis, where the cardiovascular system is affected, and there is a need for mechanical ventilation (MV) and inotropic support. In critical patients, it is essential to monitor vital and respiratory parameters, ensure safe continuation of ventilation under high pressure, provide adequate sedation to achieve MV synchronization, and prepare hyperbaric-compatible equipment and devices, such as syringes and infusion pumps suitable for dose titration.[5] Considering the unique and specific conditions of HBOT, the preparation and anesthesia management of critically ill emergency patients must be conducted meticulously.

In the literature, there is limited data on the pharmacokinetics of anesthetics during HBOT and on patients monitored with MV. The aim of this study was to describe the incidence, demographic data, anesthesia management, sedation agents used, drug doses and complications in patients with MV who underwent HBOT under emergency conditions in our center.

METHODS

This study was conducted retrospectively and observationally in a tertiary training and research hospital. It was approved by the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 05.06.2024, Decision No: AEŞH-BADEK-2024/534) and conducted in accordance with the Declaration of Helsinki. Intubated patients who received anesthesia and sedation under emergency conditions for HBOT at our center between February 10, 2023, and May 15, 2024, were included in the study. There were no age restrictions for inclusion. Patient data were obtained from the hospital information system, patient discharge summaries, and anesthesia observation forms. The evaluated parameters included demographic data, HBOT indication, number of sessions applied, need for inotropic agents, presence of acute respiratory distress syndrome (ARDS) findings, sedative agents used, their requirements and dosages, MV mode, neuromuscular blockade requirements, complications, and in-hospital mortality. Sedation doses in the first sessions of intubated patients who underwent HBOT were compared. The routine protocol for HBOT administered at our center consists of a total duration of 120 minutes per session, including a 15-minute compression phase at the beginning and a 15-minute decompression phase at the end. The treatment pressure is 2.4 ATA. The therapy involves three 30-minute intervals of oxygen administration, interspersed with 5-minute air breaks. Patients with incomplete data in their records were excluded from the study.

Mechanical Ventilator Use

In the hyperbaric unit, the Maquet Servo-i® HBO Ventilator is utilized. This MV, approved for dives up to 30 meters and pressures up to 4.000 hPa, can be used for neonatal, pediatric, and adult patients. Tidal volume and other parameters are automatically adjusted during the compression and decompression phases. Both controlled and assisted ventilation modes are available (Figure 2).

Figure 2. Mechanical ventilator used in hyperbaric environment

Statistical Analysis

Statistical data will be evaluated with SPSS 22.0 (Statistical Program Social Sciences) package program. Continuous variables will be expressed as median (minimum-maximum) and categorical variables as number and percentage.

RESULTS

Between February 10, 2023, and May 15, 2024, a total of 560 patients underwent HBOT, of whom 3.75% (21 patients) received anesthesia and sedation. Data from these 21 patients were reviewed, but 4 patients were excluded due to incomplete data, leaving 17 patients for the study (Figure 3). The included patients ranged in age from 2 to 93 years, with a median age of 54 years (Table 1). Of the patients, 58.8% were female, and 41.2% were male (Table 1). All patients were intubated and admitted to HBOT under emergency conditions, with their status assessed as ASA 4E. Comorbidities were present in 82.4% of the patients, and the associated comorbid conditions are summarized in Table 1.

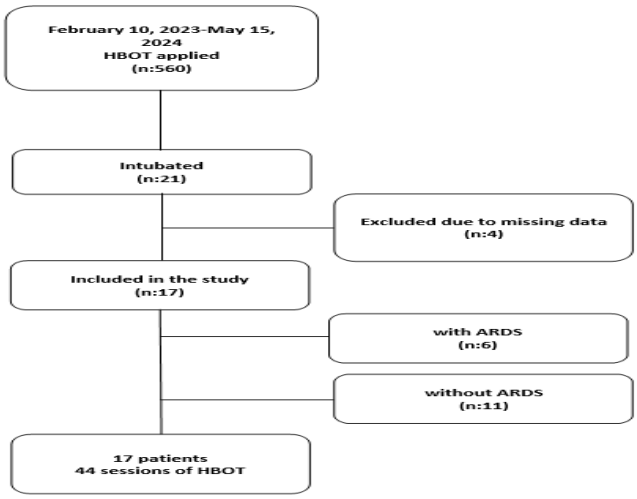

Figure 3. Working diagram
*HBOT: Hyperbaric oxygen therapy, ARDS: Acute respiratory distress syndrome, n: Number of patients.

Table 1. Demographic data and comorbidities

	n=17
Age	
Median	54
Range	2-93
Gender n (%)	
Female	10 (58.8)
Male	7 (41.2)
Weight (kg)	
Median	70
Range	10-90
Height (mt)	
Median	161
Range	80-178
Presence of comorbidity n (%)	
Yes	14 (82.4)
No	3 (17.6)
Comorbidities n (%)	
Diabetes mellitus	2 (11.8)
Hypertension	5 (29.4)
Post-CPR	4 (23.5)
Coronary artery disease	5 (29.4)
Cerebrovascular disease	1 (5.9)
Hypothyroidism	2 (11.8)
COPD	2 (11.8)
CKD	1 (5.9)
Pregnancy	1 (5.9)
Ovarian malignancy	1 (5.9)
Meningitis	1 (5.9)

kg: kilogram, CPR: Cardio pulmonary resuscitation, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, n: Number of patients

Of the patients, 70.5% received HBOT due to COI, 17.6% due to COI with burns, 5.9% due to COI with synthetic cannabinoid (bonsai) intoxication, and 5.9% due to purpura fulminans (Table 2). The number of HBOT sessions ranged from 1 to 8, with a median of 2 sessions and a total of 44 sessions. Forty-two sessions were successfully completed, while 2 sessions were terminated early due to deterioration in vital signs. ARDS was observed in 35.3% of the patients, and 41.2% required inotropic agents (Table 2). For sedation, midazolam was administered to 6 patients, dexmedetomidine to 5 patients, and remifentanil to 4 patients. During the sessions, 8 patients also received additional sedative agents, including propofol and ketamine (Table 2). Patients were managed using various ventilator modes: 41.2% with pressure regulated volume control (PRVC), 29.4% with Synchronized intermittent mandatory ventilation volume control (SIMV-VC), 17.6% with pressure control (PC), and 11.8% with Synchronized intermittent mandatory ventilation pressure control (SIMV-PC). During the sessions, 88.2% of the patients experienced MV-patient asynchrony, and neuromuscular blocking agents (rocuronium bromide) were used in 64.7% of the patients (Table 2).

Table 2. Some evaluated parameters of HBOT

	n=17
HBOT indication, n (%)	
COI	12 (70.5)
COI+bonsai intoxication	1 (5.9)
COI+burn	3 (17.6)
Purpura fulminans	1 (5.9)
Number of HBOT session	
Median	2
Range	1-8
ARDS, n (%)	
Yes	6 (35.3)
No	11 (64.7)
Inotrope use, n (%)	
Yes	7 (41.2)
No	10 (58.8)
Sedative substance, n (%)	
Absent	2 (11.8)
Midazolam	6 (35.3)
Dexmedetomidine	5 (29.4)
Remifentanyl	4 (23.5)
*Propofol	
*Ketamine	
MV mode, n (%)	
PRCV	7 (41.2)
PC	3 (17.6)
SIMV-PC	2 (11.8)
SIMV-VC	5 (29.4)
MV compatibility, n (%)	
Compatible	2 (11.8)
İncompatible	15 (88.2)
Neuromuscular blocker use, n (%)	
Yes	11(64.7)
No	6(35.3)

HBOT: Hyperbaric oxygen therapy, COI: Carbon monoxide intoxication, ARDS: Acute respiratory distress syndrome, MV: Mechanical ventilator, PRVC: Pressure Regulated volume control, PC: Pressure control, SIMV-PC: Synchronized intermittent mandatory ventilation pressure control, SIMV-VC: Synchronized intermittent mandatory ventilation volume control, n: Number of patients
* Propofol or ketamine was not used as primary sedative agents in any of the patients

Complications were recorded in 76.5% of the 44 HBOT sessions. Among these complications, 50% were bradycardia, 10% nausea and vomiting, 10% hypotension, 5% hypertension, 5% self-extubation, 10% desaturation, and 10% session incompletion (Table 3). In one patient, the endotracheal tube cuff ruptured, resulting in self-extubation. The patient was reintubated inside the hyperbaric chamber. In two patients, vital parameters deteriorated due to pressure increases, and their sessions were terminated prematurely. None of the patients who developed complications required cardiopulmonary resuscitation during HBOT. Although none of the patients received cardiopulmonary resuscitation during HBOT, in-hospital mortality (due to various causes during intensive care follow-up) was determined as 29.4% (Table 3).

According to the first session data of the patients in HBOT, the dose of sedative medication required increased in 88.2% of the patients, the dose of the sedative agent applied was increased, and propofol and ketamine were used in case of wakefulness. Details of the sedative agents used are provided in Table 4.

Table 3. Data on the complication and mortality

	n=17
Complication, n (%)	
Yes	13 (76.5)
No	4 (23.5)
Complication, n (%)	
Bradycardia	10 (50)
Nausea-vomiting	2 (10)
Hypotension	2 (10)
Hypertension	1 (5)
Extübation	1 (5)
Desaturation	2 (10)
Session interrupted	2 (10)
Mortality in hospital, n (%)	
Death in hospital	5 (29.4)
Discharge from hospital	12 (70.6)

*n: Number of patients

DISCUSSION

In our country, the number of patients undergoing HBOT is increasing with the increasing number of centers, and it is important that critically ill patients with emergencies such as fire, burns, trauma and crush injuries reach HBOT as quickly as possible. While some of these patients are monitored with spontaneous breathing, others require intubation due to compromised respiratory parameters, hemodynamic instability, or other conditions. Intubated patients, who are dependent on MV, pose unique management challenges due to the specific conditions of the hyperbaric environment. These challenges begin with the transfer process and extend to ensuring the maintenance and monitoring of vital signs within safe ranges during sessions, achieving synchronization with the MV, preventing ventilator-induced lung injury (VILI) caused by asynchrony, maintaining endotracheal tube cuff integrity, and sustaining continuous drug infusions.[6] In this study, we aimed to describe the incidence, demographic data, sedation status, complications, MV modes and anesthesia management of MV-dependent intubated patients who received HBOT in emergency conditions due to fire, smoke inhalation, burn and necrotizing tissue infection. We presented the experience of 44 HBOT sessions with anesthesia in 17 pediatric and adult patients meeting the inclusion criteria.

There is limited information in the literature regarding intubated patients undergoing HBOT, with only a few studies reporting incidence. In the study by Bessereau et al.[6], the incidence of intubated patients undergoing HBOT was reported as 14.65%. In Turkiye, there are no previous studies reporting incidence, and the incidence in our center was determined to be 3.75%. We anticipate that this difference in incidence may be attributed to several factors, including the relatively limited number of HBOT centers in Turkiye, challenges in the patient transfer process, lack of integration between emergency medicine and intensive care units, issues within the patient referral chain, and a relatively lower level of awareness about HBOT among physicians in Turkiye. While HBOT is integrated with emergency and intensive care medicine internationally, in Turkiye, it operates as a primary specialty service.[7-9] For these reasons, enhancing communication and collaboration among hyperbaric medicine, emergency medicine, intensive care, and anesthesia teams is crucial for the effective treatment of critically ill patients.

HBOT can be applied to pediatric and adult populations across various indications, regardless of age.[10] In our study, the population ranged from 2 to 93 years of age (Table 1). Comorbidities were present in 82.4% of the patients, and 23.5% (4 patients) had a history of successful cardiopulmonary resuscitation. The indications for HBOT included emergencies such as COI, burns, and purpura fulminans secondary to meningococcemia. Notably, 94.1% of the patients were intubated and underwent HBOT following forensic events (Table 2). The most common indication

Table 4. Drug doses used before and during the first session

	Age	Sedation	Pre-session dose	Dose during session	Additional medicine	Additional medicine
1	2	Midazolam	0.04 mg/kg/h	0.07 mg/kg/h	30 mg propofol	
2	7	Dexmedetomidine	0.3 mcg/kg/h	0.45 mcg/kg/h	-	
3	7	-	-	-	-	
4	8	Midazolam	0.05 mg/kg/h	0.08 mg/kg/h	50 mg propofol	
5	16	Midazolam	0.05 mg/kg/h	0.1 mg/kg/h	-	
6	72	Remifentanyl	2 mcg/kg/h	3.2 mcg/kg/h	20 mg propofol	
7	93	Dexmedetomidine	0.2 mcg/kg/h	0.35 mcg/kg/h	-	
8	74	Dexmedetomidine	0.3 mcg/kg/h	0.5 mcg/kg/h	-	
9	54	Remifentanyl	5 mcg/kg/h	9.2 mcg/kg/h	50 mg propofol	25 mg ketamine
10	79	Midazolam	0.03 mg/kg/h	0.05 mg/kg/h	30 mg propofol	
11	87	Dexmedetomidine	0.2 mcg/kg/h	0.35 mcg/kg/h	-	
12	30	-	-	-	-	
13	86	Midazolam	0.04 mg/kg/h	0.06 mg/kg/h	-	
14	55	Remifentanyl	5 mcg/kg/h	10 mcg/kg/h	100 mg propofol	
15	53	Dexmedetomidine	0.2 mcg/kg/h	0.35 mcg/kg/h	40 mg propofol	
16	30	Midazolam	0.06 mg/kg/h	0.1 mg/kg/h	80 mg propofol	50 mg ketamine
17	74	Remifentanyl	2 mcg/kg/h	3.2 mcg/kg/h	-	

mg: Milligram mcg: Microgram, kg: Kilogram, h: Hour

was COI (%94.1). While HBOT is an effective treatment for COI, its use in cyanide poisoning associated with fires is less documented in the literature, though it is widely accepted by clinicians.[11] In case of fire, COI, smoke inhalation, and cyanide poisoning, patients should be transferred to hyperbaric treatment under emergency conditions as soon as possible.[12] In our study, HBOT was administered to three patients with COI and cyanide poisoning following burns, and we believe that HBOT provides significant benefits in intoxications occurring after fires. Centers have reported varying approaches regarding the number of sessions for intoxications and other indications. In our study, the median number of sessions was 2, ranging from 1 to 8. For MV-dependent patients, we believe that the decision on the number of sessions should be individualized, considering the patient's condition, indication, and the potential benefits and risks of HBOT.

The potential complications specific to anesthesia in the hyperbaric chamber stem from the physiological effects of this unique environment.[13] The efficacy, distribution, and safety of inhalation anesthetics in the hyperbaric setting are unpredictable. Since inhalation agents will almost always leak into the hyperbaric environment, they also pose potential risks for the operating team. Therefore, the use of intravenous (IV) anesthetics instead of inhalation agents is crucial due to the behavior of gases and the risk of contamination. In our center, IV agents such as midazolam, dexmedetomidine, remifentanil, propofol, and ketamine are used in combination, tailored to the individual needs of intubated patients undergoing HBOT. The current literature only reports the use of ketamine, benzodiazepines, and neuromuscular blockers.[14] The pharmacokinetics of IV agents in HBOT have been studied only in animal experiments, and there are no studies on their pharmacokinetics and dosage in humans.[15] The doses of IV agents used in this study are detailed in **Table 4**. According to the results of this study, compared to pre-session conditions, wakefulness and sedation dose requirements increased significantly, especially at high pressure levels. MV asynchrony was observed in 88.2% of the patients, particularly during diving and at high pressures, and neuromuscular blockers were used in 64.7% of the patients. We believe this asynchrony is due to the increased sedation dose requirements caused by the altered physiology and pharmacokinetics under high pressure. In patients with MV asynchrony, sedation doses were increased, and neuromuscular blockers were used to ensure synchronization with the MV. In MV-dependent patients, providing adequate sedation and, if necessary, using neuromuscular blockers is important to mitigate the risk of VILI in cases of asynchrony.[16] In our study, 35.3% of the patients had ARDS. ARDS is associated with high Ppeak pressures and an increased risk of pneumothorax during the decompression phase of HBOT.[17] For these reasons, intubated patients undergoing HBOT should be closely monitored with appropriate equipment, drug doses should be titrated individually, and the numerous challenges encountered in anesthesia management should be optimized and evaluated in detail.

Due to the risk of fire and explosion caused by high oxygen pressure in the hyperbaric environment, electrical equipment and batteries must be kept to a minimum for safety, and all equipment used must be compatible with the hyperbaric setting.[9] For intubated patients, the most critical equipment includes the MV, infusion pumps, and monitors for tracking vital parameters. Moon et al.[14] reported the use of the Monaghan 225 ventilator under hyperbaric conditions. At our center, we use the Maquet Servo-i® HBO Ventilator, with patients managed in PRVC, PC, SIMV-PC, and SIMV-VC modes. When selecting the MV mode in the hyperbaric environment, it is crucial to closely monitor Ppeak and Pplato pressures, avoid excessive pressures to prevent pneumothorax, and ensure the delivery of adequate tidal volumes. Patients' age, comorbidities and conditions such as ARDS should also be taken into consideration when choosing the MV mode. To counteract the increased airway resistance and turbulent flow disadvantages associated with high-pressure environments, the largest suitable endotracheal tube (ETT) should be used for the patient.[18] In addition to tube size, the ETT cuff of intubated patients undergoing HBOT should be deflated and filled with saline or distilled water before the session.[6] Similarly, Foley catheter cuffs must also be evacuated from the air before the session. This precaution is necessary to mitigate the risk of cuff rupture due to changes in ambient pressure. Despite the routine practice at our clinic of filling ETT cuffs with saline prior to sessions, a cuff rupture occurred in a 7-year-old patient during a session, resulting in extubating. The patient's saturation levels dropped to 50% due to probable saline aspiration and failed ventilation, but immediate intervention prevented further complications. This incident suggests the need to evaluate the suitability of ETT cuffs for hyperbaric environments. Similar case reports have been described in the literature.[19] Another consideration in the hyperbaric environment is gastrointestinal gas/air. Under pressure, gases can expand 2-3 times their original volume, potentially impairing ventilation and causing desaturation. At our center, nasogastric tubes were routinely placed in all patients before hyperbaric sessions to prevent such complications.

Due to altered physiology caused by increased pressure and hyperoxia in the hyperbaric chamber, several complications have been reported.[20] While diving bradycardia and reflexes represent protective physiological adaptations, the environment itself is non-physiological.[21] In critically ill intubated patients managed under emergency conditions, unpredictable complications can arise in this non-physiological setting. In our study, 76.5% of patients experienced complications, the most common being bradycardia (50%). One patient experienced self-extubation due to cuff rupture, and in two patients, sessions were terminated due to deteriorated vital parameters (**Table 3**). These findings underscore the need to carefully evaluate the potential risks and benefits of HBOT in intubated patients and ensure patient safety during its application. Even with thorough preoperative assessments, it must be remembered that certain complications, such as central nervous system oxygen toxicity, may be detected late under sedation. Neurological examinations should not be overlooked during the perioperative period.[22] The complications we encountered are detailed in **Table 3**, and no patients required cardiopulmonary resuscitation. Of the 44 total sessions, 42 were successfully completed, with only two sessions being terminated prematurely. Early detection and prompt intervention in response to complications are

critical in reducing morbidity and mortality. Mortality rates for intubated patients undergoing HBOT reported in the literature range from 11% to 87%, whereas the in-hospital mortality rate in our study was 29.4%.[6,23] To reduce complications and mortality, a deeper understanding of the effects of the hyperbaric environment on humans is essential. Our study holds potential as a pioneering effort in this context.

Limitations

Our study has several limitations. These include the retrospective design, with data obtained from the hospital information system and observation forms. Patients with incomplete data were excluded from the analysis. The study covered a time period of approximately 15 months. The depth of anesthesia could not be measured due to the incompatibility of the bispectral index monitor with the hyperbaric environment. Additionally, the results reflect the patient population of a single center.

CONCLUSION

As a result, midazolam, dexmedetomidine, remifentanil, propofol, and rocuronium bromide can be safely used to avoid the adverse effects of inhalation agents in intubated patients undergoing HBOT. It should be noted that sedation requirements increase due to the unique conditions of the hyperbaric environment. To prevent asynchrony, VILI, and complications, close anesthetic monitoring and supervision should be ensured with appropriate equipment. Further prospective, randomized clinical studies with larger sample sizes are needed to better understand the physiology and pharmacokinetics in the hyperbaric environment.

ETHICAL DECLARATIONS

Ethics Committee Approval

It was approved by the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 05.06.2024, Decision No: AEŞH-BADEK-2024/534).

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.

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Case Report

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Anesthesia management in double balloon enteroscopy for a patient with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)

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ABSTRACT

This case report discusses the anesthesia management of a 70-year-old male with hereditary hemorrhagic telangiectasia, also known as Osler-Weber-Rendu disease, who underwent double balloon enteroscopy for the treatment of gastrointestinal angiodysplasia. The patient, with a history of anemia requiring frequent blood transfusions, was managed with deep sedation using a combination of midazolam, dexmedetomidine, and propofol during the procedure. The sedation approach was tailored to the patient's comorbidities and preference against general anesthesia. The procedure was completed successfully without complications, and the patient was discharged the following day. The use of dexmedetomidine and propofol ensured stable hemodynamy and airway security, making it an effective sedation strategy for complex gastrointestinal procedures in elderly patients. The report highlights the importance of appropriate sedation protocols, particularly for patients with multiple comorbidities, and emphasizes the need for further research on sedation depth monitoring to optimize anesthetic care.

Keywords: Anesthesia, double balloon enteroscopy, hereditary hemorrhagic telangiectasia, Osler-Weber-Rendu

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is a rare, autosomal dominant, multisystemic disorder characterized by mucocutaneous telangiectasias and arteriovenous malformations in various internal organs. With an average global prevalence of 1 in 5.000 to 8.000, HHT[1] primarily affects the nasal mucosa, gastrointestinal (GI) tract, lungs, liver, and central nervous system, causing arteriovenous shunts.

HHT can lead to severe anemia and high-output heart failure due to recurrent massive nosebleeds and GI bleeding. Selective cauterization of GI telangiectasias can help control anemia but does not prevent recurrent bleeding.[2] Anesthesia management under sedation is crucial for protecting the patient's physical and psychological well-being, preventing adverse events, and enhancing the effectiveness of the procedure. The appropriate technique and drug selection should be made to partially reduce the patient's level of consciousness, ensure immobility, and manage pain and stress, while closely monitoring the depth of sedation. Effective anesthesia management not only increases the success of the surgical intervention but also ensures the patient's perioperative well-being. In this case presentation, we aim to share the anesthesia management under deep sedation of a patient who underwent cauterization of GI angiodysplasia foci due to recurrent transfusion needs caused by anemia.

CASE

A 70-year-old male patient, weighing 83 kg with a BMI of 32 kg/m^2 presented to the anesthesia clinic for double balloon enteroscopy (DBE). He had a history of melena and had been receiving periodic blood transfusions, with the need for transfusion increasing over the past few months. The patient had been diagnosed with Osler-Weber-Rendu syndrome, and his jejunal angiodysplasia lesions had been previously treated with argon plasma coagulation (APC) during two prior DBE procedures.

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The patient's diagnosis was confirmed during a family screening following the hemorrhagic brain hemorrhage of his 22-year-old son, who had widespread arteriovenous malformations in the brain. Until four years ago, the patient had no symptoms related to the syndrome. There was no known angiodysplasia in areas other than the GI tract. Additionally, he had suffered a myocardial infarction 9 years ago and had undergone coronary artery bypass surgery. The patient had a 50 pack/year smoking history, with chronic obstructive pulmonary disease for the last 20 years as an ex-smoker. He had experienced ischemic cerebrovascular events after the bypass surgery and had been started on 75 mg clopidogrel.

Preoperative evaluation revealed no specific findings on body surface. His blood pressure was 116/61 mmHg, and his heart rate was 71 bpm. Peripheral oxygen saturation (SpO_2) in room air was 93%. Lab results showed a hemoglobin of 9.2 g/dl, hematocrit 29.6, platelet count 153.000/µL, INR 1.06, serum creatinine (sCrea) 0.87 mg/dl, ALT 45 U/L, AST 55 U/L, with no notable abnormalities other than anemia. The ECG showed negative T waves between leads T3 and T5. Transthoracic echocardiogram revealed left ventricular hypertrophy and a 55% ejection fraction. The estimated procedure duration was 2 hours.

The case was a procedure as an elective outpatient surgery. The patient was evaluated as ASA III and informed about the procedure and anesthesia, and consent was obtained. Due to the patient's comorbidities and preference against general anesthesia, deep sedation was planned for anesthesia management.

Upon entering the operating room, the patient was positioned supine, and monitoring included a 5-lead ECG, pulse oximeter, non-invasive blood pressure cuff, capnography, and a temperature probe. SpO_2, heart rate, and ECG were continuously monitored, and noninvasive blood pressure was measured every 5 minutes. A 21-gauge catheter was placed for peripheral venous access. The patient received oxygen via a procedural oxygen mask (POM) at 4 L/min throughout the procedure. The patient was sedated with 0.07 mg/kg of IV midazolam, 1 mcg/kg of dexmedetomidine in 10 minutes, and a propofol infusion at 75 mcg/kg/min. Only the loading dose of dexmedetomidine was administered, and the infusion dose was not given as it was necessary. On the 15th minute, 10 mg of Hyoscine-N-butyl bromide IV was administered as requested by the gastroenterologist. The procedure advanced approximately 450 cm into the duodenum, jejunum, and ileum, where 84 APC treatments were applied to the angiodysplasia lesions, more densely located in the jejunum (Figure). At the end of the procedure, the patient's blood pressure was 117/60 mmHg, and his heart rate was 77 bpm. Oxygen was administered via mask at 2 L/min, and SpO_2 was 96%. He was transferred to the recovery unit.

During the procedure was applied deep sedation. The patient was spontaneously breathing but did not any move. Blood pressure remained within normal limits. SpO2 ranged from 90- 93%, and end-tidal CO_2 was between 35-45 mmHg. Respiratory rate ranged from 12-18 breaths per minute. The procedure was completed within 75 minutes, and a total of

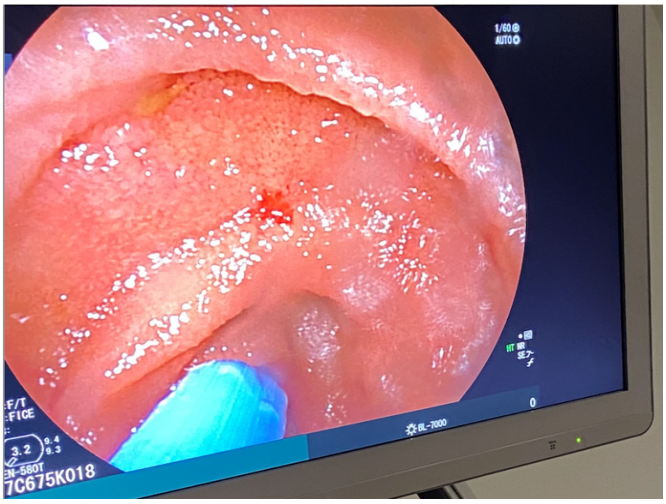

Figure. The angiodysplasia lesion

750 ml of Ringer's lactate was administered. The patient was transferred to the gastroenterology department and was discharged on the first postoperative day without issues.

DISCUSSION

This case describes our anesthesia management experience for a 70-year-old male patient with HHT who underwent double-balloon enteroscopy to treat GI telangiectasias that caused anemia and required frequent blood transfusions.

In HHT, lesions should be treated in a multidisciplinary manner. Treatments for lesions in the skin, mucosa, GI tract, and liver are symptom-driven, while vascular malformations in the lungs and brain should be treated even without symptoms due to the potential life-threatening complications. Common clinical findings include GI and nasal bleeding, which result in anemia and the need for transfusions. Pulmonary vascular malformations can cause dyspnea, heart failure, stroke, and brain abscesses. Cerebral vascular malformations can lead to hemorrhagic stroke and seizures.[3] Our patient's son was diagnosed after experiencing a hemorrhagic brain hemorrhage.

GI bleeding is common in HHT patients. A study by Kjeldsen et al.[4] showed that 25% of HHT patients over 60 years old had significant GI bleeding.

Similarly, our patient, who had no symptoms until his later years, presented with anemia and frequent blood transfusions in the recent years. Mora-Lujan et al.[5] reported that patients with GI involvement were more likely to require emergency room visits and hospital admissions, with telangiectasias larger than 3 mm requiring more frequent transfusions. Our patient also required transfusions every 15 days. Although upper GI endoscopy was normal, there were widespread telangiectasias in the duodenum, jejunum, and ileum. The size and number of telangiectasias made it difficult to assess their exact characteristics.

The APC procedure for 84 angiodysplasia lesions was completed without any complications under deep sedation, with an anesthesia duration of 75 minutes. A study by May et al.[6] demonstrated that DBE with APC is effective in treating

bleeding foci in the small intestine, and long-term follow-up data showed a significant increase in hemoglobin levels and a reduction in the need for transfusions. Many publications support APC as an effective treatment for angiodysplasia lesions.[7,8]

During invasive procedures, the sedation level and airway management are tailored based on patient safety, comorbidities, the type and duration of the procedure, and the complexity. The European Society of GI Endoscopy recommends that DBE can be performed under conscious sedation, deep sedation, or general anesthesia, with the choice based on the complexity of the procedure, clinical factors, and local protocols.[9]

Given the numerous lesions in our patient, deep sedation was necessary for this challenging procedure. Goudra et al.[10] found that most elective ERCP procedures could be performed without endotracheal intubation (intubation rate <1%), and intubation was reserved for cases with aspiration risks. A study by Thamson et al.[11] indicated that children might have lower sedation success or higher rates of general anesthesia. Our adult patient, who had previously undergone similar procedures twice, adapted well to the sedation process, aided by preprocedural counseling and administration of 0.07 mg/kg IV midazolam to reduce anxiety.

Multimodal anesthesia agents should be used based on the type and duration of the procedure. A variety of medications, including benzodiazepines (midazolam), opioids (fentanyl and meperidine), propofol, and dexmedetomidine (DEX), are available for conscious sedation during endoscopic procedures.[12]

In our case, a combination of dexmedetomidine (80 mcg loading dose) and propofol infusion (75 mcg/kg/min) provided adequate sedation depth. Dexmedetomidine allowed stable hemodynamics and deeper sedation without excessive propofol, which can lead to respiratory depression. We did not use an infusion of dexmedetomidine beyond the loading dose to avoid its side effects in elderly patients. In line with findings by Chen et al.[13], the combination provided stable sedation depth, airway security, and hemodynamic stability with reduced propofol consumption.

Concerns regarding delayed awakening in elderly patients treated with dexmedetomidine were mitigated in this case, as the patient regained adequate consciousness and spontaneous breathing within 5 minutes after stopping the propofol infusion, allowing for smooth transfer to the recovery unit.

Propofol combined with an opioid is a common sedation protocol; however, high doses or prolonged use of propofol may lead to respiratory depression, hypoxemia, and hypotension.[14] In the study conducted by Tuzlalı and colleagues[15], it was demonstrated that propofol infusion provides rapid recovery and is effective in preserving postoperative cognitive functions. In this case, we aimed to benefit from these effects of propofol. Dexmedetomidine alone, while effective for sedation, may cause hypotension and bradycardia and is not as effective as propofol for sedation.[16] In this case, we avoided continuous infusion of dexmedetomidine to prevent hypotension.

Dexmedetomidine-based conscious sedation is a safe option for long-duration GI endoscopy, with elderly patients requiring careful monitoring. Despite potential side effects like bradycardia and hypotension, dexmedetomidine has advantages in maintaining respiratory strength and airway patency during sedation.[17] Dexmedetomidine, recognized for its neuroprotective properties, may help reduce the incidence and severity of postoperative cognitive disorders.[18] However, more clinical studies are needed to assess its risks and benefits.

In future studies, it would be helpful to measure the target plasma concentration of propofol and sedation depth using BIS monitoring for more accurate results.

CONCLUSION

In this case, deep sedation during APC treatment for multiple telangiectasia foci was successfully managed according to the standard protocols recommended in the literature. However, measuring propofol plasma concentrations and sedation depth would lead to more accurate results and better optimization of sedation strategies.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

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.

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