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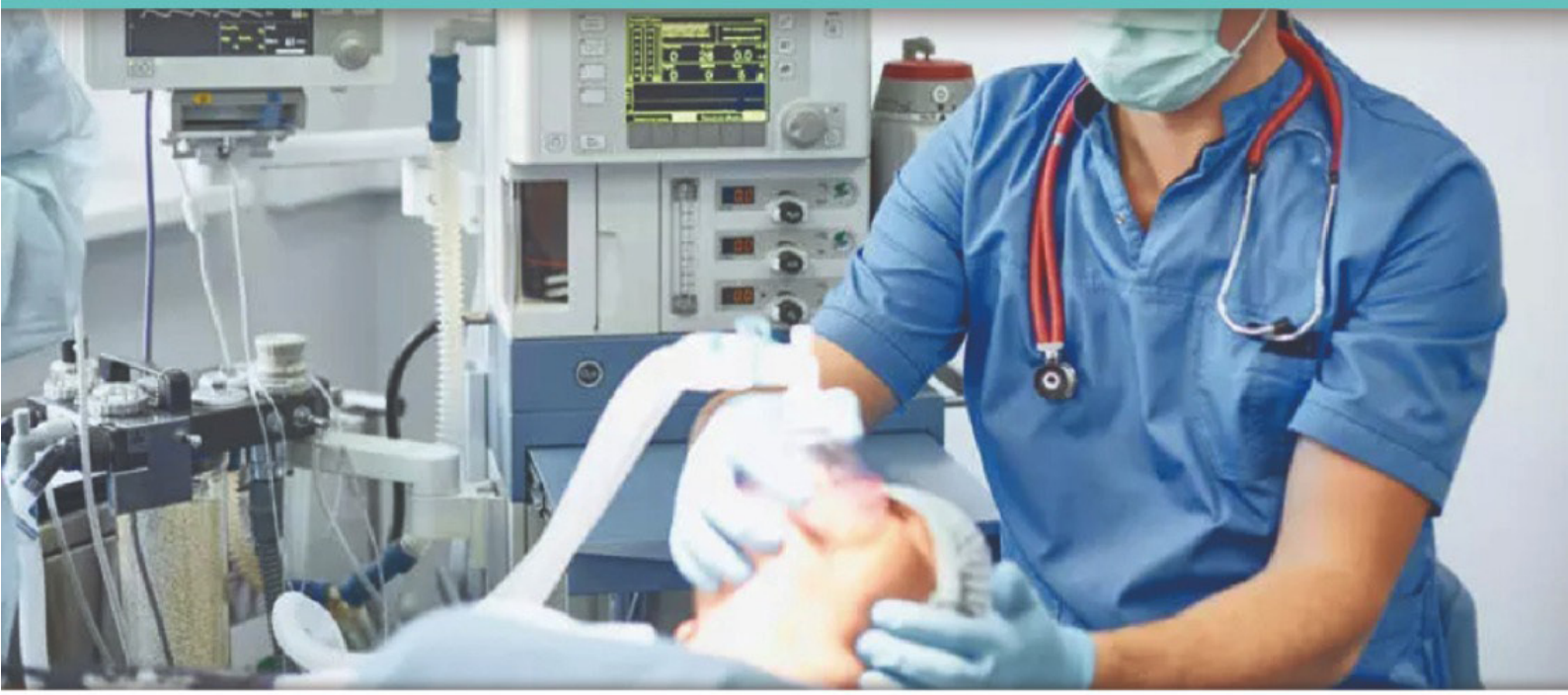

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Original Article

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Association of inflammatory markers (Inflammatory Burden Index, Systemic Inflammation Response Index, Systemic Immune-Inflammation Index) and modified Glasgow Prognostic Score with 30- and 90-day mortality in a level 3 surgical intensive care unit[a]

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ABSTRACT

Aims: We aimed to examine the relationship between systemic inflammatory markers and modified Glasgow Prognostic Score with 30- and 90-day mortality in critically ill patients who underwent various types of surgery (abdominal, neurosurgical, orthopedic, and urogynecological surgeries) and were followed up in a tertiary surgical intensive care unit.

Methods: This retrospective study included patients who were postoperatively followed in the tertiary surgical intensive care unit between January 2021-2025. A total of 455 patients were included in the study. Data regarding patients' age, gender, and preoperative 24-hour inflammatory parameters (leukocyte, neutrophil, platelet, lymphocyte, monocyte, CRP, albumin, procalcitonin), at intensive care unit admission were collected. Composite inflammatory biomarkers (Inflammatory Burden Index, Systemic Inflammation Response Index, Systemic Immune-Inflammation Index, mGPS) were calculated using formulas.

Results: A total of 455 postoperative patients were included in the study. Among them, 270 (59.3%) were male, and the mean age was 69.69±17.18 years. Of all patients, 193 (42.2%) underwent abdominal surgery, 74 (16.3%) underwent neurosurgery, 140(30.8%) underwent orthopedic surgery, and 48 (10.5%) underwent urogynecological surgery. Among the inflammatory indices, the IBI (p=0.001 for 30-day, p<0.001 for 90-day), and mGPS (p=0.005 for 30-day, p<0.001 for 90-day) were significant predictors of both short- and mid-term mortality.

Conclusion: Among postoperative surgical patients, IBI and mGPS are significant predictors of 30 days and 90 days mortality.

Keywords: Inflammatory Burden Index, Systemic Inflammatory Response Index, Systemic Immune-Inflammation Index, modified Glasgow Prognostic Score, mortality, post-surgical patients

[a]The abstract of this study was presented as an oral presentation at the "5th International Symposium on Anesthesiology and Reanimation, İstanbul, 2025."

INTRODUCTION

Intensive care units (ICU) are hospital departments where critically ill patients are monitored and treated. Surgical ICU are specialized critical care areas where critically ill patients undergoing emergency or elective surgery are monitored and treated postoperatively. Parameters that can predict mortality and morbidity in postoperative critically ill surgical patients remain a subject of ongoing research and debate. The Inflammatory Burden Index (IBI) is an inflammatory marker calculated from C-reactive protein (CRP), neutrophil, and lymphocyte levels, and has been associated with the prognosis of various tumors.[1] In particular, IBI has been reported to be the most accurate index for predicting the prognosis of patients with colorectal cancer.[2] The Systemic Inflammation Response Index (SIRI) is an inflammatory index calculated

from neutrophil, monocyte, and lymphocyte levels.[3] SIRI has been reported to predict the development and severity of acute pancreatitis and may serve as an independent prognostic factor in patients with hepatocellular carcinoma. A positive correlation has also been reported between SIRI and cardiovascular as well as all-cause mortality in the American population.[4-6] The Systemic Immune-Inflammation Index (SII) is an inflammatory marker calculated from neutrophil, platelet, and lymphocyte values.[7] SII is a biomarker used in malignancies and inflammatory diseases and has been reported as a valuable prognostic factor in conditions such as hepatocellular carcinoma, cervical cancer, and small cell carcinoma.[8] The modified Glasgow Prognostic Score (mGPS) is a parameter calculated from CRP and serum albumin levels, serving as an independent prognostic factor based on the CRP/albumin ratio.[9,10] The mGPS has been reported as a cost-effective and accessible tool for determining prognosis in patients with advanced esophageal squamous cell carcinoma.[11]

In our literature review, we found that subgroup analyses of the IBI , SIRI ,SII , and mGPS in postoperative critically ill patients monitored in surgical ICU have not yet been investigated. Therefore, in this study, we aimed to examine the relationship between systemic inflammatory markers and mGPS with 30- and 90-day mortality in critically ill patients who underwent various types of surgery (abdominal, neurosurgical, orthopedic, and urogynecological surgeries) and were followed up in a tertiary surgical intensive care unit.

METHODS

Ethics

The study was approved by the the Clinical Researches Ethics Committee of Kastamonu University Faculty of Medicine (Date: 18.09.2025, Decision No: 2025/43). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Patients Selection

This retrospective study included patients who were postoperatively followed in the tertiary surgical intensive care unit of Kastamonu University Faculty of Medicine Hospital between January 2021 and January 2025. Inclusion criteria for the study: Being 18 years of age or older, undergoing abdominal surgery due to gastrointestinal cancer, undergoing neurosurgical surgery due to intracranial hemorrhage, undergoing orthopedic surgery due to femur and pelvis fracture, undergoing urogynological surgery due to urogynological cancer (ovarian tumor, kidney tumor, prostate tumor). Exclusion criteria were as follows: continuous use of anti-inflammatory medications within the last six months, incomplete clinical or laboratory data, presence of active preoperative infection, ongoing chemotherapy or radiotherapy, known hematological or systemic immunological diseases, and death within 24 hours after surgery.

According to these criteria, a total of 455 patients were included in the study based on a retrospective search of the hospital information management system. Of these, 193 patients underwent abdominal surgery, 74 underwent neurosurgery, 140 underwent orthopedic surgery, and 48 underwent urogynecological surgery (Table 1).

Table 1. Inclusion and exclusion criteria for the study and flow chart

Inclusion criteria	Exclusion criteria
- Being 18 years of age or older - Undergoing abdominal surgery due to gastrointestinal cancer - Undergoing neurosurgical surgery due to intracranial hemorrhage - Undergoing orthopedic surgery due to femur and pelvis fracture - Undergoing urogynological surgery due to urogynological cancer.	- Continuous use of anti-inflammatory medications within the last six months - Incomplete clinical or laboratory data - Presence of active preoperative infection - Ongoing chemotherapy or radiotherapy - Known hematological or systemic immunological diseases - Death within 24 hours after surgery
Total patients (n): 455	
- 193 patients; abdominal surgery (gastrointestinal cancer operations)	
- 74 patients; neurosurgery surgery (for intracranial hemorrhage)	
- 140 patients; orthopedic surgery (femur and pelvic fracture operations)	
- 48 patients; urogynecological surgery (urogynecological malignancies).	

Data Collection

The patients' age and 24-hour preoperative inflammation parameters were recorded. If there was only one blood parameter within the last 24 hours before surgery, that parameter was recorded; if there were two or more blood parameters, the highest values were recorded.

The composite inflammatory biomarkers were calculated using the following formulas:

- IBI=CRP×neutrophils/lymphocytes
- SIRI=neutrophils×monocytes/lymphocytes
- SII=neutrophils×platelets/lymphocytes.[12-14]
- The mGPS was defined as follows.[9]
- mGPS 0=CRP≤10 mg/L and albumin ≥3.5 g/dl
- mGPS 1=CRP>10 mg/L and albumin ≥3.5 g/dl
- mGPS 2=CRP>10 mg/L and albumin <3.5 g/dl

Postoperative 30-day and 90-day mortality data were obtained from patient medical records or follow-up via telephone.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics for continuous variables were presented as mean±standard deviation (SD) or median with interquartile range (IQR), depending on the distribution. Categorical variables were expressed as frequencies and percentages. The Mann–Whitney U test was used to compare continuous variables with non-normal distribution. Categorical variables were analyzed using Pearson's Chi-squared test or Fisher's exact test, as appropriate. Multivariate logistic regression analysis was performed to evaluate the association between systemic inflammatory indices (SIRI,

SII, IBI, and mGPS) and 30-day and 90-day mortality among patients undergoing different types of surgery. All statistical tests were two-tailed, and a p-value of <0.05 was considered statistically significant.

RESULTS

A total of 455 postoperative patients were included in the study. Among them, 270 (59.3%) were male, and the mean age was 69.69±17.18 years. Of all patients, 193 (42.2%) underwent abdominal surgery, 74 (16.3%) underwent neurosurgery, 140 (30.8%) underwent orthopedic surgery, and 48 (10.5%) underwent urogynecological surgery. Table 2 shows the statistical comparison of systemic inflammation parameters, independent of surgery, for 30 and 90-day mortality in surviving and non-surviving patients. Age was significantly associated with mortality, with deceased patients being older both at 30-day (p=0.005) and 90-day (p<0.001) follow-ups. Among the inflammatory indices, the IBI (p=0.001 for 30-day, p<0.001 for 90-day) and mGPS (p=0.005 for 30-day, p<0.001 for 90-day) were significant predictors of both short- and mid-term mortality. In contrast, the SIRI and the SII did not show a statistically significant association with mortality. Regarding the type of surgery, abdominal surgery was the most frequent among patients who died within 30 days postoperatively, and this was statistically significant (p=0.006).

Among patients who underwent abdominal surgery, age was identified as a significant risk factor for both 30-day (p=0.002) and 90-day mortality (p<0.001), as shown in Table 3. Female patients exhibited a significantly higher 30-day mortality rate compared to males (p=0.013), whereas male patients had a higher 90-day mortality rate (p=0.028). The IBI was significantly higher in both 30-day (p=0.030) and 90-day (p=0.001) mortality groups.

In Table 4, age was identified as a significant risk factor for both 30-day (p=0.009) and 90-day mortality (p<0.001) among patients undergoing neurosurgery. Significant differences were observed in the mGPS with respect to both 30-day (p=0.023) and 90-day mortality (p=0.001). furthermore, the IBI was significantly elevated in the 30-day (p=0.014) and 90-day (p=0.001) mortality groups.

Table 5 reveals a significant difference between age and 90-day mortality (p=0.006) in orthopedic surgery patients. There was a statistically significant differences between mGPS level, and 90-day (p=0.007) mortality.

In patients undergoing urogynaecological surgery, there was no significant difference in inflammatory indices; 30-day and 90-day mortality rates (Table 6).

Multivariate logistic regression analysis was performed for parameters that were clinically statistically significant in 30 days and 90 days mortality. As shown in Figure 1, Patients with an mGPS score of 1 demonstrated significantly lower 30-day mortality compared to those with mGPS 2, a finding consistent in the total surgery cohort (OR: 0.369; p = 0.003), abdominal surgery subgroup (OR: 0.255; p=0.002), and neurosurgery subgroup (OR: 0.167; p=0.010). No significant differences were observed for mGPS 2 in other cohorts. In Figure 2, the IBI showed a borderline significant association with 90-day mortality in the neurosurgery group (p=0.058; OR: 1.002), suggesting a potential link between higher IBI values and increased mortality risk. Furthermore, in the patient group with mGPS 1, 90-day mortality rates were a significant parameter in the total surgical cohort (OR: 0.292; p<0.001), in the abdominal surgery subgroup (OR: 0.345; p=0.026), and in the neurosurgery subgroup (OR: 0.239; p=0.034).

Table 2. Comparison of all postoperative patients based on 30-day and 90-day mortality

	Alive at 30 days median (IQR) n=378	30-day mortality median (IQR) n=77	p	Alive at 90 days median (IQR) n=334	90-day mortality median (IQR) n=121	p
Age	71.0 (62.0-81.0)	79.0 (69.0-84.5)	0.005	70.0 (60.0-80.0)	79.0 (69.0-85.0)	<0.001
Gender, n (%)						
Female	148 (39.2%)	37 (48.1%)	0.147	126 (37.7%)	59 (48.8%)	0.034
Male	230 (60.8%)	40 (51.9%)		208 (62.3%)	62 (51.2%)	
Modified Glasgow Prognostic Score, n (%)						
0	126 (33.3%)	13 (16.9%)	0.005	120 (35.9%)	19 (15.7%)	<0.001
1	52 (13.8%)	8 (10.4%)		48 (14.4%)	12 (9.9%)	
2	200 (52.9%)	56 (72.7%)		166 (49.7%)	90 (74.4%)	
Inflammatory Burden Index	243.9 (40.2-1025.9)	651.2 (133.1-1860.9)	0.001	191.8 (36.3-981.6)	651.3 (169.1-2021.2)	<0.001
Systemic Inflammation Response Index	4.5 (2.2-9.4)	5.9 (1.5-13.1)	0.266	4.5 (2.1-9.5)	5.8 (1.9-11.4)	0.352
Systemic Immune-Inflammation Index	1670.5 (887.1-3016)	1657.5 (832.2-3487.7)	0.620	1655.3 (848.4-3053.9)	1693.6 (874.7-3339.3)	0.459
Surgery type						
Abdominal	150 (39.7)	43 (55.8)	0.006	136 (40.7)	57 (41.1)	0.084
Neurosurgery	58 (15.3)	16 (20.8)		49 (14.7)	25 (20.7)	
Orthopedic	126 (33.3)	14 (18.2)		109 (32.6)	31 (25.6)	
Other	44 (11.6)	4 (5.2)		40 (12.0)	8 (6.6)	

IQR: Interquartile range

Table 3. Comparison of postoperative abdominal surgery patients based on 30-day and 90-day mortality

	Alive at 30 days median (IQR) n=150	30-day mortality median (IQR) n=43	p	Alive at 90 days median (IQR) n=136	90-day mortality median (IQR) n=57	p
Age	70.0 (61.7-78.2)	80 (69.0-84.0)	0.002	69.0 (60.2-77.7)	79.0 (69.0-84.0)	<0.001
Gender, n (%)						
Female	49 (32.7%)	23 (53.5%)	0.013	44 (32.4%)	28 (49.1%)	0.028
Male	101 (67.3%)	20 (46.5%)		92 (67.6%)	29 (50.9%)	
Modified Glasgow Prognostic Score (mGPS), n (%)						
0	46 (30.7%)	6 (14%)		45 (33.1%)	7 (12.3%)	
1	14 (9.3%)	3 (7%)	0.062	14 (10.3%)	3 (5.3%)	0.003
2	90 (60%)	34 (79.1%)		77 (56.6%)	47 (82.5%)	
Inflammatory Burden Index	243.7 (40.04-1345.3)	570.4 (134-2650.8)	0.03	174.3 (29.1-1106.5)	651.3 (223.5-2885)	0.001
Systemic Inflammation Response Index	4.1 (1.6-8.7)	5.2 (1.1-7.7)	0.933	4.1 (1.6-8.9)	5.2 (1.4-7.7)	0.832
Systemic Immune-Inflammation Index	1585.8 (744.5-2924.9)	1220.2 (809.2-3266.1)	0.596	1511.5 (729.6-2981.6)	1463.0 (857.9-3181.1)	0.810

IQR: Interquartile range

Table 4. Comparison of postoperative neurosurgery patients based on 30-day and 90-day mortality

	Alive at 30 days median (IQR) n=58	30-day mortality median (IQR) n=16	p	Alive at 90 days median (IQR) n=49	90-day mortality median (IQR) n=25	p
Age	62.5 (42.2-76.2)	72.00 (63.75-83.75)	0.009	57.0 (39.0-68.0)	74.0 (64.5-83.0)	<0.001
Gender, n (%)						
Female	20 (34.5%)	6 (37.5%)	0.823	17 (34.7%)	9 (36%)	0.911
Male	38 (65.5%)	10 (62.5%)		32 (65.3%)	16 (64%)	
Modified Glasgow Prognostic Score (mGPS), n (%)						
0	36 (62.1%)	4 (25%)		34 (69.4%)	6 (24%)	
1	10 (17.2%)	4 (25%)	0.023	6 (12.2%)	8 (32%)	0.001
2	12 (20.7%)	8 (50%)		9 (18.4%)	11 (44%)	
Inflammatory Burden Index	63.9 (21.7-244.8)	216.1 (66.0-965.3)	0.014	53.5 (18.1-170.2)	245.6 (56.1-1074.4)	0.001
Systemic Inflammation Response Index	4.1 (1.9-8.4)	12.2 (2.8-18.4)	0.097	4.1 (1.9-9.1)	6.6 (1.9-15.7)	0.417
Systemic Immune-Inflammation Index	1884.1 (984.3-2812.5)	2278.3 (1024.1-5591.9)	0.390	1880.1 (1009.8-2771.4)	2236.1 (786.8-3339.3)	0.493

IQR: Interquartile range

Table 5. Comparison of postoperative orthopedic surgery patients based on 30-day and 90-day mortality

	Alive at 30 days median (IQR) n=126	30-day mortality median (IQR) n=14	p	Alive at 90 days median (IQR) n=109	90-day mortality median (IQR) n=31	p
Age	78.0 (69.0-86.0)	82.5 (72.75-91.0)	0.224	77.0 (68.0-85.0)	84.0 (74.0-91.0)	0.006
Gender, n (%)						
Female	68 (54%)	6 (42.9%)	0.429	55 (50.5%)	19 (61.3%)	0.286
Male	58 (46%)	8 (57.1%)		54 (49.5%)	12 (38.7%)	
Modified Glasgow Prognostic Score, n (%)						
0	21 (16.7%)	2 (14.3%)		21 (19.3%)	2 (6.5)	
1	22 (17.5%)	1 (7.1%)	0.559	22 (20.2%)	1 (3.2)	0.007
2	83 (65.9%)	11 (78.6%)		66 (60.6%)	28 (90.3)	
Inflammatory Burden Index	633.01 (132.02-1174.4)	991.3 (378-4660.8)	0.111	532.6 (104.9-1162.5)	762.1 (430.2-1594.0)	0.052
Systemic Inflammation Response Index	6.16 (3.3-10.14)	6.4 (3.3-20.4)	0.530	6.0 (3.2-10.2)	6.3 (4.0-10.7)	0.567
Systemic Immune-Inflammation Index	1788.6 (1137.9-3206.4)	1901.1 (976.8-9223.3)	0.498	1796.0 (1087.2-3266.2)	1659.2 (1159.3-3672.3)	0.857

IQR: Interquartile range

DISCUSSION

This study investigated detailed inflammatory parameters in critically ill postoperative patients, including subgroup analyses. The IBI emerged as a significant predictor of 30-day mortality in the total surgical cohort, as well as in patients undergoing abdominal surgery and neurosurgery. Moreover, IBI was significantly associated with 90-day mortality in the total

Table 6. Comparison of postoperative urogynecological surgery patients based on 30-day and 90-day mortality

	Alive at 30 days median (IQR) n=44	30-day mortal median (IQR) n=4	p	Alive at 0 days median (IQR) n=40	90-day mortal median (IQR) n=8	p
Age	70.5 (63.0-76.0)	56.0 (37.7-72.7)	0.204	69.5 (62.25-75.75)	71.5 (49.0-80.5)	0.698
Gender, n(%)						
Female	11 (25%)	2 (50%)	0.281	10 (25%)	5 (62.5%)	0.468
Male	33 (75%)	2 (50%)		30 (75%)	3 (37.5%)	
Modified Glasgow Prognostic Score, n(%)						
0	23 (52.3%)	1 (25%)		20 (50%)	4 (50%)	
1	6 (13.6%)	0	0.256	6 (15%)	0	0.449
2	15 (34.1%)	3 (75%)		14 (35%)	4 (50%)	
Inflammatory Burden Index	68.3 (14.5-305.9)	1109.6 (280.4-2316.2)	0.263	76.8 (16.8-315.1)	580.1 (9.07-1985.3)	0.782
Systemic Inflammation Response Index	4.3 (2.2-10.8)	9.2 (4.9-17.2)	0.156	4.2 (2.2-10.8)	8.45 (2.3-16.6)	0.407
Systemic Immune-Inflammation Index	69.6 (15.6-315.1)	2742.8 (1225.4- 4586.9)	0.168	1151.3 (741.5-2432.3)	1762.3 (567.1-4586.8)	0.543

IQR: Interquartile range

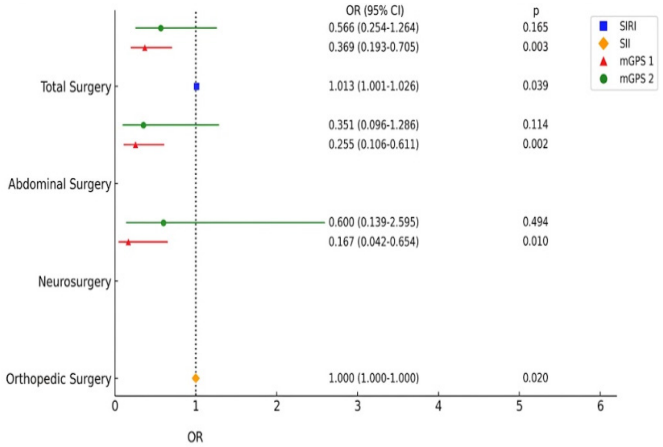

Figure 1. The multivariate regression analysis of the association between in SIRI, SII and mGPS for 30 day-mortality

SIRI: Systemic Inflammatory Response Index, SII: Systemic Immune-Inflammation Index, mGPS: Modified Glasgow Prognostic Score, OR: Odds ration, CI: Confidence interval

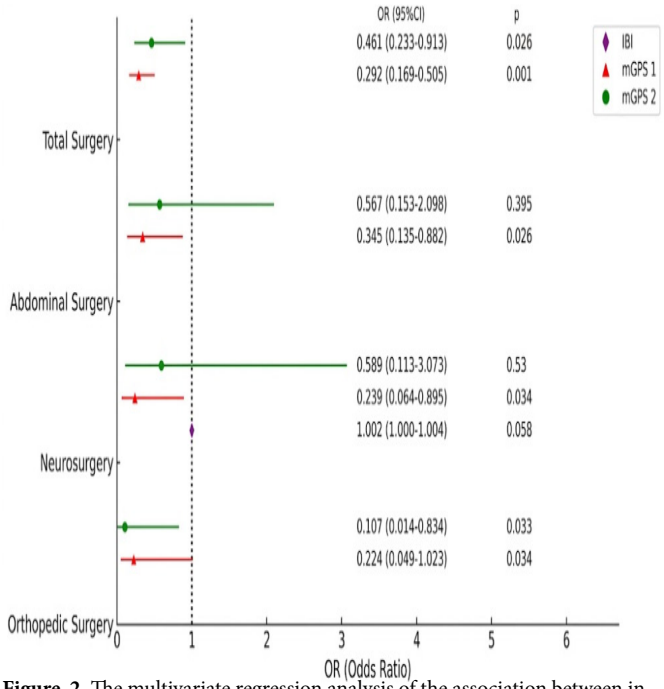

Figure 2. The multivariate regression analysis of the association between in IBI and mGPS for 90 day-mortality

IBI: Inflammatory Burden Index, mGPS : Modified Glasgow Prognostic Score, OR: Odds ration, CI: Confidence interval

surgical cohort, and specifically in the abdominal surgery, neurosurgery, and orthopedic surgery subgroups.

The mGPS was identified as a significant predictor of 30-day mortality in the total surgical cohort, for 90-day mortality, mGPS showed significant associations across the total surgical cohort, and in the abdominal surgery, neurosurgery, and orthopedic surgery subgroups. According to multivariate logistic regression analysis, IBI was associated with 90-day mortality in the neurosurgery. Inflammation is a fundamental characteristic of critically ill patients, and its extent can be assessed using various biomarkers in clinical practice.[15] Composite inflammatory indices, which combine these biomarkers, have proven valuable in guiding clinicians regarding patient prognosis.

The IBI , one such index, was originally studied as a prognostic and inflammatory burden marker in various cancers.[2] Interest in IBI grew due to the established link between its components CRP ,neutrophils, and lymphocytes and inflammation, which plays a pivotal role in cancer pathogenesis.[16,17] In 2024, He et al.[18] evaluated the association between IBI and all-cause mortality in a general population aged 45 and older, including 8827 participants. They identified a nonlinear relationship between IBI and all-cause mortality, noting that increasing IBI values corresponded with higher mortality risk. Our study population comprised critically ill patients requiring intensive care monitoring, a group inherently characterized by heightened inflammation. Unlike previous studies, our research focused specifically on critically ill postoperative patients. We found that IBI was a significant predictor of both 30-day and 90-day mortality in the overall cohort and in the subgroups undergoing abdominal surgery and neurosurgery. Additionally, IBI was significantly associated with 90-day mortality in patients who underwent orthopedic surgery.

In our study, the IBI was a significant predictor of both 30- and 90-day mortality. Since CRP is used in calculating IBI, and CRP is widely recognized in the literature as the most representative clinical marker of acute systemic inflammation.[19,20] We think that the significance of IBI in predicting mortality is primarily driven by the critical role of CRP in inflammation.

The mGPS , calculated using CRP and albumin levels, integrates CRP as a key inflammation marker and albumin as a parameter reflecting both disease severity and nutritional status.[21-23] Wu et al.[24] demonstrated in a large cohort of 4629 pancreatic cancer patients that a high pre-treatment mGPS was associated with poor prognosis. Similarly, Saal et al.[25] reported that mGPS could be used to monitor treatment response in patients with metastatic renal cell carcinoma. However, not all studies have confirmed the prognostic value of mGPS. For instance, Son et al.[26] found that mGPS did not predict overall survival in non-metastatic colon cancer patients, and Chan et al.[27] reported that mGPS was not a prognostic factor in colorectal cancer based on multivariate analysis. In our study, mGPS was significantly associated with 30-day mortality in the total surgical cohort and in patients undergoing abdominal surgery and neurosurgery in subgroup analyses. Additionally, mGPS was significant for 90-day mortality in the total cohort and in patients undergoing abdominal surgery, neurosurgery, and orthopedic surgery. One notable finding of our study was that no systemic inflammation index was significantly associated with mortality in patients undergoing urogynecological surgery. We attribute this result to the relatively small sample size within this subgroup, which may have limited the statistical power to detect significant associations.

Limitations

Our study has some restrictions. These limitations include its retrospective design, single-center structure, small sample size within the urogynecological subgroup, and the inclusion of a heterogeneous patient group.

CONCLUSION

Among postoperative surgical patients, IBI and mGPS are significant predictors of 30- and 90-day mortality. In subgroup analyses, IBI was significantly associated with both 30- and 90-day mortality in patients undergoing abdominal surgery (due to gastrointestinal cancer) and neurosurgery surgery (due to intracranial hemorrhage). Although some parameters were significant for mortality in our study, the results of our study are not suitable for generalization due to the heterogeneity of the patient groups. More comprehensive results can be obtained from studies with homogeneous groups.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the the Clinical Researches Ethics Committee of Kastamonu University Faculty of Medicine (Date: 18.09.2025, Decision No: 2025/43)

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: VGS, AY; Methodology: VGS, AY, ÖT, UD; Data Collection and Investigation: VGS, AY, ÖT, UD, BTK, AD, HE, ZD; Formal Analysis: FÇİ; Writing–Original Draft: VGS, AY; Writing–Review and Editing: VGS,AY, ÖT, UD; Supervision: ZD; Critical Review: All authors.

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Original Article

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Antibacterial effects of levobupivacaine against *Staphylococcus aureus* in a patient-controlled epidural analgesia model: an in vitro experimental study

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ABSTRACT

Aims: Catheter-related infections remain an important complication of epidural analgesia. Local anesthetics may contribute to infection prevention because of their antimicrobial properties. This study aimed to evaluate the antibacterial effects of clinically relevant concentrations of levobupivacaine against *Staphylococcus aureus* in a simulated patient-controlled epidural analgesia (PCEA) model.

Methods: An in vitro experimental PCEA infusion system was established using epidural catheter tubing and 0.2-µm bacterial filters. Four study groups were prepared: 0.125% levobupivacaine+fentanyl, 0.0625% levobupivacaine+fentanyl, fentanyl-only solution, and saline control. Each solution was inoculated with *S. aureus* adjusted to a 0.5 McFarland standard. Solutions were infused continuously for 24 hours. Samples obtained from the filter inlet, outlet, and collection chambers were cultured microbiologically. Scanning electron microscopy was used to evaluate bacterial retention at the filter surface.

Results: The saline control group demonstrated the highest bacterial colony counts, whereas levobupivacaine-containing solutions demonstrated significantly lower bacterial colony counts compared with the saline control group ($p<0.05$). Increasing levobupivacaine concentration was associated with stronger antibacterial activity. No bacterial growth was detected distal to the epidural bacterial filter in any study group. SEM analysis confirmed bacterial accumulation on the proximal surface of the filter membrane.

Conclusion: Levobupivacaine exhibited concentration-dependent antibacterial activity against *S. aureus* in a simulated PCEA model, while epidural bacterial filters effectively prevented bacterial passage under experimental conditions. These findings suggest that levobupivacaine may contribute to infection prevention in epidural analgesia systems; however, further in vivo and clinical studies are required to confirm these findings.

Keywords: Levobupivacaine, epidural analgesia, antibacterial activity, *Staphylococcus aureus*, regional anesthesia, PCEA

INTRODUCTION

Regional anesthesia techniques, including epidural and combined spinal-epidural analgesia, are widely used for perioperative analgesia, obstetric anesthesia, and chronic pain management.[1,2] Although epidural analgesia provides effective pain control and improved postoperative recovery, catheter-related infections remain an important concern.[1,2]

The reported incidence of epidural catheter-related infections varies according to catheter duration, patient comorbidities, and aseptic conditions.[1,2] Common causative organisms include skin flora microorganisms such as *Staphylococcus aureus* and *Staphylococcus epidermidis*.[1,3] Epidural abscesses and meningitis, although rare, may lead to severe neurological complications.[2]

To reduce the risk of epidural catheter contamination, strict aseptic technique and bacterial filtration systems are routinely recommended.[1,2] In addition to mechanical barriers, local anesthetics themselves may exhibit antimicrobial effects.[3] Previous studies have reported antibacterial properties of lidocaine, bupivacaine, ropivacaine, and levobupivacaine against various microorganisms.[3-7]

Levobupivacaine is the S(-)-enantiomer of bupivacaine and is widely used in epidural analgesia because of its favorable safety profile and lower cardiotoxicity compared with racemic bupivacaine.[10,11] However, data regarding its antibacterial properties remain limited and conflicting.[10-12] Most previous studies investigated antimicrobial activity under static laboratory conditions using direct bacterial incubation models.[10-14] To our knowledge, few studies have evaluated the antibacterial activity of levobupivacaine using a clinically simulated patient-controlled epidural analgesia (PCEA) infusion model.

Therefore, the aim of this study was to investigate the antibacterial effects of clinically relevant concentrations of levobupivacaine against *S. aureus* in a simulated PCEA system.

METHODS

Ethics

This in vitro experimental study was approved by the Dokuz Eylül University Non-interventional Clinical Researches Ethics Committee (Date: 01.10.2010, Decision No: 271). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki

Study Groups

The experimental solutions were prepared in 100-ml volumes under aseptic conditions.

Group 1 (n=10) 0.125% levobupivacaine+fentanyl

Group 2 (n=10) 0.0625% levobupivacaine+fentanyl

Group 3 (n=10) Fentanyl only

Group 4 (n=10) Saline control

Each solution was inoculated with 1 ml of *S. aureus* suspension adjusted to 0.5 McFarland standard (1.5×10^8 CFU/ml).

The sample size of ten experiments per group was determined based on feasibility considerations and consistency with previous in vitro antimicrobial studies.

Experimental Setup

The experimental infusion system was prepared under strict aseptic conditions. Epidural catheters were connected to 0.2-µm bacterial filters (Portex®, Smiths Medical, USA). The infusion system was attached to a PCA pump (Abbott APM Epidural PCA Pump, USA). Solutions were continuously infused at 4 ml/h for 24 hours at room temperature (Figure 1).

Samples were obtained from:

- Filter inlet
- Filter outlet
- Collection bottles

All samples were cultured on blood agar plates and incubated aerobically at 37°C for 16–24 hours.

SEM Imaging

Scanning electron microscopy (SEM) was performed using a JEOL-JSM-6060 microscope. Filter samples from group 1 and group 4 were processed under vacuum conditions and coated with gold-palladium prior to imaging.

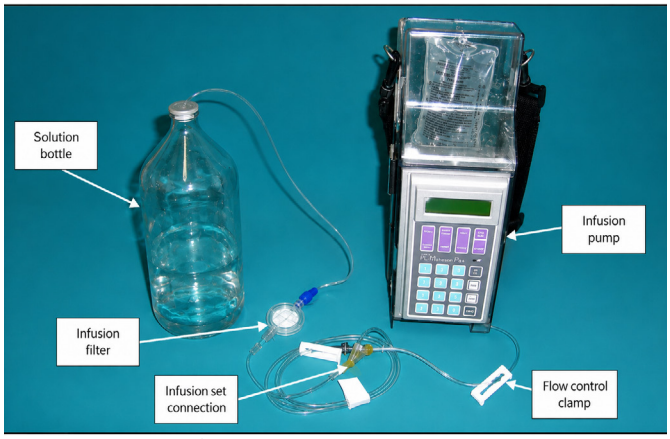

Figure 1. Experimental setup
Schematic representation of the simulated patient-controlled epidural analgesia (PCEA) experimental model.

Statistical Analysis

The data analyses were performed using SPSS version 15.0. Normality of data distribution was assessed using the Shapiro–Wilk test. Since colony count data were not normally distributed, non-parametric statistical methods were used. Data are presented as mean±standard deviation. Comparisons among groups were performed using the Kruskal–Wallis test, followed by Mann–Whitney U tests for pairwise comparisons. A p value<0.05 was considered statistically significant.

RESULTS

Bacterial growth was observed at the filter inlet in all groups. Colony counts at the filter inlet were highest in the saline control group and lowest in the 0.125% levobupivacaine group (Table 1).

Compared with the saline control group, bacterial colony counts were reduced by approximately 56.4% in group 1, 41.3% in group 2, and 27.3% in group 3 (Table 1). Overall group differences were statistically significant (Kruskal–Wallis p<0.0001).

Post-hoc Mann–Whitney U analyses demonstrated statistically significant differences between group 1 and group 4 (p=0.002), group 2 and group 4 (p=0.002), and group 3 and group 4 (p=0.002) (Tables 2–4).

Table 1. Colony counts obtained from filter inlet, outlet, and bottles in all groups (mean±SD) and p values

Groups	Bacterial inoculum (n)	Filter inlet colony count	Filter outlet colony count	Bottle colony count	Overall p value (Kruskal–Wallis)
Group 1	1500000±00	9446±2173	0±00	0±00	
Group 2	1500000±00	12742±2240	0±00	0±00	<0.0001
Group 3	1500000±00	15770±2540	0±00	0±00	
Group 4	1500000±00	21692±2223	0±00	0±00	

Data are presented as mean±SD. Overall group differences were assessed using the Kruskal–Wallis test (p<0.0001). Post-hoc Mann–Whitney U analyses demonstrated significant differences between group 1 versus group 4 (p=0.002), group 2 versus group 4 (p=0.002), group 3 versus group 4 (p=0.002), group 1 versus group 2 (p=0.019), and group 1 versus group 3 (p=0.0001). SD: Standard deviation

The comparison between group 1 and group 2 showed a statistically significant difference (p=0.019), as did the comparison between group 1 and group 3 (p=0.0001) (Tables 5 and 6). The overall comparison among groups 1, 2, and 3 also demonstrated a statistically significant difference (p=0.013) (Table 7).

Table 2. Comparison of bacterial colony counts between group 1 and group 4

Groups	Bacterial inoculum	Filter colony count	Bottle colony	p
Group 1	1500000±00	9446±2173	0±00	0.002
Group 4	1500000±00	21692±2223	0±00	

Table 3. Comparison of group 2 and group 4 colony counts

Groups	Bacterial inoculum	Filter colony count	Bottle colony	p
Group 2	1500000±00	12742±2240	0±00	0.002
Group 4	1500000±00	21692±2223	0±00	

Table 4. Comparison of group 3 and group 4 colony counts

Groups	Bacterial inoculum	Filter colony count	Bottle colony	p
Group 3	1500000±00	15770±2540	0±00	0.002
Group 4	1500000±00	21692±2223	0±00	

Table 5. Comparison of group 1 and group 2 colony counts

Groups	Bacterial inoculum	Filter colony count	Bottle colony	p
Group 1	1500000±00	9446±2173	0±00	0.019
Group 2	1500000±00	12742±2240	0±00	

Table 6. Comparison of group 1 and group 3 colony counts

Groups	Bacterial inoculum	Filter colony count	Bottle colony	p
Group 1	1500000±00	9446±2173	0±00	0.0001
Group 3	1500000±00	15770±2540	0±00	

Table 7. Comparison of group 1, Group 2, and group 3 colony counts

Groups	Bacterial inoculum	Filter colony count	Bottle colony	p
Group 1	1500000±00	9446±2173	0±00	0.013
Group 2	1500000±00	12742±2240	0±00	
Group 3	1500000±00	15770±2540	0±00	

No bacterial growth was detected at the filter outlet or in the collection bottles in any study group (Table 1). SEM imaging demonstrated bacterial accumulation at the filter surface and confirmed the absence of bacterial passage through the filter membrane (Figures 2–4).

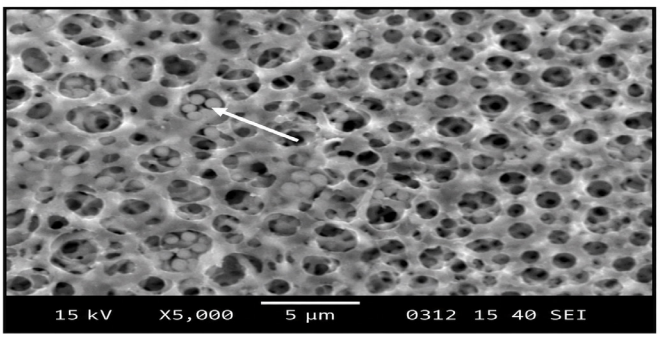

Figure 2. Scanning electron microscopy image of the inlet side of the filter inoculated with *Staphylococcus aureus* in group 1 at a magnification of X5,000. Scanning electron microscopy image demonstrating *Staphylococcus aureus* accumulation on the proximal surface of the epidural bacterial filter membrane in group 1 (×5,000 magnification).

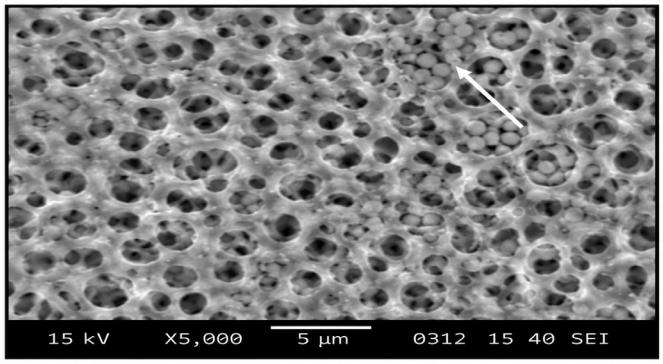

Figure 3. Scanning electron microscopy image of the inlet side of the filter inoculated with *Staphylococcus aureus* in group 4 at a magnification of X5,000. Scanning electron microscopy image demonstrating *Staphylococcus aureus* accumulation on the proximal surface of the epidural bacterial filter membrane in group 4 (×5,000 magnification).

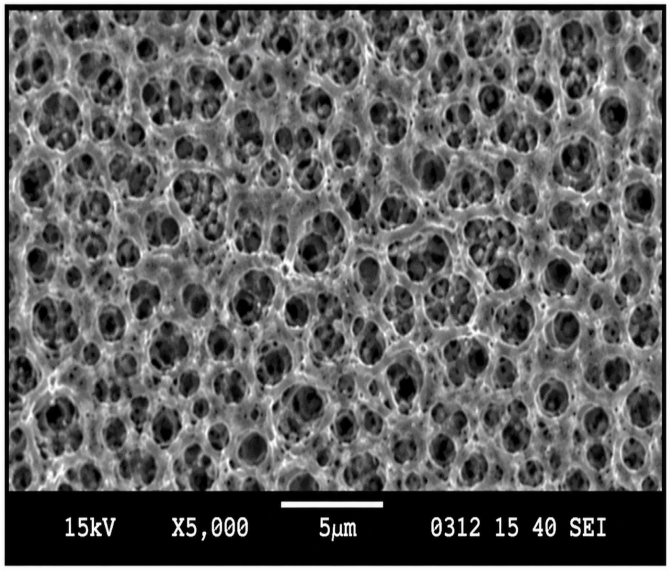

Figure 4. Scanning electron microscopy image of the outlet side of the filter inoculated with *Staphylococcus aureus* at a magnification of X5,000.
Scanning electron microscopy image of the distal surface of the epidural bacterial filter membrane, demonstrating no bacterial passage (×5,000 magnification).

DISCUSSION

The present in vitro experimental study demonstrated that levobupivacaine has a concentration dependent antibacterial effect against *S. aureus* in a simulated PCEA model. The reduction in colony counts was greatest in the 0.125% levobupivacaine group, followed by the 0.0625% levobupivacaine group and fentanyl-only group, while the saline control group had the highest bacterial growth. In addition, no bacterial growth was observed beyond the epidural bacterial filter, suggesting complete bacterial retention under the experimental conditions of this study. These findings are consistent with the original microbiological results and SEM observations of the thesis. Catheter-related infection remains an important safety issue in regional anesthesia, although serious neuraxial infections are rare. Recent regional anesthesia safety recommendations emphasize that contamination may occur through skin flora migration along the catheter, contamination of injected solutions, or breaks in aseptic technique during catheter manipulation.[1,2] Therefore, any pharmacological or mechanical factor that reduces bacterial contamination may have clinical relevance. The antibacterial activity of local anesthetics has been recognized for decades, but recent studies have renewed interest in this topic, particularly because of catheter-associated infections and biofilm formation.[3] Experimental investigations have demonstrated antimicrobial

effects of local anesthetics against clinically important pathogens including *S. aureus*, *S. epidermidis*, and multidrug-resistant bacteria.[4,5] Proposed mechanisms include disruption of bacterial cell membrane integrity, altered membrane permeability, inhibition of membrane-associated enzymatic activity, and interference with cellular metabolic pathways.[6,7]

Recent evidence also suggests that local anesthetics may inhibit biofilm formation. Faustova et al.[8] demonstrated that local anesthetics affected both planktonic forms and biofilm formation capacity of clinical *S. aureus* strains. This observation is clinically important because biofilm formation on epidural catheters contributes to bacterial persistence, resistance to antimicrobial therapy, and chronic catheter colonization.[9]

Our findings are consistent with previous studies reporting antibacterial effects of levobupivacaine against gram-positive microorganisms. Earlier investigations by Hodson et al.[10] demonstrated that levobupivacaine inhibited the growth of *S. aureus* and *S. epidermidis* at clinically relevant concentrations. Guillier et al.[11] also reported that levobupivacaine-containing epidural solutions did not increase bacterial proliferation risk during regional anesthesia applications. However, some studies have reported conflicting findings regarding the antimicrobial potency of levobupivacaine.[12] These discrepancies may be explained by methodological differences including incubation conditions, bacterial inoculum density, exposure duration, and microbiological techniques.

The concentration-dependent effect observed in our study is clinically important. Lower concentrations of local anesthetics are commonly preferred in obstetric and postoperative epidural analgesia to minimize motor blockade and hemodynamic instability. However, our results suggest that dilute concentrations may provide less antibacterial protection than higher concentrations. Similar concentration-dependent antibacterial effects have also been demonstrated for lidocaine and bupivacaine.[13,14]

Compared with the saline control group, bacterial colony counts were reduced by approximately 56.4% in the 0.125% levobupivacaine group, 41.3% in the 0.0625% levobupivacaine group, and 27.3% in the fentanyl-only group. These findings provide a quantitative estimate of the antibacterial activity observed in the present study and further support a concentration-dependent effect of levobupivacaine.

More recent studies further support these findings. Lee et al.[5] reported antibacterial activity of several local anesthetics against multidrug-resistant organisms, with bupivacaine demonstrating strong antimicrobial effects in vitro. Likewise, Heller et al.[4] showed that lidocaine significantly inhibited the growth of *S. Aureus*, MRSA, and *S. epidermidis*. Collectively, these findings support the hypothesis that local anesthetics may contribute to infection prevention during regional anesthesia practice.

One of the major strengths of the present study is the use of a clinically simulated PCEA infusion model rather than a static incubation design. Most previous studies evaluated bacterial growth after direct exposure of microorganisms to local anesthetic solutions under laboratory conditions.[10-14] In contrast, our model included continuous infusion, epidural catheter tubing, bacterial filtration, and prolonged exposure duration, thereby reproducing conditions closer to routine epidural analgesia practice. This methodological approach increases the translational relevance of our findings.

Another important finding was the complete absence of bacterial growth after the epidural bacterial filter. No bacterial colonies were identified in cultures obtained from the filter exit or collection bottles. These findings confirm the effectiveness of 0.2-µm epidural bacterial filters as an additional mechanical barrier against contamination. Recent infection-control literature continues to support the importance of maintaining closed epidural systems and minimizing contamination during catheter manipulation.[1,2]

SEM imaging provided additional confirmation of bacterial retention at the filter surface and strengthened the microbiological findings of the study. The use of SEM imaging constitutes another strength because ultrastructural visualization improves the reliability of microbiological observations and directly demonstrates bacterial entrapment within the filtration system.

Limitations

Several limitations should be acknowledged. First, this was an in vitro study and cannot fully reproduce patient-related variables such as immune response, protein binding, tissue interaction, catheter dwell time, and repeated clinical manipulation. Second, only *S. aureus* was evaluated; future studies should include *S. epidermidis*, methicillin-resistant *S. aureus* (MRSA), gram-negative bacteria, and fungal pathogens. Third, molecular mechanisms responsible for the antibacterial effects were not directly investigated. Therefore, membrane disruption and enzymatic inhibition should be regarded as potential mechanisms suggested by previous studies rather than mechanisms demonstrated in the present study. Fourth, a levobupivacaine-only group was not included. Consequently, the independent antibacterial contribution of levobupivacaine could not be completely separated from any potential antimicrobial effect of fentanyl. Fifth, the infusion system was operated at room temperature rather than physiological temperature (37°C), which may have influenced bacterial growth kinetics and solution stability. Sixth, SEM analysis was performed only in groups 1 and 4; inclusion of the fentanyl-only group could have provided additional comparative information. Finally, biofilm biomass and biofilm-related gene expression analyses were not performed.

CONCLUSION

As a result, levobupivacaine demonstrated concentration-dependent antibacterial activity against *S. aureus* in a clinically simulated PCEA model. Epidural bacterial filters effectively prevented bacterial passage under the experimental conditions of the study. These findings suggest that levobupivacaine may contribute to infection prevention during epidural analgesia; however, further in vivo and clinical studies are required before definitive clinical conclusions can be drawn.

ETHICAL DECLARATIONS

Ethics Committee Approval

This in vitro experimental study was approved by the Dokuz Eylül University Non-interventional Clinical Researches Ethics Committee (Date: 01.10.2010, Decision No: 271).

Informed Consent

As this study was carried out on bacteria in a laboratory setting, written consent was not required.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

The author is solely responsible for the entirety of conception, execution, analysis, and writing of the manuscript.

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Clinical, microbiological, and biomarker profiles of mechanically ventilated ICU patients with positive tracheal aspirate cultures

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ABSTRACT

Aims: To evaluate antimicrobial resistance patterns, clinical characteristics, and inflammatory biomarker profiles in mechanically ventilated intensive care unit patients with positive tracheal aspirate (TA) cultures.

Methods: Between January 2020 and December 2024, 187 intubated ICU patients with positive TA cultures and complete biomarker data were retrospectively analyzed. Demographic characteristics, AMR patterns, clinical and microbiological findings, and exploratory biomarker profiles were recorded. Exploratory receiver operating characteristic (ROC) analyses were performed to descriptively assess potential relationships between selected biomarkers and in-hospital mortality.

Results: Gram-negative pathogens predominated (89.3%), and overall in-hospital mortality was 95.7%. Mortality was higher among patients with gram-negative microorganisms than among those with gram-positive microorganisms (97.0% vs. 83.3%, p=0.007) and increased progressively across resistance categories. APACHE II scores did not differ significantly between groups. Among the evaluated biomarkers, the Prognostic Nutritional Index, lactate, and the C-reactive protein-to-albumin ratio (CAR) demonstrated moderate-to-high discriminatory performance and were associated with in-hospital mortality in exploratory ROC analyses.

Conclusion: Gram-negative microorganisms and AMR were more frequently observed among patients with adverse outcomes in this high-risk ICU cohort. Biomarker findings should be interpreted as exploratory observations requiring validation in prospective studies.

Keywords: Mechanical ventilation, drug resistance microbial, critical illness, prognosis, nutritional status, nosocomial infection

INTRODUCTION

Antimicrobial resistance (AMR) is recognized as one of the most important global health threats. In 2019, approximately 1.3 million deaths were directly attributable to AMR, and projections suggest that this number may increase to 10 million deaths annually by 2050.[1] Intensive care unit (ICU) patients are particularly vulnerable to resistant infections because of frequent invasive procedures, prolonged hospitalization, mechanical ventilation, and extensive exposure to broad-spectrum antimicrobial agents. Gram-negative microorganisms, particularly *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, represent major challenges in ICU settings because of their virulence factors and complex resistance mechanisms. Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan-drug-resistant (PDR) strains have been associated with increased mortality, prolonged ICU stay, and higher healthcare costs.[2–4]

Although established severity scoring systems such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) score are widely used to assess prognosis in critically ill patients, they may not fully reflect the clinical heterogeneity associated with antimicrobial resistance. Therefore, several inflammatory and nutritional biomarkers, including lactate, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein-to-albumin ratio (CAR), blood urea nitrogen-to-albumin ratio

(BAR), and Prognostic Nutritional Index (PNI), have been investigated as potential indicators of disease severity and outcome in critically ill and septic populations. [5–10]

Recent evidence suggests that inflammatory and nutritional biomarkers may provide additional prognostic information when evaluated together with microbiological characteristics and AMR patterns. However, data regarding their clinical significance in mechanically ventilated ICU patients with positive tracheal aspirate (TA) cultures remain limited. Furthermore, although conventional inflammatory indices have been extensively studied, the potential role of newer hematological biomarkers, including pan-immune inflammation value (PIV), red cell distribution width (RDW), and mean platelet volume (MPV), has not been adequately investigated in this patient population. PIV reflects the overall immune-inflammatory burden and has been associated with mortality in inflammatory conditions such as sepsis.[11] RDW has been linked to systemic inflammation, oxidative stress, mortality, and prolonged hospitalization in critically ill patients.[12] MPV, an indirect marker of platelet activation, has also been proposed as a potential indicator of disease severity and adverse outcomes in sepsis and critical illness.[13] Nevertheless, studies simultaneously evaluating these biomarkers together with AMR profiles and microbiological characteristics in mechanically ventilated ICU patients remain scarce. Therefore, the present study aimed to evaluate the associations between microorganism type, AMR patterns, inflammatory biomarker profiles, and clinical outcomes in mechanically ventilated ICU patients with positive TA cultures.

METHODS

Ethics

This study was approved by the Health Sciences Researches Ethics Committee of Yüksek İhtisas University (Date: 30.10.2025, Decision No: 17/348). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

Medical records of adult ICU patients admitted between January 1, 2020, and December 31, 2024, were retrospectively reviewed. Eligible patients were mechanically ventilated individuals with documented microbial growth in TA cultures.

TA cultures were obtained from mechanically ventilated patients with clinical suspicion of lower respiratory tract infection or ventilator-associated pneumonia (VAP). Clinical indications included new or worsening pulmonary infiltrates, fever, leukocytosis or leukopenia, purulent respiratory secretions, and/or worsening oxygenation. These findings were evaluated according to routine ICU practice and documented by the treating physicians during the study period.

Because of the retrospective design and the inherent limitations of TA cultures, differentiation between true infection, colonization, and contamination could not be standardized in all cases. Therefore, positive TA cultures were interpreted within the overall clinical context rather than being considered definitive evidence of infection alone. Patients were followed until hospital discharge or in-hospital death.

The inclusion criteria were as follows:

- Age≥18 years
- ICU stay≥48 hours
- Documented pathogen growth in TA culture
- Availability of complete clinical data, including APACHE II score, mortality status, ICU length of stay, and duration of mechanical ventilation
- Availability of laboratory parameters, including complete blood count, CRP, albumin, urea, creatinine, lactate, and inflammatory indices

The exclusion criteria were as follows:

- Polymicrobial growth in TA cultures
- Growth detected only in bronchoalveolar lavage, blood, or urine cultures without corresponding growth in TA cultures
- Missing clinical, laboratory, or microbiological data
- Confirmed COVID-19 infection

Data Collection

Data were retrospectively extracted from the Hospital Information Management System, Laboratory Information System, and institutional microbiology databases.

The following variables were recorded:

Laboratory parameters: complete blood count, C-reactive protein (CRP), albumin, urea, creatinine, and lactate levels obtained at the time of microbiological sampling.

Inflammatory and nutritional indices: NLR, PLR, LMR, SII, SIRI, CAR, BAR, PNI, and PIV.

Microbiological variables: pathogen identification, gram classification, and AMR phenotype.

AMR categories were defined according to the international expert consensus criteria proposed by Magiorakos et al. Multidrug resistance (MDR) was defined as non-susceptibility to at least one agent in three or more antimicrobial categories. XDR organisms were defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories, whereas PDR organisms were defined as non-susceptibility to all agents in all antimicrobial categories.

Two isolates classified as “other microorganisms” were identified in the study cohort. Because of the limited sample size (n=2), these isolates were included in the overall descriptive analyses but were excluded from organism-specific subgroup analyses.

The primary outcome was in-hospital mortality. Secondary outcomes included ICU length of stay and duration of mechanical ventilation.

Biomarker and Index Definitions

In this research, a range of inflammatory and exploratory biomarkers were assessed to define immune response, nutritional status, and organ dysfunction in critically ill

patients. The NLR was determined by calculating the absolute neutrophil count in relation to the absolute lymphocyte count, while the platelet-to-lymphocyte ratio (PLR) was established as the platelet count divided by the lymphocyte count.[14,15] The Systemic Immune-Inflammation Index (SII) was derived using the formula platelet count×neutrophil count/lymphocyte count, whereas the Systemic Inflammation Response Index (SIRI) was calculated as neutrophil count×monocyte count/lymphocyte count.[16,17] All inflammatory indices were calculated using absolute cell counts expressed as/mm^3.

The CAR was calculated by dividing serum CRP levels (mg/l) by serum albumin concentration (g/dl). The blood urea nitrogen–to–albumin ratio (BAR) was defined as blood urea nitrogen (mg/dl) divided by serum albumin (g/dl).[18,19]

Additional biomarkers included RDW, which reflects erythrocyte size variability and has been associated with systemic inflammation, oxidative stress, and increased mortality risk in critically ill patients.[20] MPV, an indirect marker of platelet activation, has been linked to prothrombotic states and adverse outcomes.[21] Nutritional status and immune competence were assessed using the PNI , calculated according to the standard formula as (10×serum albumin [g/dl])+(0.005×absolute lymphocyte count [/mm^3]).[22] Finally, the PIV, defined as neutrophil×monocyte×platelet counts divided by lymphocyte count, was used as a composite indicator of overall systemic inflammatory burden.[23]

Statistical Analysis

The primary endpoint was in-hospital mortality. Associations between clinical variables, AMR patterns, gram stain results, and biomarkers were first evaluated using univariate analyses.

Comparisons between groups were performed using:

- χ^2 or Fisher's exact test for categorical variables
- Independent samples t-test or Mann–Whitney U test for continuous variables, as appropriate

Continuous variables with skewness>1 were $\log_1$p-transformed before analysis.

An exploratory receiver operating characteristic (ROC) analysis was conducted to evaluate the potential discriminatory power of the chosen biomarkers for in-hospital mortality. The area under the curve (AUC), ideal cut-off values (based on the Youden index), and sensitivity and specificity were determined. Ninety-five percent confidence intervals were estimated using bootstrap resampling with 5000 iterations. Correlation analyses were performed utilizing Pearson's correlation coefficient.

Missing data were handled using complete-case analysis. Multiple comparisons were adjusted using the Benjamini–Hochberg false discovery rate procedure. Statistical significance was defined as $p<0.05$. All analyses were performed using Python (Pandas, Statsmodels, Scikit-Learn) and. IBM SPSS Statistics version 26.0.

RESULTS

Patient Characteristics

Between January 2020 and December 2024, 1,680 patients were admitted to the intensive care unit. Fourteen patients who died on the day of ICU admission were excluded because complete clinical and laboratory data were unavailable. Among the remaining patients, 935 were intubated and had TA cultures obtained. Of these, 187 patients with documented microbial growth and complete laboratory data were included in the final analysis. The patient selection process is summarized in (Figure 1).

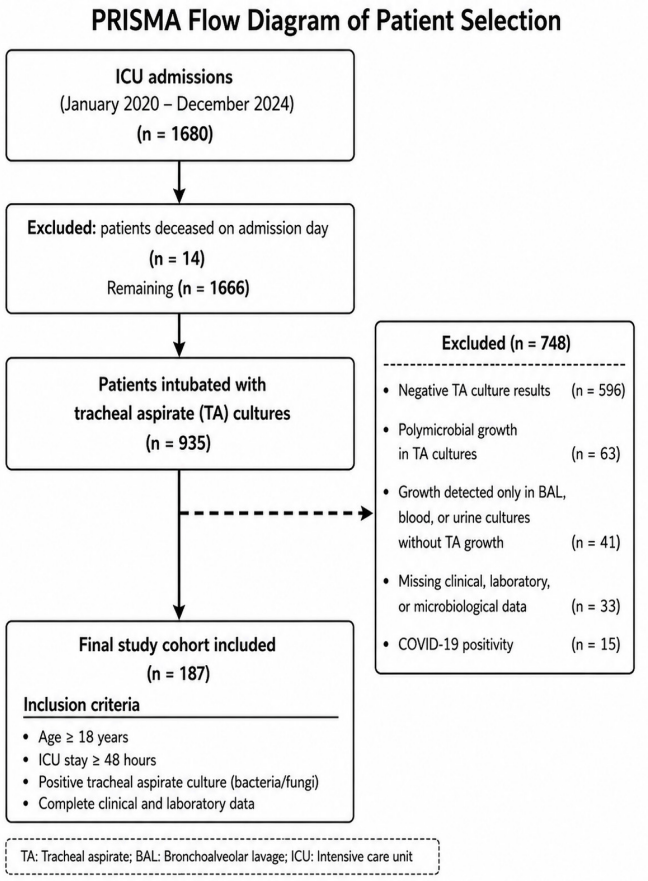

Figure 1. PRISMA flow diagram of patient selection

A total of 187 patients (93 females, 94 males; mean age 76.7±12.1 years) were included. The mean APACHE II score was 26.7±9.2, corresponding to an expected mortality of 56.3%±25.3. Hypertension (55.6%), cardiovascular disease (51.3%), and diabetes mellitus (25.7%) were the most common comorbidities. Gram-negative microorganisms predominated (89.3%). Sepsis was present in 26.2% of patients, and urosepsis in 9.6%.

Two isolates (1.1%) were classified as other microorganisms. Because of their limited number, they were not included in organism-specific subgroup analyses. The observed in-hospital mortality rate was 95.7% (Table 1).

Resistance Patterns

Only 9.6% of isolates were susceptible, while most exhibited antimicrobial resistance, including MDR: 36.4% and extensive drug resistance (XDR: 52.9%). Pandrug resistance (PDR) was identified in 1.1% of cases. Resistance to carbapenems was notably high (68.4%), and ESBL positivity was detected in 43.9% of isolates. Resistance to colistin (17.1%), oxacillin (14.4%), and methicillin (11.8%) was also observed, whereas resistance to ceftazidime–avibactam remained relatively low (8.0%).

Table 1. Socio/demographic and clinical characteristics of ICU patients

Variable	n (%) or mean±SD	95% CI
Gender		
- Male	93 (49.7%)	42.6–56.8%
- Female	94 (50.3%)	43.2–57.4%
APACHE II Score	26.7±9.2	25.4–28.0
Expected mortality (%)	56.3±25.3	52.7–59.9
Comorbidities		
- Diabetes mellitus	48 (25.7%)	19.6–31.7%
- Hypertension	104 (55.6%)	48.5–62.7%
- COPD/asthma	49 (26.2%)	20.1–32.2%
- Chronic kidney disease	31 (16.6%)	11.2–22.0%
- Cardiovascular disease	96 (51.3%)	44.2–58.4%
- Malignancy	28 (15.0%)	9.8–20.2%
- Neurological disease	73 (39.0%)	32.1–45.8%
Microorganism type		
- Gram negative	167 (89.3%)	84.7–93.9%
- Gram positive	18 (9.6%)	5.3–13.9%
- Other	2 (1.1%)	0–2.6%
Sepsis	49 (26.2%)	20.1–32.2%
Urosepsis	18 (9.6%)	5.3–13.9%
Outcome		
- Survived	8 (4.3%)	2.18–8.21 %
- Deceased	179 (95.7%)	91.79–97.82 %

Data are presented as mean±standard deviation or n (%), CI: Confidence interval, ICU: Intensive care unit, APACHE II: Acute Physiology and Chronic Health Evaluation II COPD: Chronic obstructive pulmonary disease. SD: Standard deviation.

MDR and XDR phenotypes accounted for 36.4% and 52.9% of isolates, respectively (Table 2).

Table 2. Antibiotic resistance profile

Category/resistance type	Percentage (%)	95% CI
No resistance	9.6%	6.2–14.7%
MDR	36.4%	29.8–43.5%
XDR	52.9%	45.8–60.0%
PDR	1.1%	0.3–3.8%
Colistin resistance	17.1%	12.4–23.2%
Oxacillin resistance	14.4%	10.1–20.2%
Carbapenem resistance	68.4%	61.5–74.7%
Ceftazidime–avibactam resistance	8.0%	4.9–12.8%
Methicillin resistance	11.8%	7.9–17.2%
ESBL positivity	43.9%	36.9–51.0%

CI: Confidence interval, MDR: Multi-drug resistant, XDR: Extensively drug-resistant, PDR: Pandrug-resistant, ESBL: Extended-spectrum beta-lactamase

Laboratory and Inflammatory Markers

Most patients exhibited marked leukocytosis, pronounced neutrophilia, and lymphopenia, along with relatively elevated monocyte counts and wide variability. Anemia was evident, while platelet counts were within the normal range but showed substantial interindividual variability. Inflammatory activity was prominent, as reflected by markedly elevated CRP levels (133.75±89.59 mg/L) and increased composite inflammatory indices.

Hypoalbuminemia was common (2.58±0.56 g/dl), resulting in significantly elevated inflammatory ratios, particularly the (CAR: 56.61±41.11) and blood urea nitrogen–to-albumin ratio (BAR: 20.27±13.98). The majority of patients exceeded a BAR value of 7.5, a threshold previously associated with poor prognosis. Renal dysfunction was frequently observed, with elevated urea (105.54±64.82 mg/dl), creatinine (1.81±1.43 mg/dl), and blood urea nitrogen (49.68±30.10 mg/dl) levels. Mean lactate concentration was markedly increased (5.36±5.13 mmol/l). Among hematological inflammatory indices, NLR and PLR were elevated, with mean values of 20.81±20.74 and 314.69±343.38, respectively. PLR values showed considerable variability across the study population. The lymphocyte-to-monocyte ratio (LMR) also exhibited considerable variability (2.66±3.05). The SII and SIRI reached high levels, with marked heterogeneity (4181.14±5644.45 and 11.99±16.32, respectively). BAR>7.5 was observed in 164 patients (87.7%; 95% CI 82.4–91.9). The PNI was 26.94±6.18, and the PIV was 2804.22±5878.22.

Markedly elevated CRP, lactate, CAR, BAR, NLR, SII, SIRI, and PIV values, together with low albumin and PNI levels, were observed in the study cohort (Table 3).

Table 3. Laboratory and inflammatory findings in ICU patients

Parameter (unit)	Mean±SD	95% CI
White blood cell count (K/µL)	15.04±7.75	13.93–16.15
Neutrophil count (K/µL)	13.17±7.46	12.10–14.24
Lymphocyte count (K/µL)	1.03±0.83	0.91–1.15
Monocyte count (K/µL)	0.60±0.42	0.54–0.66
Platelet count (K/µL)	210.78±124.22	192.98–228.58
Hemoglobin (g/dl)	10.35±2.44	10.00–10.70
Hematocrit (%)	31.95±7.82	30.83–33.07
RDW	16.39±2.59	16.02–16.76
MPV	11.19±1.67	10.95–11.43
CRP (mg/L)	133.75±89.59	120.91–146.59
Albumin (g/dl)	2.58±0.56	2.50–2.66
Urea (mg/dl)	105.54±64.82	96.25–114.83
Creatinine (mg/dl)	1.81±1.43	1.61–2.01
BUN (mg/dl)	49.68±30.10	45.37–53.99
BUN/creatinine ratio	32.95±16.68	30.56–35.34
BUN/albumin ratio (BAR)	20.27±13.98	18.27–22.27
Calcium (mg/dl)	8.13±0.95	7.99–8.27
Lactate (mmol/l)	5.36±5.13	4.62–6.10
NLR	20.81±20.74	17.84–23.78
PLR	314.69±343.38	265.48–363.91
LMR	2.66±3.05	2.23–3.10
SII	4181.14±5644.45	3372.12–4990.15
SIRI	11.99±16.32	9.65–14.33
CAR	56.61±41.11	50.71–62.50
PNI	26.94±6.18	26.05–27.82
PIV	2804.22±5878.22	1961.69–3646.74

Data are presented as mean±standard deviation with 95% confidence intervals.
WBC: White blood cell, RDW: Red cell distribution width, MPV: Mean platelet volume, CRP: C-reactive protein, BUN: Blood urea nitrogen, BAR: Bun-to-albumin ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammatory Response Index, CAR: C-reactive protein-to-albumin ratio, PNI: Prognostic Nutritional Index, PIV: Pan-immune Inflammation Value.

Outcomes by Gram Status

Mortality was significantly higher in the gram-negative group than in the gram-positive group (97.0% vs. 83.3%, p=0.007), and ICU length of stay was longer among patients with gram-negative microorganisms (17.8±13.5 vs. 11.7±10.9 days, p=0.041). APACHE II scores (26.7±9.3 vs. 26.1±8.3, p>0.05) and expected mortality rates (56.4%±25.6% vs. 54.6%±24.5%, p>0.05) did not differ significantly between the groups.

Inflammatory indices, including NLR, PLR, LMR, SII, SIRI, CAR, and PIV, tended to be higher in patients with gram-negative microorganisms, whereas PNI values tended to be higher in the gram-positive group; however, none of these differences reached statistical significance (Table 4).

higher among non-survivors and correlated positively with APACHE II scores and expected mortality. Lactate showed significant associations with mortality and severity indices, including positive correlations with APACHE II scores and expected mortality and an inverse correlation with ICU length of stay.

Among inflammatory indices, NLR, SIRI, and CAR were significantly associated with mortality, whereas PLR demonstrated limited discriminatory performance. LMR was not associated with mortality but correlated with prolonged ICU stay. PNI values were significantly higher among survivors. PIV values were higher among non-survivors and were associated with both mortality and prolonged ICU stay.

Table 4. Clinical outcomes by gram status and organism group

Panel A. outcomes by gram status

Outcome	Gram-negative (n=167)	Gram-positive (n=18)	p-value
Mortality rate, n (%)	162 (97.0%)	15 (83.3%)	0.007
ICU stay (days),mean±SD	17.80±13.53	11.72±10.92	0.041
APACHE II score,mean±SD	26.72±9.32	26.06±8.32	0.799
Expected mortality (%), mean±SD	56.42±25.59	54.64±24.52	0.769

Panel B. outcomes by organism group

Organism group	Mortality rate (%)	ICU stay (days, mean±SD)	OR for mortality vs gram-positive (95% CI)	p value
Klebsiella	94.8	19.71±15.37	3.67 (0.67–20.05)	0.130
Acinetobacter	100.0	18.14±10.48	20.10 (0.98–411.42)	0.016
Pseudomonas	100.0	20.43±15.62	6.55 (0.31–138.06)	0.274
Serratia	88.9	11.17±12.97	1.60 (0.23–10.94)	0.658
Escherichia coli	100.0	12.59±10.30	10.16 (0.49–210.94)	0.074
Gram-positive	83.3	11.72±10.92	Reference	—

Note: Data are presented as mean±standard deviation (SD) or n (%). Mortality rates were compared using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared using the independent samples t-test or Mann–Whitney U test, as appropriate. A p-value <0.05 was considered statistically significant. Organism-specific mortality rates and odds ratios should be interpreted cautiously because small subgroup sizes, zero-event cells, and wide confidence intervals indicate substantial statistical uncertainty. Mortality rates were compared using χ^2 or Fisher's exact test, as appropriate, and continuous variables were compared using independent samples t test or Mann–Whitney U test. In Panel B, gram-positive organisms were used as the reference group for odds ratio calculations. A continuity correction was applied where necessary due to sparse data. Two isolates categorized as "other microorganisms" were included in the overall descriptive analyses but were not analyzed as a separate subgroup because of the limited sample size (n=2). OR: Odds ratio, CI: Confidence interval, ICU: Intensive care unit, SD: Standard deviation

When outcomes were further examined according to individual microorganism groups, marked heterogeneity was observed (Table 4). The highest observed mortality rates were noted in cases involving *Acinetobacter, Pseudomonas,* and *Escherichia coli* isolates, all of which reached 100% mortality in this cohort. *Klebsiella* isolates were also associated with a very high mortality rate (94.8%), whereas *Serratia* isolates demonstrated a relatively lower—but still substantial—mortality rate (88.9%). Gram-positive microorganisms demonstrated an intermediate mortality rate (83.3%).

In odds ratio analyses using gram-positive organisms as the reference, point estimates suggested a trend toward higher mortality risk for *Acinetobacter, Escherichia coli*, and *Pseudomonas* isolates. However, because of the small subgroup sizes and the presence of zero-event cells, confidence intervals were extremely wide and included unity in most comparisons, indicating substantial statistical uncertainty. Therefore, these organism-specific findings should be interpreted cautiously and should not be considered definitive evidence of increased mortality risk.

Biomarker Performance and Mortality

Associations between key biomarkers and clinical outcomes are summarized in Table 5. BAR levels were significantly

In ROC analyses with bootstrap-derived confidence intervals, PNI demonstrated discriminatory performance for in-hospital mortality (AUC=0.88, 95% CI 0.71–0.98). Lactate (AUC=0.80) and CAR (AUC=0.73) also demonstrated moderate-to-high discriminatory performance, whereas NLR, PIV, and BAR showed moderate performance. APACHE II demonstrated limited discrimination (AUC=0.61) (Table 5).

Outcomes by Resistance Category

Mortality and ICU length of stay increased progressively from susceptible isolates to MDR, XDR, and PDR categories, with the highest observed mortality in the PDR subgroup (Table 6). Interpretation of the PDR subgroup should be made with considerable caution because only two patients were included (n=2), precluding meaningful comparative analyses or generalizable conclusions. APACHE II scores and expected mortality estimates did not increase proportionally across resistance categories. The PDR subgroup demonstrated an expected mortality rate of 33% despite adverse clinical outcomes (Table 6).

Blood and Urine Culture Findings

Microbial growth was detected in blood cultures from 50 patients. *Staphylococcus* spp. were the most frequently isolated organisms (52% of positive blood cultures), followed by *Klebsiella* spp. and

Table 5. Association of key biomarkers with mortality and their prognostic performance

Parameter	Survivors (mean±SD)	Non-survivors (mean±SD)	p (mortality)	AUC (95% CI)	Cut-off	Sensitivity	Specificity
PNI	36.75± 6.50	26.66±5.98	0.003	0.88 (0.71–0.98)	≤32.78	0.87	0.88
Lactate	2.04±0.87	5.51±5.19	<0.001	0.80 (0.64–0.92)	≥1.70	0.89	0.62
BAR	8.08±4.28	20.81±14.01	<0.001	0.83 (0.72–0.93)	≥13.41	0.65	1.00
NLR	10.96±6.36	21.07±21.18	0.002	0.64 (0.48–0.79)	≥19.28	0.36	1.00
SIRI	5.81±2.72	12.27±16.62	<0.001	0.61 (0.35–0.84)	≥10.00	0.60	0.58
CAR	27.56±22.94	57.90±41.30	0.007	0.73 (0.51–0.90)	≥9.96	0.93	0.50
PIV	2150.32±1850.22	5630.41±7200.18	0.001	0.66 (0.45–0.85)	≥2500	0.72	0.65
APACHE II	—	—	—	0.61 (0.48–0.73)	≥31.00	0.37	1.00

Data are presented as mean±standard deviation. Comparisons between survivors and non-survivors were performed using the independent samples t test or the Mann–Whitney U test, as appropriate. Prognostic performance was evaluated using receiver operating characteristic (ROC) curve analysis. The AUC and 95% confidence intervals (CI) were calculated using bootstrap resampling (5,000 iterations). Optimal cut-off values were determined using the Youden index. Because only eight patients survived, the reported AUC values, optimal cut-off values, sensitivity, and specificity estimates should be considered exploratory and should not be interpreted as definitive clinical thresholds.BAR: Blood urea nitrogen-to-albumin ratio, NLR: Neutrophil-to-lymphocyte ratio, SIRI: Systemic Inflammation Response Index, CAR: C-reactive protein-to-albumin ratio, PNI: Prognostic Nutritional Index, PIV: Pan-immune inflammation value, ICU: Intensive care unit, SD: Standard deviation, CI: Confidence intervals, AUC: Area under the curve, APACHE II: Acute Physiology and Chronic Health Evaluation II.

Table 6. Clinical outcomes according to antimicrobial resistance category

Outcome	No resistance (n=18)	MDR (n=68)	XDR (n=99)	PDR (n=2)	p-value
Mortality rate, n (%)	16 (88.9%)	64 (94.1%)	97 (98.0%)	2 (100.0%)	0.256*
ICU stay (days), mean±SD	8.5±6.9	15.1±12.1	20.4±14.8	24.0±2.8	0.001
APACHE II score, mean±SD	26.6±8.1	29.1±9.9	25.2±8.6	19.0±4.2	0.053
Expected mortality (%), mean±SD	56.3±23.9	62.9±25.1	52.4±25.1	33.0±13.4	0.037

*p-values represent overall comparisons among antimicrobial resistance categories. Data are presented as number (%) or mean±standard deviation. Clinical outcomes are shown descriptively according to antimicrobial resistance categories (susceptible, MDR, XDR, and PDR). Interpretation of the PDR subgroup should be made with considerable caution because only two patients were included (n=2), which is insufficient for meaningful comparative analyses or generalizable conclusions. MDR: Multidrug-resistant, XDR: Extensively drug-resistant, PDR: Pandrug-resistant, ICU: Intensive care unit, CI: Confidence interval, APACHE II: Acute Physiology and Chronic Health Evaluation II.

Escherichia coli. *Enterobacter* spp. and *Serratia* spp. were identified less frequently.

No growth was detected in urine cultures from 169 patients (90.4%). Among the 18 patients (9.6%) with positive urine cultures, *Klebsiella* spp. were the most frequently isolated organisms (50% of positive urine cultures), followed by *Escherichia coli*. *Staphylococcus* spp. and *Acinetobacter* spp. were identified less frequently.

DISCUSSION

In this study, 187 critically ill, intubated ICU patients with positive TA cultures were evaluated with respect to clinical outcomes, antimicrobial resistance, and the performance of inflammatory biomarkers. The overall in-hospital mortality rate was remarkably high (95.7%), indicating the severely ill and highly selected nature of this cohort. Within this high-risk population, gram-negative microorganisms and antimicrobial-resistant pathogens—particularly MDR, XDR, and PDR organisms—were associated with adverse clinical outcomes.

The exceptionally high mortality likely reflects several contextual factors and is consistent with previous reports describing high mortality among mechanically ventilated ICU patients with suspected lower respiratory tract infections associated with antimicrobial resistance.[2,24] The cohort consisted exclusively of elderly, mechanically ventilated patients with positive TA cultures obtained in the setting of suspected lower respiratory tract infection, representing a highly selected subgroup of ICU admissions. As a tertiary referral center, our ICU frequently manages patients transferred at advanced stages of illness, often after initial treatment failure elsewhere. In addition, end-of-life decisions or limitations of life-sustaining therapy may have contributed to the observed mortality, although such variables were not systematically captured. Therefore, these outcomes should be interpreted within the context of a high-risk referral population rather than generalized to broader ICU settings. The inclusion of only intubated patients with positive TA cultures may have introduced selection bias toward more severe cases, which should also be considered when interpreting the exceptionally high mortality rate.

Furthermore, the exceptionally high in-hospital mortality substantially limits the external validity and generalizability of our findings. Therefore, the observed associations between antimicrobial resistance, biomarker profiles, and clinical outcomes should be interpreted within the context of this highly selected cohort and should not be extrapolated to broader ICU populations with different patient characteristics, illness severity, or case mix.

Mortality was significantly higher among patients with gram-negative microorganisms compared with those with gram-positive microorganisms (97% vs. 83%; p=0.007), and ICU length of stay was significantly longer (17.8±13.5 vs. 11.7±10.9 days; p=0.041). In contrast, APACHE II scores and predicted mortality did not differ between groups, suggesting that conventional severity scoring systems may not fully reflect the additional clinical burden associated with gram-negative pathogens and antimicrobial resistance. The results are consistent with previous reports reporting an association between gram-negative bacteremia, antimicrobial resistance, and higher mortality.[2,4] Differences in host inflammatory responses and pathogen-related factors may have contributed to the more severe clinical course observed among patients with gram-negative microorganisms.[3]

Gram-negative pathogens predominated in our cohort, consistent with previous ICU-based TA studies reporting

similar microbial distributions.[25] Similar microbiological distributions and high AMR rates have also been reported in ICU-based studies from Turkiye.[26,27] At the pathogen-specific level, mortality remained extremely high across nearly all organism groups. In this cohort, cases involving *Acinetobacter* isolates, *Pseudomonas*, and *Escherichia coli* were associated with very high observed mortality rates, reaching 100% in small subgroups. *Klebsiella* and *Serratia* isolates also demonstrated markedly elevated mortality rates. Gram-positive pathogens demonstrated comparatively lower—but still substantial—mortality. Although odds ratio analyses suggested higher mortality risk for certain gram-negative organisms, wide confidence intervals due to small subgroup sizes and zero-event cells warrant prudent interpretation.

A clear resistance gradient was observed. Mortality and ICU length of stay increased progressively from susceptible isolates to MDR, XDR, and PDR phenotypes, with the highest observed mortality in the PDR subgroup. However, APACHE II scores and predicted mortality did not increase in proportion to the severity of resistance. This difference may reflect deficiencies of traditional scoring systems, which do not incorporate pathogen-specific characteristics or resistance phenotypes. Similar limitations of APACHE II and SOFA scores in critically ill patients with AMR have been reported previously.[10]

It is noteworthy that the in-hospital mortality rate remained high (88.9%) even among patients with susceptible (non-resistant) isolates. This finding likely reflects the overall severity of illness in the study cohort rather than the antimicrobial susceptibility profile alone. All patients were critically ill, mechanically ventilated ICU patients with suspected lower respiratory tract infection, advanced age, multiple comorbidities, and high baseline disease severity. Therefore, mortality was probably influenced by multiple factors beyond antimicrobial resistance, including the underlying critical illness, organ dysfunction, and other concurrent medical conditions. Accordingly, antimicrobial susceptibility should not be interpreted as the sole determinant of clinical outcome in this highly selected population.

Biomarker analyses provided additional exploratory clinical and inflammatory insights in this high-risk ICU cohort. The cohort exhibited pronounced leukocytosis, neutrophilia, lymphopenia, hypoalbuminemia, and elevated CRP levels, consistent with marked systemic inflammatory and physiological stress responses. Among evaluated biomarkers, PNI showed relatively higher discriminatory performance for mortality and was significantly higher among survivors. This finding may suggest a possible association between preserved nutritional and immunological reserve and clinical outcomes in critically ill patients; however, further prospective validation is required.[9] Lactate also demonstrated moderate-to-high discriminatory performance and was associated with mortality, consistent with previous studies in critically ill and sepsis populations.[5,6] Similarly, CAR and BAR were associated with mortality and disease severity parameters in exploratory analyses, possibly indicating the combined effects of systemic inflammation, renal dysfunction, and nutritional compromise.[7,8,28]

Inflammatory indices, including NLR, SIRI, and CAR, were significantly associated with mortality, whereas SII and PLR showed limited discriminatory performance.[14-17,28] The PIV, integrating neutrophil, monocyte, platelet, and lymphocyte counts, was associated with both mortality and prolonged ICU stay in exploratory analyses. In contrast, RDW and MPV showed limited associations with clinical outcomes in this cohort, consistent with heterogeneous findings reported in previous studies.[12,13]

From a clinical perspective, the observed associations between AMR patterns and adverse clinical outcomes demonstrate the complexity of managing critically ill ICU patients with positive TA cultures. However, because treatment-related variables, such as the timing and appropriateness of empirical antibiotic therapy, were not systematically available, the independent contribution of AMR to mortality could not be fully determined. Although treatment-related variables were not systematically available in the present study, previous studies have highlighted the potential importance of timely empirical antimicrobial therapy and antimicrobial stewardship strategies in critically ill patients. Integration of biomarker-based assessment—particularly incorporating PNI and lactate—may reflect additional inflammatory and physiological alterations not entirely captured by conventional severity scores. Prolonged ICU stays associated with resistant microorganisms also have important consequences for resource utilization, infection control, and healthcare costs.

It should also be acknowledged that the precise causes of death were not systematically documented in this retrospective study. Critically ill ICU patients often have multiple concurrent conditions, including multiorgan failure, severe underlying comorbidities, and other life-threatening complications that may independently contribute to mortality. Therefore, the observed associations between antimicrobial resistance, biomarker profiles, and mortality should not be interpreted as evidence that the isolated microorganisms were the direct cause of death but rather as associations observed within this critically ill population.

In conclusion, mortality was exceptionally high in this elderly, mechanically ventilated ICU population with positive TA cultures. Gram-negative microorganisms and AMR patterns were more frequently observed among patients with prolonged ICU stays and adverse clinical outcomes that were not fully reflected by conventional severity scoring systems. Biomarkers—particularly PNI and lactate—showed exploratory associations with mortality and may reflect additional inflammatory and physiological alterations not completely captured by conventional severity scores. These exploratory findings may help generate hypotheses for future prospective investigations integrating AMR profiles and biomarker assessment.

Limitations

The primary limitations of this research include its retrospective design conducted at a single center, a limited number of participants in the PDR subgroup, the risk of type I error from multiple comparisons, and measurement variability. Multivariable regression analysis could not be conducted due to a significant imbalance in events (95.7% mortality), which may have led to model instability, overfitting, and unreliable parameter estimates.

In addition, only eight patients survived, resulting in an extreme imbalance between survivors and non-survivors. Consequently, the exploratory ROC analyses were based on a very small survivor

group, substantially reducing the statistical power of the calculated AUC values and increasing the risk of overfitting when estimating optimal cut-off values, sensitivity, and specificity. Therefore, these findings should be interpreted as hypothesis-generating rather than definitive clinical thresholds and require validation in larger prospective cohorts before clinical application.

Several inflammatory and hematological biomarkers evaluated in this study, including PIV, RDW, MPV, NLR, and PNI, may be affected by multiple comorbid conditions such as malignancy, hematological disorders, corticosteroid exposure, immunosuppressive therapy, and chronic systemic inflammation. Because these variables were not systematically available in the retrospective dataset, residual confounding could not be fully excluded. Therefore, the observed biomarker associations should be interpreted cautiously and considered exploratory rather than definitive indicators of clinical severity or prognosis.

In addition, primary ICU admission diagnoses and indications for ICU admission were not systematically available in a standardized format because of the retrospective design. As these factors are important determinants of disease severity and mortality, their absence limited further characterization of the study population and may have introduced residual confounding.

Furthermore, data regarding the appropriateness and timing of empirical antibiotic therapy were not systematically available, representing a potentially important unmeasured confounder that may have influenced clinical outcomes. Because TA cultures may reflect colonization rather than true infection in mechanically ventilated patients, the retrospective design limited the ability to fully differentiate infection from colonization or contamination in all cases.

Moreover, the specific causes of death were not systematically documented in a standardized format. Consequently, it was not possible to determine the extent to which mortality was directly attributable to the microorganisms isolated from TA cultures rather than to underlying critical illness or other concurrent medical conditions. Therefore, the observed associations between antimicrobial resistance, biomarker profiles, and mortality should be interpreted as associations rather than evidence of direct causality.

Although a 100% mortality rate was observed in the PDR group, this finding should be interpreted with considerable caution because only two patients were included (n=2). Therefore, the PDR subgroup is insufficient for meaningful comparative analyses or for drawing generalizable conclusions.

Therefore, these outcomes should be validated in larger, multicenter, prospective cohorts that incorporate standardized infection definitions, treatment-related variables, and more comprehensive adjustment for potential confounding factors. Future studies evaluating the resistance–outcome relationship may also benefit from advanced multivariable and competing-risk analytical approaches.

CONCLUSION

In this cohort of elderly mechanically ventilated ICU patients with positive TA cultures, overall mortality was remarkably high, indicating the critically ill and highly selected nature of the study population. Gram-negative microorganisms and increasing AMR patterns were more frequently associated with adverse clinical outcomes and prolonged ICU stay and may be associated with poorer clinical outcomes in this highly selected cohort. Observed mortality tended to increase progressively across resistant phenotypes, particularly among MDR and XDR isolates, although interpretation of the PDR subgroup should be cautious given the limited sample size.

Conventional severity scoring systems, such as APACHE II, did not fully reflect the adverse clinical outcomes observed in patients with resistant microorganisms. In contrast, several inflammatory and nutritional biomarkers, including PNI, lactate, and CAR, demonstrated associations with mortality in exploratory analyses. However, given the retrospective design, the exceptionally high mortality rate, and the inability to fully differentiate true infection from colonization in all cases, these biomarker findings should be interpreted cautiously.

Overall, this study suggests possible associations among AMR patterns, biomarker profiles, and adverse clinical outcomes in mechanically ventilated ICU patients with positive TA cultures. However, because of the retrospective design, the lack of treatment-related data, and the inability to fully distinguish colonization from true infection, these findings should not be interpreted as evidence of causality. Larger prospective multicenter studies incorporating standardized infection definitions and treatment-related variables are required to confirm these exploratory observations.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Health Sciences Researches Ethics Committee of Yüksek İhtisas University (Date: 30.10.2025, Decision No: 17/348).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

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Case Report

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Challenges in airway management in patients undergoing thyroid surgeries–a case series

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ABSTRACT

Airway management in patients undergoing thyroid surgery poses unique challenges due to potential anatomical distortions caused by thyroid enlargement. Difficult intubation in such cases occurs in 2–12.7% of patients, with a failure rate of up to 0.5%. This case series highlights varied clinical scenarios of thyroid-related airway difficulties and underscores the importance of individualized anaesthetic strategies. We present four distinct cases of patients with large thyroid swellings, each illustrating different aspects of airway compromise and anesthetic management. A 56-year-old woman with a massive longstanding goiter underwent successful awake fiberoptic intubation and thyroidectomy, with postoperative tracheomalacia requiring delayed extubation after 48 hours. 40-year-old woman with bilateral thyroid enlargement and minimal compressive symptoms underwent conventional intubation following induction, with an uneventful perioperative course. A 55-year-old woman with longstanding multinodular goiter developed acute airway compromise. Difficult intubation was managed using video laryngoscopy and bougie, followed by delayed extubation for tracheomalacia. A 64-year-old woman with massive thyroid enlargement causing tracheal deviation and vascular compression underwent successful nasal fiberoptic intubation, uneventful surgery, and safe extubation. This series highlights that the complexity of airway management in thyroid surgery varies significantly based on goiter size, anatomical distortion, and airway involvement. Awake fiberoptic intubation remains a cornerstone technique in managing difficult airways, especially in the presence of tracheal compression or deviation. Video-assisted devices and a multidisciplinary approach enhance safety and outcomes. An individualized, well-planned anesthetic approach based on thorough preoperative assessment is crucial in minimizing morbidity and ensuring safe airway management in thyroid surgery.

Keywords: Airway management, thyroid surgeries, fibreoptic intubation

INTRODUCTION

Managing the airway in individuals with significant thyroid swelling can pose a challenging task for anesthesiologists Surgeries for these types of swellings can range from relatively simple procedures, such as nodulectomy or thyroidectomy, to more complex operations that may require a sternotomy. When patients with such conditions undergo general anesthesia, anatomical variations can pose significant challenges in airway management.[1] An anterior neck mass can limit neck mobility, reduce mouth opening, and cause deviation or compression that narrows the trachea. If the swelling extends past the thoracic inlet, it may also compress the trachea, esophagus, or major mediastinal blood vessels.[2] Studies have reported that thyroid masses cause tracheal compression in up to 91% of cases, while retrosternal extension occurs with a variable incidence ranging from 0.2% to 45%.[3] A long-standing thyroid swelling is not only a risk factor for a difficult airway but is also linked to complications such as acute airway obstruction, hemorrhage, thyroid dysfunction, infection, tracheomalacia, hypocalcemia, and voice changes.[4] The occurrence of challenging intubation in cases of thyroid swellings ranges from 2-12.7%, with a failure rate of up to 0.5%.[5] Consequently, a comprehensive preoperative assessment is crucial to identify any indications or symptoms of a difficult airway. It is essential to thoroughly investigate these aspects and establish a prearranged strategy, including alternative techniques, before proceeding with surgery.

Here we present a case series of anaesthetic challenges faced in airway management of patients (Table) posted for thyroid surgery,each case highlighting a distinct pattern of airway involvement—ranging from minimal compressive symptoms

Table. Comparison of airway management across four thyroid surgery cases

Parameter	Case 1	Case 2	Case 3	Case 4
Age/gender	56/Female	40/Female	55/Female	64/Female
Thyroid size	12×14 cm	7×3 cm	Right: 50×32 mm; left: 54×60 mm; isthmus thickness: 20 mm	9.6×9.7×10.2 cm
CT findings	Tracheal narrowing (AP diameter ~0.5 cm), elongation, and rightward deviation; no retrosternal extension	Enlarged thyroid with heterogeneous attenuation and nodular changes; no significant tracheal compression	Massive thyroid enlargement with rightward tracheal deviation and near-complete compression over 4–5 cm; retrosternal extension present	Large mixed solid–cystic lesion from right thyroid lobe with leftward tracheal deviation; compression of adjacent vascular structures
Primary airway strategy	Awake fiberoptic intubation (6.5 mm ETT) using spray-as-you-go technique	Conventional induction followed by direct laryngoscopy and intubation (7.5 mm ETT)	Video laryngoscopy-assisted intubation with tracheal introducer (bougie) and 6.0 mm ETT	Awake nasal fiberoptic intubation using flexible bronchoscope
Postoperative complications	Tracheomalacia requiring delayed extubation; ICU stay; persistent left vocal cord palsy	None	Tracheomalacia requiring prolonged ventilation and delayed extubation	None

CT: Computed tomography, AP: Anteroposterior, ETT: Endotracheal tube, ICU: Intensive care unit

to severe tracheal deviation, acute airway compromise, and postoperative tracheomalacia—thereby capturing the heterogeneity of airway presentations associated with thyroid enlargement.

CASE 1

56-year-old female, presented with a gradually increasing midline neck swelling for 20 years with the present size of 12x14 cm (Figure 1). Patient also complained of pain at the swelling site, hoarseness of voice, difficulty in swallowing and difficulty in breathing which was worse on lying flat. Local examination revealed anterior asymmetrical midline neck swelling extending to submental region above and up to sternum below, laterally extending till the posterior border of sternocleidomastoid muscle bilaterally. Lower border of the swelling noted just above the sternal notch. Patient had negative Pemberton sign, negative Berry's sign, positive Kocher's test. Airway examination showed restricted mouth opening and neck flexion, and Mallampati grade IV.

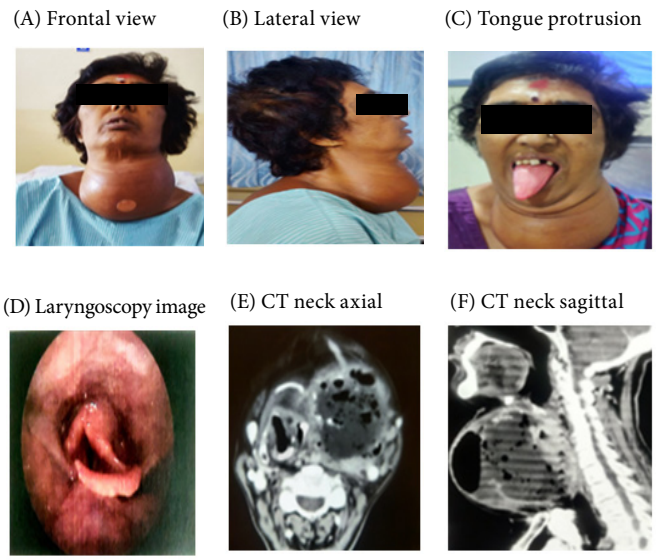

Figure 1. Clinical photographs of (A) Frontal view, (B) lateral view, and (C) tongue protrusion in case 1 with a large anterior neck swelling. (D) Video laryngoscopy image showing distorted laryngeal anatomy. (E) Axial and (F) sagittal computed tomography (CT) images demonstrating a large thyroid mass with significant tracheal compression and deviation.

Computed tomography (CT) of the neck demonstrates marked rightward displacement of the larynx and cervical trachea. No evidence of retrosternal extension is identified. The trachea appears narrowed and elongated in the anteroposterior dimension, with a transverse luminal diameter of approximately 0.5 cm. Video-laryngoscopy done by Ear, Nose & Throat(ENT) surgeon showed larynx pushed to the right and fixed left vocal cord (Figure 1).

Fiberoptic-guided awake endotracheal intubation was performed using a 6.5 mm cuffed endotracheal tube with the "spray-as-you-go" technique. Airway topicalization was achieved using 2% Lidocaine, with a total dose carefully titrated to remain within the safe limit of 3-4 mg/kg. Continuous oxygen supplementation was done via side port of the bronchoscope. After Correct placement of the tube in the trachea was confirmed by end-tidal carbon dioxide, Patient was induced with Inj. Propofol 2 mg/kg and relaxed with Inj Atracurium 0.5 mg/kg and was maintained on oxygen, air and isoflurane.

Thyroid abscess was present along with the goiter and about 1000ml of pus drained and then total thyroidectomy was performed. Postoperatively, in view of complication of tracheomalacia, extubation was postponed, and the patient was shifted to intensive care unit (ICU). After 48 h, after confirming positive leak test, extubation was done by the anaesthetist in the presence of ENT surgeon with the backup for tracheostomy. Extubation was uneventful. Repeat video laryngoscopy showed fixed left vocal cord with bowing, mobile right vocal cord, phonatory gap present. Biopsy result was negative for malignancy and indicated nonspecific abscess and colloid goiter. Later patient was discharged with further follow up for speech therapy.

CASE 2

40-year-old female presented with swelling in front of neck since 4 years ,and complained of pain during swallowing in the last 15 days. There were no other compressive symptoms. Examination revealed neck swelling, which was

approximately 7x3 cm bilaterally. It was extending laterally up to sternocleidomastoid muscle, lower border of the swelling was palpable above the suprasternal notch, suggesting no retrosternal extension. Swelling was firm in consistency. Airway examination was normal except for restricted neck flexion.

CT scan of the neck revealed a markedly enlarged thyroid gland with heterogeneous attenuation and areas of nodular enlargement. Video laryngoscopy showed bilaterally mobile vocal cords. As there was no compression noted in the neck X-rays (Figure 2), patient was induced and relaxed after confirming adequate mask ventilation, direct laryngoscopy was attempted, and airway secured with 7.5 mm cuffed endotracheal tube. Intraoperative period was uneventful. After ensuring mobile vocal cords, adequate ventilatory efforts and positive leak test, extubation was done on table.

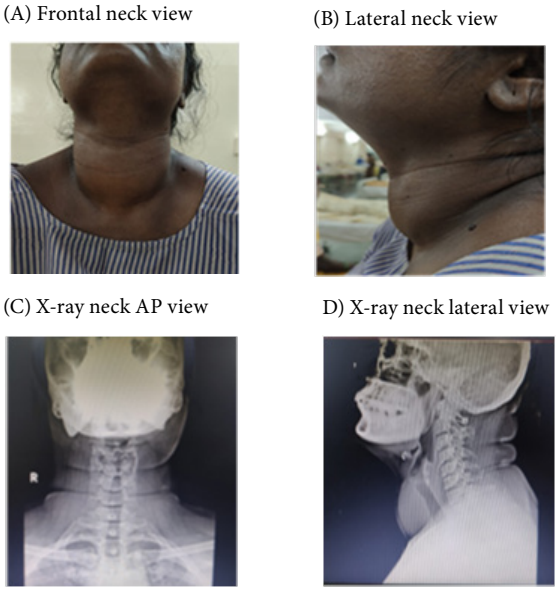

Figure 2. (A) Frontal and (B) lateral clinical photographs showing anterior neck swelling in case 2. (C) Anteroposterior (AP) and (D) lateral neck radiographs demonstrating an enlarged thyroid gland without significant tracheal compression or deviation.

CASE 3

A 55-year-old female had difficulty in breathing for 5 months, aggravated since 4 days and she was rushed to the hospital as it gotten worse for last 3 hours. She had cough with expectoration and fever in the last 4 days, for which she was treated with antibiotics and nebulization at a local hospital and was diagnosed with multinodular goiter with lower respiratory tract infection (LRTI) before presenting to our hospital. She had history of hypothyroidism for 20 years and was treated with levothyroxine regularly. She was asymptomatic till 2 years ago, when she developed a visible neck swelling and was suggested to undergo thyroidectomy. She stopped thyroxine medication 5 months ago after which the goitre increased in size.

CT scan of the neck showed diffuse gross enlargement of both lobes of thyroid (right lobe 50x32 mm; left lobe 54x60 mm; anteroposterior×transverse, isthmus thichkness 20 mm). Mass effect noted over trachea causing right sided deviation and near complete compression for length of approximately 4-5 cm from subglottic to upper tracheal region (Figure 3).

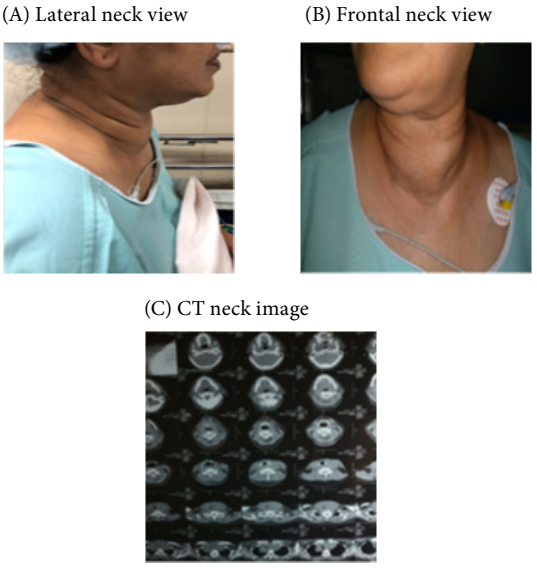

Figure 3. (A) Lateral and (B) frontal clinical photographs showing anterior neck swelling in case 3. (C) computed tomography (CT) image demonstrating diffuse enlargement of both thyroid lobes with marked tracheal deviation and near-complete compression.

On admission, she was immediately nebulized. Her vitals were stable with bilateral rhonchi and both inspiratory and expiratory stridor was heard. She was shifted to the ICU and the need for total thyroidectomy was explained. In this case, the decision to proceed with early surgical intervention was driven by the severity and progression of airway compromise rather than the infection alone. Moreover, the infectious component was being actively managed with antibiotics and supportive therapy, and the patient was hemodynamically stable at the time of intervention. Patient was explained the procedure of awake intubation and the difficulty in securing an airway. The patient underwent a flexible video laryngoscopy by the ENT surgeon which showed a clear view of the glottis with bilateral mobile vocal cords.

A cardiothoracic surgeon was consulted, and preparations were made in case of emergency sternotomy and cardiopulmonary bypass was required. After airway preparation, patient was shifted to the OT, She was placed in a propped-up position. Video laryngoscopy (C-MAC® video laryngoscope, Karl Storz, Germany) done, and vocal cords visualized. A tracheal introducer (bougie) was advanced beyond the vocal cord and a 6.0 mm cuffed endotracheal tube was advanced over it. After confirmation of intubation, patient was induced with inj. propofol 2 mg/kg & relaxed with Inj. Atracurium 0.5 mg/kg. Both lobes were removed, and retrosternal component was delivered by blunt digital dissection. Tracheomalacia was noted by the surgeon and hence patient was not extubated after surgery.

She was shifted to the ICU where she was on mechanical ventilation. On 2nd post operative day a leak test was performed but only 30 ml leak was present. On 3rd post operative day patient had a leak test of 150 ml on pressure support ventilation (PSV). A ventilating bougie inserted through endotracheal tube as a reintubation bridge and extubation was done.

CASE 4

A 64- year -old female presented with complaints of swelling in right side of neck for 15 years, increasing in size since the last 2 years. (Figure 4) Patient had acute onset of pain over the swelling with no history of dysphagia, dyspnoea or hoarseness of voice. On evaluation, patient was euthyroid. Airway examination showed mouth opening more than 3 finger breadths, Mallampati grade IV. Flexion and extension of neck was restricted.

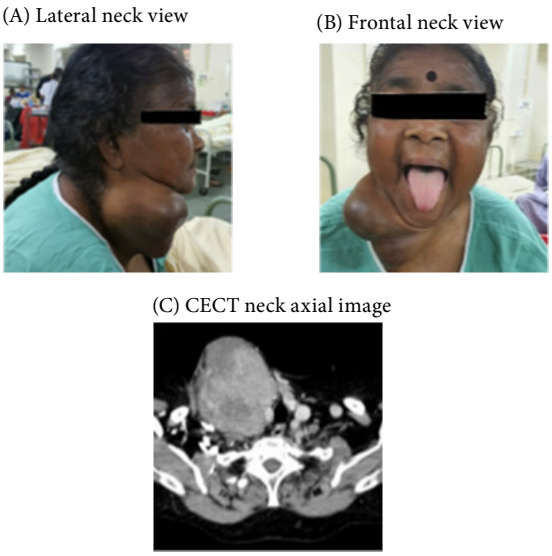

Figure 4. (A) Frontal and (B) lateral clinical photographs showing a large right-sided thyroid swelling with significant anterior neck distortion in case 4. (C) Axial contrast-enhanced computed tomography (CECT) image demonstrating a large thyroid mass causing leftward deviation of the trachea with compression of adjacent soft tissue structures.

The contrast-enhanced computed tomography (CECT) of the neck revealed a large, well-defined mixed solid–cystic lesion measuring approximately 9.6×9.7×10.2 cm, arising from the right lobe of the thyroid. The lesion extended superiorly up to the angle of the mandible and inferiorly to the root of the neck, abutting the right brachiocephalic artery, along with mass effect on the right internal jugular vein and common carotid artery. The trachea was deviated to the left. Bilateral vocal cords were mobile on indirect laryngoscopy. The patient was scheduled for total thyroidectomy. In view of anticipated difficult airway, right nasal intubation guided by single-use flexible bronchoscope was done. Patient underwent total thyroidectomy and right modified radical neck dissection without any intraoperative complications. Patient was reversed and an uneventful extubation was done postoperatively.

DISCUSSION

The management of the airway poses a concern for both the anesthetist and the surgeon when dealing with patients undergoing thyroidectomy. Challenges may arise throughout the preoperative, intraoperative, and postoperative phases. An in-depth pre-anaesthetic assessment, encompassing symptoms, airway evaluation, blood profile, and imaging studies, forms the foundation for effective anaesthetic management.[6] Thyroid enlargement can induce tracheal compression, deviation, and softening of tracheal rings, potentially leading to tracheal collapse during anesthesia. However, the impact varies based on factors such as size, duration, pathological type, or invasion into surrounding tissues. Airway ultrasound can provide real-time, bedside evaluation of tracheal diameter, degree of compression, tracheal deviation, and soft tissue characteristics, which may aid in anticipating airway difficulty and planning intubation strategies. It may also be useful in identifying the cricothyroid membrane and guiding emergency airway access if required. Additionally, the retrosternal extension of the thyroid may compress the intrathoracic part of the trachea, posing more intricate management issues.[7]

Managing a difficult airway in patients with thyroid enlargement offers various modalities, contingent on the anesthesiologist's expertise and familiarity. Malhotra and Sodhi[8] outlined a strategy for airway management in thyroid patients, incorporating options like inhalation induction with sevoflurane, awake fiberoptic intubation (AFOI), tracheotomy, or ventilation using a rigid bronchoscope. In cases of challenging airways with substantial, compressive thyroid masses, maintaining tissue oxygenation through cardiopulmonary bypass has also been documented. In our case scenario 1, the airway obstruction was likely multifactorial, resulting not only from the structural enlargement of the thyroid gland but also from acute inflammatory edema, mass effect from the abscess collection, and possible surrounding tissue involvement, hence we planned AFOI. For small enlargements without deviation or compression, and with a normal airway examination, standard airway management is pursued. In a study by Bouaggad et al,[9] easy tracheal intubation was observed in 36.9% of patients, mild tracheal difficulty in 57.8%, while 5.3% experienced moderate to major airway challenges.

Managing the airway in the presence of a substantial retrosternal goiter can be challenging, with the potential for cardiorespiratory collapse. The primary objective of airway management in this scenario is to maintain airway patency while choosing a technique that is likely to secure the airway on the first attempt. In cases of significant airway compression, many airway experts recommend delaying the induction of anesthesia and muscle relaxation until after securing the airway. Among these patients, AFOI is often considered the safest method for airway securing and is frequently the initial choice. Nevertheless, contingency plans are essential in case of intubation failure or inability to bypass the obstruction following AFOI. In a consensus of expert opinions on difficult airway management in patients with a retrosternal goiter, seven out of eight airway management experts selected rigid bronchoscopy as a backup plan.[10]

Saxena et al.[11] highlighted that utilizing AFOI can effectively minimize bleeding and edema, resulting in a higher likelihood of success in airway management. Sendasgupta et al.[12] and Tan and Esa,[13] in their respective studies, indicated that AFOI contributes to enhanced hemodynamic stability, improved patient tolerance, and the maintenance of airway patency. Ghai et al.[14] recommended the strategic planning of early fiberoptic intubation when there is suspicion of significant airway obstruction.

Although fiberoptic bronchoscopy (FOB)-assisted intubation may encounter a certain failure rate in challenging airways, with some reports suggesting rates as high as 66%, it is a technique

that demands training and experience. A well-organized execution under the guidance of experienced practitioners has the potential to significantly enhance the success rate.[15]

Recent literature indicates that incorporating video-assisted devices into the challenging airway algorithm can enhance patient outcomes and increase the success rate of intubation, as done in our case 3. These devices prove beneficial even in scenarios where alignment of the oral, pharyngeal, and tracheal axis is challenging, offering assistance and facilitating the intubation process.[16] The choice of AFOI in case 1 was guided by the anticipated difficult airway, severity of tracheal compression, and the need to maintain spontaneous ventilation during airway securing. In contrast, in case 3, video laryngoscopy was considered feasible due to the presence of a relatively preserved glottic view on preoperative assessment, as confirmed by flexible laryngoscopy, along with the ability to visualize the vocal cords despite tracheal deviation.

Patients with large thyroid cancer pose complexities in airway management due to both regional invasion and intrathoracic extension, leading to a mass effect on the airway and major vessels Various approaches for managing tracheal tumors have been reported in the literature, encompassing awake intubation with or without extracorporeal circulation assistance, laryngeal mask airways, tracheal stents, high-frequency jet ventilation, and regional anesthesia, particularly if the airway is not the surgical site. In rare instances, intubation may necessitate diverse positions such as sitting or even lateral decubitus.[17]

Most common complications encountered in these patients include laryngeal edema that necessitate immediate re-intubation following extubation. This occurrence is typically indicative of multiple intubation attempts, potential trauma to the vocal cords during intubation, and excessive dissection during surgery. Tracheomalacia is the predominant airway complication seen in patients with long standing goitres as seen in 2 of our cases. Key risk factors associated with the development of tracheomalacia in patients with long-standing goiter include prolonged duration of goiter (particularly >10–15 years), significant tracheal compression and narrowing (especially when the tracheal diameter is reduced to <1 cm on imaging), retrosternal extension, and long-segment tracheal involvement. Chronic external compression is thought to result in weakening of tracheal cartilaginous rings, predisposing to airway collapse following thyroidectomy when the supporting mass is removed. Previous studies have indicated that tracheomalacia is frequently the leading indication for tracheostomy.[18]

CONCLUSION

Not all situations warrant a single, universal intubation technique. The careful selection of techniques is determined by evaluating the risk versus benefit of available methods, considering evidence-based studies. Thorough preoperative airway assessment, adequate preparation, and timely decision-making, coupled with skillful management, contribute to the reduction of morbidity and mortality in cases involving difficult airways due to thyroid enlargement. This is underscored by instances where, after the failure of awake fiberoptic intubation, subsequent success has been achieved through direct laryngoscopic intubation. A personalized approach is essential for each case, taking into account preoperative and intraoperative findings when deciding on tube retention.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patients included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

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Author Contributions

Concept: MS, AT, AS, NK; Design: MS, AT, AS, NK; Data Collection and/or Processing: MS, AT, AS, NK; Analysis and/or Interpretation: MS, AT, AS, NK; Literature Review: MS, AT, AS, NK; Writing the Article: MS, AT, AS, NK; Critical Review: MS, AT, AS, NK.

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CASE REPORT

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Suspected sevoflurane-associated hypersensitivity reaction in a pediatric patient: a case report

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ABSTRACT

Perioperative hypersensitivity reactions are uncommon but potentially serious complications that require early recognition and appropriate management. Although numerous drugs and substances used during anesthesia may cause hypersensitivity reactions, reactions associated with volatile anesthetic agents are extremely rare. We present a six-year-old girl who developed an acute cutaneous hypersensitivity reaction approximately five minutes after inhalational induction with sevoflurane. Erythema and swelling developed over the trunk without respiratory distress, oxygen desaturation, hemodynamic instability, or other systemic manifestations. Sevoflurane was discontinued, the anesthesia circuit was changed, and 100% oxygen was administered. Following establishment of intravenous access, crystalloid fluid and pharmacological treatment with an antihistamine, corticosteroid, and inhaled bronchodilator were administered. The clinical findings improved without progression and surgery was subsequently completed. This case highlights that hypersensitivity reactions may rarely occur during inhalational induction with sevoflurane and may pose a particular challenge when intravenous access has not yet been established.

Keywords: Sevoflurane, inhalational anesthesia, hypersensitivity reaction, pediatric anesthesia, perioperative allergy

INTRODUCTION

Perioperative hypersensitivity may present with findings ranging from isolated skin changes to severe respiratory and cardiovascular compromise.[1,2] During anesthesia, recognizing such reactions can be difficult because symptoms that would normally be reported by an awake patient are unavailable and changes in respiratory or circulatory status may have several competing explanations.[2]

Potential perioperative triggers include neuromuscular blocking agents, antibiotics, latex, chlorhexidine, colloids, and other drugs or materials encountered around the time of anesthesia.[2,3] Volatile anesthetics are rarely implicated. Nevertheless, their role becomes relevant when a reaction begins during inhalational induction before other commonly suspected intravenous agents have been administered.

Sevoflurane is commonly selected for inhalational induction in children, especially when anxiety or poor cooperation makes awake intravenous cannulation difficult. Published evidence of immediate hypersensitivity to sevoflurane is very limited, although a pediatric case with allergy testing supportive of sevoflurane as the trigger has been reported.[4]

Here, we describe a six-year-old child who developed acute erythema and swelling during sevoflurane induction while intravenous access was still being obtained. The case is notable for the isolated cutaneous presentation, stable respiratory and cardiovascular status, and the practical difficulty of managing an unexpected reaction before vascular access is available.

CASE

A six-year-old, 24-kg girl was scheduled for elective adenoidectomy. Her preoperative evaluation revealed no known history of allergy. Physical examination findings were normal, and the patient was classified as American Society of Anesthesiologists (ASA) physical status I.

Standard monitoring, including electrocardiography, non-invasive blood pressure measurement, and pulse oximetry,

was initiated. Anesthesia was induced with 7% sevoflurane in 100% oxygen. No medication other than sevoflurane and oxygen had been administered before the onset of the cutaneous findings.

Approximately five minutes after the initiation of sevoflurane administration, while peripheral intravenous cannulation was being performed, erythematous lesions accompanied by swelling developed over the trunk. No oxygen desaturation or respiratory distress was observed. The patient's hemodynamic parameters and other monitored vital signs remained stable throughout the event.

Considering the temporal relationship between exposure to sevoflurane and the onset of the cutaneous findings, an acute hypersensitivity reaction associated with sevoflurane was suspected. Sevoflurane administration was immediately discontinued, the anesthesia circuit was changed, and 100% oxygen was administered.

Peripheral intravenous access was subsequently established, and crystalloid fluid was administered at a rate of approximately 80 ml/h. pheniramine maleate (Avil) was administered intravenously at a dose of 2 mg/kg, and dexamethasone (Dekort) was administered intravenously at a dose of 0.3 mg/kg. salbutamol (Ventolin) was administered as a single puff through the endotracheal tube. Epinephrine was not administered because the reaction remained limited to cutaneous manifestations without respiratory or cardiovascular compromise.

Following treatment, the cutaneous findings did not progress to systemic involvement and resolved during the emergence phase of anesthesia. After discontinuation of sevoflurane, rocuronium (Esmeron) 0.6 mg/kg was administered intravenously, and the patient was subsequently intubated. Anesthesia was maintained using total intravenous anesthesia (TIVA), with a propofol infusion initiated at 6 mg/kg/h. The surgical procedure lasted approximately one hour and was completed without further complications. The patient recovered from anesthesia uneventfully and was transferred to the post-anesthesia care unit for postoperative observation.

Further evaluation by a pediatric allergy and immunology department was recommended to investigate the suspected hypersensitivity reaction and to assist in planning future anesthetic procedures.

DISCUSSION

The clinical spectrum of perioperative hypersensitivity is broad. Skin findings such as erythema, urticaria, flushing, and edema may occur alone or together with respiratory or cardiovascular abnormalities.[1,2] In our patient, erythema and swelling were confined to the trunk and appeared approximately five minutes after sevoflurane was started. Oxygen saturation, respiration, and hemodynamic parameters remained normal. The presentation therefore differed from anaphylaxis, in which clinically significant involvement beyond isolated cutaneous manifestations is expected according to current diagnostic criteria.[1]

The sequence of exposures is central to interpretation of this case. The reaction began during inhalational induction, while peripheral intravenous access was being attempted. The close temporal relationship made sevoflurane a plausible trigger. However, chronology alone cannot prove drug allergy. Perioperative reactions should be assessed with attention to all relevant exposures, and specialist investigation is recommended when identification of the responsible agent may influence subsequent anesthetic care.[3] Because confirmatory allergy testing was not available in this patient, we describe the event as a suspected sevoflurane-associated hypersensitivity reaction rather than confirmed sevoflurane allergy.

Evidence for immediate hypersensitivity to sevoflurane remains scarce. Simonini et al.[4] described a six-year-old child who developed anaphylactic shock during anesthesia for adenotonsillectomy, with subsequent allergy investigation supporting sevoflurane as the causative agent. The comparison with our patient is clinically relevant: both reactions occurred in young children exposed to sevoflurane, but the severity was markedly different. Our patient had cutaneous involvement only, without desaturation, respiratory distress, hypotension, or other hemodynamic deterioration. This contrast illustrates that a suspected reaction associated with the same anesthetic exposure may present across different levels of clinical severity.

The absence of intravenous access at symptom onset was another important feature. Inhalational induction is often chosen in pediatric practice because awake cannulation is difficult, as in this patient. If a reaction progresses rapidly to bronchospasm or cardiovascular compromise, lack of immediate vascular access may complicate treatment. In the present case, sevoflurane was stopped, the circuit was changed, and 100% oxygen was administered while intravenous access was established. Crystalloid fluid, an antihistamine, a systemic corticosteroid, and inhaled salbutamol were subsequently given. The skin findings improved and no systemic progression occurred.

Epinephrine is the first-line pharmacological treatment for anaphylaxis.[1] It was not administered in this case because the patient remained hemodynamically stable, maintained normal oxygenation, and showed no respiratory compromise. The procedure was completed after clinical improvement, and recovery from anesthesia was uneventful.

From a practical perspective, this case draws attention to an uncommon event at a vulnerable stage of pediatric anesthesia. Even when inhalational induction is undertaken in an otherwise healthy child with no known allergy history, unexpected hypersensitivity may occur before intravenous access is secured. Readiness to discontinue a suspected trigger, support oxygenation and circulation, obtain vascular access rapidly, and escalate treatment according to clinical severity remains essential.

CONCLUSION

Hypersensitivity reactions associated with sevoflurane are extremely rare but should be considered when compatible clinical findings develop during inhalational induction.

In the present case, a six-year-old girl developed isolated cutaneous findings approximately five minutes after exposure to sevoflurane, without respiratory or cardiovascular involvement. Although the temporal association raised suspicion of a sevoflurane-associated hypersensitivity reaction, confirmatory allergy testing was not available and therefore sevoflurane could not be established as the definitive causative agent. Prompt recognition, discontinuation of the suspected agent, close monitoring, and appropriate supportive treatment were followed by clinical improvement. This case emphasizes the challenges of managing suspected hypersensitivity during pediatric inhalational induction before intravenous access has been established.

The temporal association raised suspicion of a sevoflurane-associated hypersensitivity reaction; however, in the absence of confirmatory allergy testing, sevoflurane cannot be established as the definitive causative agent. Prompt recognition, discontinuation of the suspected agent, close monitoring, and appropriate supportive treatment were followed by clinical improvement.

This case particularly emphasizes the challenges posed by hypersensitivity reactions occurring during pediatric inhalational induction before intravenous access has been established. Clinicians should remain prepared for rapid recognition and management of such reactions, even when volatile anesthetic agents are the only major anesthetic exposure at the time of onset.

ETHICAL DECLARATIONS

Informed Consent

Informed consent was obtained from the legal guardians of the pediatric patient described in this report. Where developmentally appropriate, assent was also sought from the child.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

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Author Contributions

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