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AIMS AND SCOPE

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Journal of Critical and Intensive Care (J Crit Intensive Care) is the scientific and official publication of the Society of Turkish Intensivists (STI) (www.tuyud.org.tr). The Journal is an international open access journal, published 3 times a year (April, August, December). All processing is conducted through the online submission system on the web site: www.jcritintensivecare.org. Manuscripts are accepted for publication through an independent unbiased and double-blinded peer review process. Only manuscripts written in English are accepted and only unpublished manuscripts that are not under review for publication elsewhere can be submitted. Journal of Critical and Intensive Care does not accept multiple submissions even though the previous one was published in a different language.

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The journal is an open access journal, published 3 times a year and all of its contents are freely available with no cost and there is no fee for submission. It accepts manuscripts written only in English and evaluates submissions through its online submission system on the web site www.jcritintensivecare.org. It publishes original clinical, basic and translational research articles, case reports and letters to the editor related to intensive/critical care medicine and acute medicine. Editorials and review articles are only accepted upon invitation of the editor.

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Journal of Critical and Intensive Care

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Journal of Critical and Intensive Care

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The Journal publishes the reviewer list every year in the last issue to express the appreciation for the reviewers.

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ORIGINAL INVESTIGATION

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Comparison of Fentanyl Versus Morphine-Ketamine-Lidocaine Infusion for Postoperative Pain Following Coronary Artery Bypass Grafting (CABG): A Randomized Clinical Trial

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Abstract

Aim: This study aimed to compare the effectiveness and safety of fentanyl infusion with a combination of morphine, ketamine, and lidocaine (multimodal analgesia) for postoperative pain management in patients undergoing coronary artery bypass grafting (CABG).

Study Design: This randomized clinical trial was conducted from 2024 to 2025 and included 74 patients undergoing elective CABG at the study hospital. Patients received either fentanyl (500 µg/100 mL) or a combination of morphine (20 mg), ketamine (20 mg), and lidocaine (200 mg) diluted to 100 mL, administered as an infusion at 4 mL/h for the first 24 postoperative hours. Pain was assessed using the Visual Analog Scale (VAS) at 1, 4, 8, 12, 16, 20, and 24 hours after surgery. Additional recorded parameters included hemodynamic variables, respiratory depression, and the need for rescue analgesia.

Results: Patients receiving fentanyl infusion demonstrated a statistically significant greater reduction in pain scores at 4 and 8 hours postoperatively compared to those receiving the multimodal regimen. However, at the remaining assessment times (1, 12, 16, 20, and 24 hours), no significant differences in pain intensity were observed. Over the full 24-hour period, both regimens provided comparable analgesia. Additionally, no significant differences were found between the groups regarding adverse effects or the need for rescue analgesia.

Conclusions: Fentanyl infusion demonstrated greater efficacy in early postoperative pain control compared to the multimodal regimen; however, this benefit was of short duration. Over the first 24 hours following surgery, both strategies showed comparable efficacy and safety; therefore, both may be considered viable options for post-CABG analgesia.

Keywords: Coronary artery bypass, fentanyl, ketamine, lidocaine, morphine, pain management.

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Introduction

Coronary artery bypass grafting (CABG) utilizes grafts from the saphenous vein and other vessels to reroute blood flow around obstructed coronary arteries, thereby improving blood flow to the heart.[1] For patients with severe myocardial ischemia, CABG significantly enhances both quality of life and survival rates.[2] Effective pain management in CABG patients is essential, as adequate pain control facilitates earlier mobilization, improves postoperative cardiac performance, and reduces the risk of postoperative complications.[3]

Pain serves as the body's warning and protective mechanism against potential harmful injury.[4] Continuous intravenous infusion of analgesia via pain pumps offers an innovative solution for improved pain management compared to other infusion techniques. This approach allows for more precise dosage control, provides optimal pain control, and minimizes the need for systemic opioids, thereby reducing associated risks and enhancing patient safety.[5] Opioids, particularly morphine, are commonly used for pain management during and after surgery, as well as for severe postoperative or cancer-related pain. Morphine carries a known risk of addiction and is therefore more tightly regulated than fentanyl. Fentanyl misuse, however, can result in fatal outcomes.[6] Unlike morphine, fentanyl is less likely to cause long-term dependence and is primarily used for potent pain relief.[7] This synthetic opioid is often administered alongside morphine for pain management in advanced cancer patients and during the perioperative period. Fentanyl is 50 to 100 times more potent than morphine and provides powerful pain relief.[8]

Comparative studies demonstrate some variability depending on clinical context. Some studies suggest that morphine may provide superior analgesia compared to fentanyl in the postoperative period.[9] Conversely, in opioid-dependent patients experiencing acute trauma or undergoing surgery, fentanyl produces more rapid refractory analgesia than morphine, while both drugs demonstrate comparable long-term efficacy. These findings highlight the importance of individualized pain management strategies.[10] The dissociative anesthetic ketamine has a broad range of clinical applications. In addition to its anesthetic properties, it provides analgesia and immobilization while preserving respiratory function.[11] Lidocaine, a local anesthetic and antiarrhythmic agent, blocks sodium channels in nerve cell membranes to inhibit nerve impulse transmission and provide analgesia, thereby facilitating pain relief.[12]

The development of pain pumps has significantly enhanced pain management strategies. This study aimed to assess the effectiveness of fentanyl infusion compared to a postoperative analgesic regimen consisting of morphine, ketamine, and lidocaine for pain control in patients undergoing CABG. Pain intensity during the first 24 hours after surgery was evaluated using the Visual Analog Scale (VAS). Cardiovascular and respiratory side effects, the need for rescue analgesia, and overall pain control were assessed to determine the degree of pain control achieved.

Materials and Methods

Study Design and Participants

This randomized clinical trial included patients eligible for CABG who were referred to the hospital between 2024 and 2025. The primary endpoint was the comparison of mean pain intensity scores, measured by the VAS, between the two groups at 1, 4, 8, 12, 16, 20, and 24 hours after initiation of the intervention. Secondary endpoints included comparisons of mean arterial pressure (MAP), incidence of respiratory depression, and the need for additional analgesic administration between the two groups. Additional secondary outcomes were duration of mechanical ventilation (defined as the time from intensive care unit [ICU] admission to successful extubation), ICU length of stay, and total hospital length of stay.

The sample size was calculated using the following formula:

$$n = (2 \times (z\_(1-\alpha/2) + z\_(1-\beta))^2 \delta^2) \; / \; d^2$$

Based on data from a previous study, and assuming a test power of 80% and a confidence level of 95%, the calculated sample size was 70 patients (35 per group).[12] To account for potential attrition, a 10% increase was applied, resulting in 37 patients in each group.

Patients were randomly allocated to one of the two study groups using a computer-generated randomization sequence. Allocation concealment was ensured using sealed, opaque envelopes, which were opened only at the time of intervention. The attending anesthesiologists and nursing staff responsible for managing the pumps were not blinded to group assignments. However, the patients and the anesthesiology resident responsible for collect-

ing postoperative data (VAS scores and hemodynamic parameters) were blinded to the group assignments.

Age, gender, and body mass index were collected as part of the demographic data through structured interviews with the patients. A checklist was used for data collection and documentation of clinical parameters, including the cardiac pump time and the intubation grade. Blood pressure measurements, pain intensity assessed using the Visual Analog Scale, the presence or absence of pain, timing and loading doses of administered analgesics during the pre-study period and at 1, 4, 8, 12, 16, 20, and 24 hours post-intervention were recorded for both groups. The occurrence of postoperative respiratory depression was also documented.

Inclusion and Exclusion Criteria

Patients aged 30 to 80 years who were undergoing elective CABG surgery and were classified as anesthesia class II and III were included. Eligible patients had an ejection fraction of ≥40% and had not received analgesics within 6 hours prior to surgery. Patients with a history of kidney, liver, gastrointestinal, or pulmonary failure; diabetes mellitus; neurological disorders associated with pain insensitivity; or alcohol or drug dependence were excluded. All participants provided written informed consent prior to enrollment. Exclusion criteria included patients who became critically ill after surgery and required additional medical treatment or ICU admission; those with excessive postoperative bleeding requiring reoperation; patients who developed progressive heart failure requiring high-dose inotropic support; patients undergoing emergency surgery; those undergoing concomitant valve surgery with CABG; patients with allergies to the study drugs; patients who experienced seizures or hemodynamic instability or required a balloon pump support after drugs administration; and patients who did not provide consent.

Research Method

After obtaining approval from the Hormozgan University of Medical Sciences Research Ethics Committee (Approval Number: IR.HUMS.REC.1402.393, Date: 24.01.2024), and registering the study with the Iranian Clinical Trial Registration Center (IRCT20231227060539N1), the research was conducted in accordance with the Declaration of Helsinki. The study methodology was explained to eligible patients, and permission for participation was obtained. Clinical records of patients awaiting CABG surgery were accessed through the Clinical Information System. Patients selected for sampling met the study's inclusion criteria. The study methodology was explained to them, and written informed consent was obtained. Relevant demographic variables, including age, gender, and body mass index, were collected through interviews. Patients underwent anesthesia assessment one day prior to surgery.

Prior to surgery, angiotensin-converting enzyme inhibitors (ACEI) therapy was temporarily discontinued. Upon arrival in the operating room, patients were positioned on the operating table, and routine monitoring was initiated. This included application of a noninvasive blood pressure (NIBP) cuff, cardiopulmonary monitoring leads, and pulse oximetry. Baseline hemodynamic parameters—systolic blood pressure, diastolic blood pressures, and mean arterial pressure—were recorded. Subsequently, the left (non-dominant) radial artery was infiltrated with 2% lidocaine, after which the pulse was augmented to facilitate insertion of an angio-cannula for blood pressure monitoring (size 20). The angio-cannula was connected to a blood pressure monitor to obtain and record the required parameters. Subsequently, the patient underwent induction of general anesthesia with etomidate (0.2 mg/kg), cisatracurium (0.2 mg/kg), and fentanyl (10 μg/kg), after which the surgical procedure was commenced. Fixed drug doses were used in this study to enable a more accurate comparison of the efficacy and safety of the drug regimens by eliminating confounding variables related to dose adjustment. The selected doses were determined based on standard clinical protocols and previous studies.

Each patient received equal volumes of serum and the same type of fluid therapy during surgery. In addition, identical types and dosages of propofol, atracurium, and sufentanil infusions were administered for maintenance of anesthesia. Intraoperative blood loss was assessed by the surgical team and anesthesiologist based on the volume in suction canisters and the weight of used surgical swabs. All patients received standardized crystalloid fluid therapy according to institutional protocols to maintain hemodynamic stability, with the aim of administering a comparable volume per kilogram of body weight.

After surgery, patients were transferred to the ICU for close monitoring and were subsequently categorized into two groups: the fentanyl pain pump group (500 µg/10 mL, Caspian Tamin Co., Iran) and the combination group (morphine 10 mg/1 mL ampule, Daroo Pakhsh Co., Iran;

ketamine 500 mg/10 mL ampoule, Rotexmed Co., Germany; and lidocaine 2%, 100 mg/5 mL, Caspian Tamin Co., Iran). In the first group, the pain pump was set up for continuous intravenous (IV) infusion of fentanyl (500 micrograms) diluted in 100 cc of distilled water and administered at a preset rate of 4 cc/h. In the second (combination) group, ketamine (20 mg), lidocaine (200 mg), and morphine (20 mg) were diluted in 100 cc of distilled water and administered via a pain pump. The selected doses were based on previous studies investigating similar postoperative pain management approaches.[13,14] Although establishing an exact clinically relevant equianalgesic comparison between fentanyl monotherapy and a multimodal combination regimen is challenging, the doses chosen for each approach were consistent with those reported to provide adequate clinical pain control.

Blood pressure values and pain intensity scores based on the VAS criteria were recorded at 1, 4, 8, 12, 16, 20, and 24 hours after the intervention by the anesthesia resident. If the VAS score was greater than 3, the patient received 2.5 mg of intravenous methadone as rescue analgesia. Methadone was selected due to its long half-life, proven efficacy in the postoperative period, and availability in the hospital formulary. The collected data were statistically analyzed and compared between the two groups. A CONSORT (Consolidated Standards of Reporting Trials) flow diagram detailing patient enrollment, allocation, follow-up, and analysis is presented in Figure 1.

Statistical Analysis

Statistical analysis and data processing were performed using SPSS version 27.0 (IBM Corporation, Armonk, New York, USA). Descriptive statistics, including mean, variance, and standard deviation, were calculated. Data normality was assessed using the Kolmogorov-Smirnov test. Quantitative data are presented as mean ± standard deviation, and qualitative data as frequency and percentage. Depending on data distribution, comparisons between groups were performed using the independent t-test or the Mann-Whitney test. A p-value of less than 0.05 was considered statistically significant.

Results

Seventy-four patients were included in the study, with 37 patients in each group (fentanyl pump vs. morphine, ketamine, and lidocaine combination). No significant differences were observed between the groups in demographic and baseline clinical variables, including age (p=0.677), sex (p=0.814), body mass index, and cardiac pump duration (p=0.098) (Table 1).

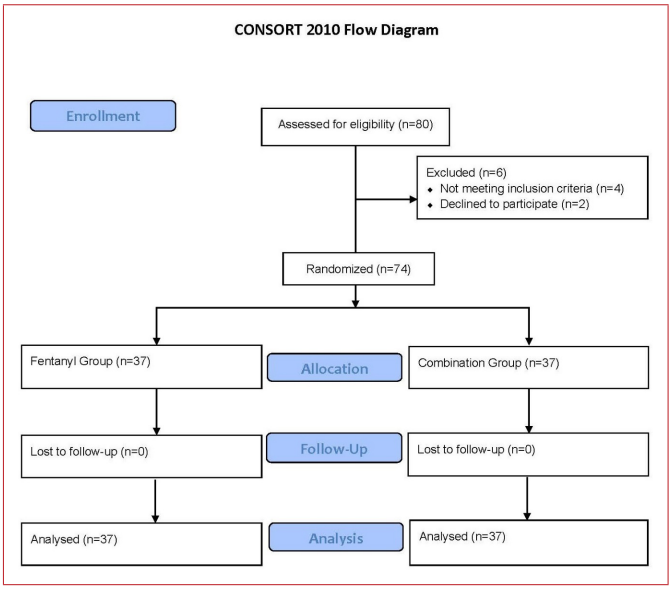

Figure 1. CONSORT flow diagram of patient enrollment, randomization, allocation, and analysis.

Caption: Study flow diagram according to the CONSORT guidelines. Both groups were followed for 24 hours after coronary artery bypass graft (CABG) surgery. Pain intensity and hemodynamic parameters were recorded at intensive care unit (ICU) admission and at 1, 4, 8, 12, 16, 20, and 24 hours post-intervention.

Primary Endpoint: Pain Intensity

No differences in pain intensity, measured using the Visual Analog Scale were observed between the fentanyl and combination groups at any time point: 1 hour (p=0.662), 4 hours (p=0.256), 8 hours (p=0.070), 12 hours (p=0.767), 16 hours (p=0.947), 20 hours (p=0.672), and 24 hours (p=0.498) (Table 2). However, within-group analysis over time showed that the fentanyl group demonstrated a significant reduction in VAS pain scores at 4 hours (p=0.015) and 8 hours (p=0.032) post-intervention compared with 1 hour post-intervention (Table 3). No statistically significant between-group differences were observed at the remaining time points (p>0.05) (Table 4).

Secondary Endpoints

Across the entire assessment period, no statistically significant differences in mean arterial pressure were observed between groups at any measurement time point: pre-intervention (p=0.186), 1 hour (p=0.513), 4 hours (p=0.777), 8 hours (p=0.834), 12 hours (p=0.402), 16 hours (p=0.228), 20 hours (p=0.314), and 24 hours post-intervention (p=0.777) (Table 5).

Table 1. Baseline demographic and clinical characteristics of patients in the two groups

Parameter	Group				p
	Fentanyl group		Combination group		
	Frequency	Percent	Frequency	Percent	
Sex					
Female	15	40.5	16	43.2	0.814*
Male	22	59.5	21	56.8	
Intubation grade					
1	6	16.2	7	18.9	
2	28	75.7	29	78.4	0.699**
3	3	8.1	1	2.7	
Parameter	**Mean**	**SD**	**Mean**	**SD**	**p**
Age (years)	61.02	11.53	60.01	9.49	0.677***
BMI (kg/m²)	23.84	3.50	24.30	3.48	0.573***
Pumping duration (min)	118.59	23.18	127.48	22.41	0.098***

Abbreviations: BMI: Body mass index; CPB: Cardiopulmonary bypass. Data are presented as mean±standard deviation (SD) or n (%). P>0.05 for all comparisons. *Chi-square test; **Fisher's exact test; ***Independent samples t-test

Table 2. Comparison of Visual Analog Scale (VAS) scores between groups

Time Point	Fentanyl group (Mean±SD)	Combination group (Mean±SD)	Mean difference	p
1 hour	5.08±1.73	4.86±2.32	0.21	0.662
4 hours	4.67±1.71	5.18±2.18	0.51	0.256
8 hours	4.64±1.75	5.43±1.90	0.78	0.070
12 hours	4.67±1.65	4.78±1.47	0.10	0.767
16 hours	4.62±1.75	4.64±1.71	0.02	0.947
20 hours	4.45±1.65	4.62±1.62	0.16	0.672
24 hours	4.48±1.64	4.24±1.42	0.24	0.498

Statistical analysis: Independent samples t-test for continuous variables; Chi-square test for categorical variables. Abbreviations: SD: Standard deviation; VAS: Visual Analog Scale; MAP: Mean arterial pressure. p<0.05 was considered statistically significant.

Changes in MAP from baseline were also analyzed at each time point and showed no significant intergroup differences at 1 hour (p=0.134), 4 hours (p=0.187), 8 hours (p=0.213), 12 hours (p=0.511), 16 hours (p=0.609), 20 hours (p=0.610), and 24 hours (p=0.192) post-intervention (Fig. 2). Similarly, when comparing MAP changes relative to the 1-hour post-intervention time point, no significant differences were observed at 4 hours (p=0.723), 8 hours (p=0.660), 12 hours (p=0.124), 16 hours (p=0.086), 20 hours (p=0.163), and 24 hours (p=0.768) (Fig. 2). Further analyses of MAP changes using other reference time points (4, 8, 12, 16, and 20 hours) also revealed no significant intergroup differences (all p>0.05) (Table 5).

The incidence of respiratory depression was low and comparable between groups (p=0.691). Among affected patients, 10.8% (4/37) were in the fentanyl group and 8.1% (3/37) were in the combination group.

The requirement for rescue opioids (methadone) was similar between groups (p=0.639), with 59.5% (22/37) of patients in the fentanyl group and 54.1% (20/37) in the combination group requiring additional analgesia.

Analysis of postoperative recovery parameters revealed no significant between-group differences. The mean duration of mechanical ventilation was 8.2±2.1 hours in the fentanyl group and 7.9±1.8 hours in the combination

Table 3. Comparison of the mean change in Visual Analog Scale (VAS) score from baseline (one hour post-intervention) at subsequent time points between groups

Time point	Fentanyl group (Mean±SD)	Combination group (Mean±SD)	Mean difference	*p*
1 hour				
4 hours	-0.40±1.30	0.32±1.20	0.72	0.015
8 hours	-0.43±1.64	0.56±2.24	1.00	0.032
12 hours	-0.40±1.57	-0.08±2.26	0.32	0.477
16 hours	-0.45±2.00	-0.21±2.43	0.24	0.641
20 hours	-0.62±2.12	-0.24±2.80	0.37	0.515
24 hours	-0.59±1.70	-0.62±2.44	0.02	0.956
4 hours				
8 hours	-0.02±1.48	0.24±1.70	0.27	0.469
12 hours	0.01±1.88	-0.40±2.00	0.40	0.373
16 hours	-0.05±2.18	-0.54±2.20	0.48	0.344
20 hours	-0.21±1.94	-0.56±2.40	0.35	0.492
24 hours	-0.18±1.98	-0.94±2.14	0.75	0.120

Statistical analysis: Independent samples t-test for continuous variables; Chi-square test for categorical variables. Abbreviations: SD: Standard deviation; VAS: Visual Analog Scale; MAP: Mean arterial pressure. $p<0.05$ was considered statistically significant.

Table 4. Comparison of the mean change in Visual Analog Scale (VAS) score from the 4-hour post-intervention time point at subsequent time points between groups

Time point	Fentanyl group (Mean±SD)	Combination group (Mean±SD)	Mean difference	*p*
8 hours				
12 hours	0.02±1.70	-0.64±1.60	0.67	0.083
16 hours	-0.02±2.24	-0.78±1.95	0.75	0.127
20 hours	-0.18±1.98	-0.81±1.88	0.62	0.171
24 hours	-0.16±1.87	-1.18±2.07	1.02	0.059
12 hours				
16 hours	-0.05±1.97	-0.13±1.00	0.08	0.824
20 hours	-0.21±1.43	-0.16±1.25	0.05	0.864
24 hours	-0.18±1.44	-0.54±1.53	0.35	0.315
16 hours				
20 hours	-0.16±1.93	-0.02±1.62	0.13	0.764
24 hours	-0.13±1.73	-0.40±1.95	0.27	0.531
20 hours				
24 hours	0.02±1.36	-0.37±1.36	0.40	0.205

Statistical analysis: Independent samples t-test for continuous variables; Chi-square test for categorical variables. Abbreviations: SD: Standard deviation; VAS: Visual Analog Scale; MAP: Mean arterial pressure. $p<0.05$ was considered statistically significant.

group (p=0.513). The length of ICU stay was 5.1±1.3 days versus 4.9±1.2 days, respectively (p=0.494). The total hospital stay was 7.3±1.5 days versus 7.1±1.4 days (p=0.556). Since there was little difference in the time required for these parameters between the two groups, it may be concluded that both analgesic techniques provide similar pain control without adversely affecting postoperative recovery.

Table 5. Mean arterial pressure (MAP) values at different time points

Time point	Fentanyl group (Mean±SD)	Combination group (Mean±SD)	*p*
Baseline (ICU)	100.75±12.23	105.40±15.66	0.186
1 hour	87.48±10.61	85.92±9.77	0.513
4 hours	88.83±8.97	88.10±12.79	0.777
8 hours	87.36±9.55	86.88±9.97	0.834
12 hours	86.78±10.00	88.91±11.72	0.402
16 hours	83.08±8.08	85.81±10.99	0.228
20 hours	84.86±10.14	87.38±11.20	0.314
24 hours	86.32±10.32	85.60±11.42	0.777

Statistical analysis: Independent samples t-test for continuous variables; Chi-square test for categorical variables. Abbreviations: SD: Standard deviation; VAS: Visual Analog Scale; MAP: Mean arterial pressure. $p<0.05$ was considered statistically significant.

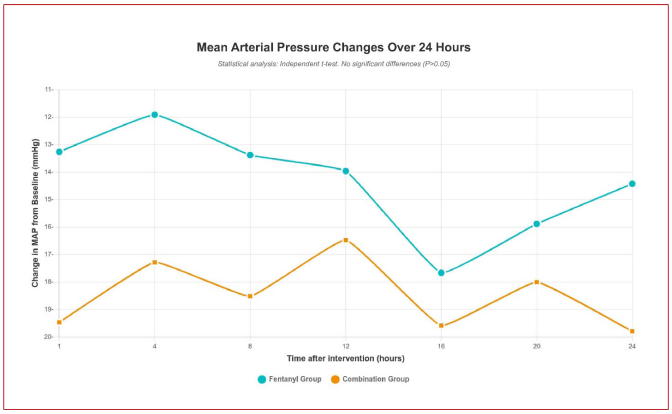

Figure 2. Mean arterial pressure changes: fentanyl vs. combination therapy over 24 hours.

Caption: Comparison of mean arterial pressure (MAP) changes from baseline between the fentanyl (cyan) and combination therapy (orange) groups over the 24-hour post-intervention period. Both groups demonstrated sustained reductions in MAP, with no statistically significant differences observed between groups (p>0.05, independent samples t-test).

Discussion

The results of this study demonstrated that during the early postoperative period (4 and 8 hours), fentanyl produced significantly greater pain reduction compared to the multimodal regimen (combination of morphine, ketamine, and lidocaine) ($p<0.05$). However, this superiority was not sustained at later time points (12, 16, 20, and 24 hours), where no statistically significant differences were observed between the two groups. These findings suggest that although fentanyl provides rapid pain relief, concerns remain regarding the duration of its analgesic effect. Incorporating a multimodal pain relief strategy may reduce overall pain burden. This approach may require less fentanyl during the recovery period while maintaining adequate long-term pain control. This is particularly relevant in the clinical setting when considering postoperative pain management strategies following CABG surgery.

The faster onset of fentanyl can be attributed to its high potency (50-100 times that of morphine), rapid onset of action (1-2 minutes), and efficient penetration of the blood-brain barrier. In contrast, the multimodal regimen, which combines agents with different mechanisms of action (morphine with a slower onset, ketamine as an N-methyl-D-aspartate [NMDA] antagonist, and lidocaine as a local anesthetic), requires more time for synergistic effects to develop, which may become apparent in the later postoperative hours.[7]

Based on the results of the present study, although pain reduction in the early hours after injection was significantly greater in patients receiving the fentanyl pump compared to those receiving the combination of morphine, lidocaine, and ketamine, no statistically significant difference in pain intensity was observed between the groups over time. Additionally, the need for supplemental analgesic injections did not differ significantly between the two groups. This study is the first to compare the effectiveness of fentanyl with the simultaneous combination of morphine, lidocaine, and ketamine for pain relief. Previous studies have reported mixed findings regarding the effectiveness of different analgesics in the early postoperative period. One study reported that lidocaine provided better pain relief than morphine and ketamine at 20 minutes postoperatively; however, after 40 minutes, the differences were no longer statistically

significant. These findings are consistent with the present study, suggesting that although some drugs may provide more pronounced initial pain relief, this advantage may diminish over time.[15] In a study of patients undergoing CABG surgery, the three opioids (morphine, fentanyl, and remifentanil) were compared for postoperative pain control, and no statistically significant difference in VAS pain scores was observed among the groups.[16] Similarly, another study comparing morphine with non-opioids after cardiac surgery found no difference in pain scores between the two groups during the first 48 postoperative hours.[17] However, a separate study evaluating an intravenous remifentanil pain pump versus a morphine pump after coronary artery surgery demonstrated that pain intensity scores at 12 and 24 hours postoperatively were significantly lower in the remifentanil group than in the morphine group.[18] A systematic review comparing different opioid regimens for postoperative pain concluded that although short-term differences in analgesic onset may exist, most opioid regimens provide comparable pain relief over 24 hours, supporting our findings of transient early differences.[19] In our study, although pain intensity was significantly lower during the early postoperative hours (4 and 8 hours after surgery) in patients receiving fentanyl, no significant difference was observed between the two groups at 24 hours postoperatively. Similarly, there was no significant difference between the groups in the need for additional analgesics. A 2019 study comparing different analgesic modalities in cardiac surgery also reported no significant differences in overall pain scores or opioid requirements among various analgesic protocols, which aligns with our long-term findings.[20] However, one comparative study evaluating analgesia after CABG surgery with fentanyl and morphine reported that VAS scores and analgesic consumption were lower in patients treated with morphine.[21] Overall, the finding of the present study that there was no significant difference in the need for additional analgesics between the two groups is consistent with other studies showing that different analgesic combinations do not result in significantly different requirements for supplementary pain management over time.[22,23] The results of this study contribute to the ongoing debate regarding optimal pain management strategies in postoperative CABG care. The initial efficacy of fentanyl compared with the combination of morphine, lidocaine, and ketamine highlights its potential usefulness in acute settings where rapid pain control is essential. However, the diminishing differences over time emphasize that, although immediate pain relief is important, sustained pain management strategies are equally critical to ensure patient comfort and satisfaction. Furthermore, the findings suggest that relying solely on potent opioids such as fentanyl may not be sufficient for comprehensive postoperative pain management. Combining multimodal analgesia using agents such as lidocaine and ketamine alongside opioids such as morphine may be beneficial in reducing overall opioid consumption while effectively managing pain over longer periods.

The results also showed no statistically significant difference in adverse effects between patients receiving fentanyl pump analgesia and those receiving a combination of morphine, lidocaine, and ketamine. Specifically, no significant differences were observed in hemodynamic parameters, including blood pressure or respiratory depression, between the two groups. Despite the sympathomimetic properties of ketamine, no significant difference in MAP was observed between groups ($p>0.05$). This stability may be attributed to the low dose of ketamine (20 mg/100 cc), the slow infusion rate, and the moderating effects of morphine and lidocaine. These findings suggest that ketamine can be administered in a controlled manner without causing hemodynamic instability.[17] This finding is consistent with several previous studies investigating the efficacy and safety profiles of these analgesics in the postoperative setting. One study comparing the clinical efficacy of fentanyl, esmolol, and lidocaine in preventing hemodynamic responses to intubation demonstrated that mean arterial blood pressure after intubation and extubation was lower in the intervention groups than in the control group. Additionally, systolic and diastolic blood pressure at the first, third, and fifth minutes after intubation and extubation were significantly lower in the esmolol group compared to the fentanyl and lidocaine groups, while no hemodynamic differences were observed among the three groups at other time points.[24] Another study comparing the effects of lidocaine and fentanyl on hemodynamic parameters reported that lidocaine was associated with a greater reduction in systolic blood pressure and an increased need for ephedrine.[25] Furthermore, a recent study (2023) comparing different analgesic combinations in cardiac surgery found no significant differences in respiratory depression or hemodynamic instability among various multimodal regimens, further supporting the safety findings of the present study.[26] A study investigating and comparing fentanyl alone with fentanyl plus lido-

caine for reducing hemodynamic responses to tracheal intubation in patients under general anesthesia reported that systolic and diastolic blood pressures before induction, 3 minutes before intubation, and at 1, 3, and 5 minutes after intubation did not differ significantly between the two groups.[27] The absence of a significant difference in blood pressure between the two groups suggests that both treatment strategies involving the use of a fentanyl pump or the combination of morphine, lidocaine, and ketamine are relatively safe with respect to hemodynamic stability. This finding is particularly important given concerns regarding opioid-induced respiratory depression. Although some studies have shown that combining ketamine with opioids can improve pain control while potentially reducing opioid requirements and related adverse effects, the present study did not demonstrate such advantages. The lack of significant differences may be attributed to factors such as drug dosage, individual patient responses, and the specific surgical setting. Consequently, the present findings support the conclusion that both fentanyl and drug combinations including morphine, lidocaine, and ketamine can be effective for postoperative pain management without significant differences in hemodynamic adverse effects. Cardiopulmonary bypass (CPB) time was longer in the multimodal group (127 vs. 118 minutes, p=0.098). Although this near-significant difference may have influenced the inflammatory response, it did not have a clinically significant impact on pain outcomes. Future studies should further evaluate CPB duration as a potential confounding variable.[28] Additionally, future research should focus on dose optimization and patient-specific factors to identify the most effective pain management protocols.[29]

Limitations

Other studies have reported limitations similar to those of the present research. For example, the study population was drawn from a single center, which may affect how the findings are applied. The use of methadone as rescue medication in both groups may have influenced the results and contributed to the reduction of observed differences between the groups at later time points. One of the main threats to the external validity of the findings is the single-center design and relatively small sample size. Furthermore, the 24-hour follow-up period does not capture the long-term efficacy and safety of the analgesic regimens. Although the study was designed to be double-blind, subjective pain assessments remain susceptible to individual bias. The absence of a placebo or non-analgesic control group, along with the potential influence of psychosocial factors, may also have affected the results. Finally, we were unable to systematically assess the full spectrum of postoperative complications due to incomplete documentation in the available medical records.

Conclusion

The results of this study demonstrate that fentanyl provides better pain relief during the early postoperative hours compared to the multimodal regimen (morphine, ketamine, and lidocaine), without increasing adverse effects. However, over the 24-hour postoperative period, no significant differences were observed between the two groups, particularly between 12 and 24 hours after surgery. These findings support the use of fentanyl as an effective option for immediate postoperative pain control following CABG surgery.

Ethics Committee Approval: Ethics committee approval was obtained from Hormozgan University of Medical Sciences Research Ethics Committee (Approval Number: IR.HUMS.REC.1402.393, Date: 24.01.2024).

Informed Consent: Written informed consent was obtained from the participants.

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Prognostic Value of APACHE II, SAPS II, and SOFA Scores in Critically Ill Hematologic Patients: A Single-Center, Retrospective Analysis

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Abstract

Aim: Critically ill hematologic patients (CIHPs) represent a distinct population in the intensive care unit (ICU), characterized by complex pathophysiology and high mortality rates. Prognostic assessment in this group remains challenging. This study aimed to evaluate the utility of acute illness severity and organ dysfunction scores in predicting ICU outcomes in CIHPs.

Study Design: This retrospective, single-center study was conducted in a dedicated hematology ICU. The prognostic performance of commonly used acute illness severity and organ dysfunction scores (APACHE II, SAPS II, and SOFA) was evaluated in CIHPs. ICU mortality was assessed as the primary outcome. Additionally, early trajectories of these scores—particularly changes by ICU day 3—were analyzed for their association with prognosis.

Results: A total of 107 patients were included. The median age of the patients was 62 (range: 53–70), and 69 (64.5%) were male. The ICU mortality rate was 40.2%. The most frequent underlying diagnoses were multiple myeloma (31.8%) and non-Hodgkin lymphoma (20.6%). Respiratory failure (68.2%) and sepsis (54.2%) were the leading reasons for ICU admission. Non-survivors had significantly higher APACHE II, SAPS II, and SOFA scores on both day 1 and day 3. Furthermore, non-survivors demonstrated a significant increase in all three scores over the first three ICU days. Among these parameters, the day 3 SOFA score was the strongest independent predictor of ICU mortality (OR 2.042, 95% CI 1.407–2.962; p = 0.001), suggesting that early organ dysfunction and its progression during the ICU stay are critical determinants of ICU mortality.

Conclusions: Acute illness severity and organ dysfunction scores are valuable tools for predicting ICU outcomes in CIHPs. In particular, early SOFA score trajectories—especially the day 3 SOFA score—provide superior prognostic information and may support clinical decision-making in this high-risk population.

Keywords: APACHE II; Critically ill hematologic patients; Intensive care unit mortality; SAPS II; SOFA.

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Introduction

The prognosis of patients admitted to intensive care units (ICUs) is primarily determined by the severity of acute illness and the degree of organ dysfunction. To quantify these parameters and facilitate prognostic assessment, several scoring systems have been developed and widely implemented in critical care practice. Acute illness severity scores—such as the Acute Physiology and Chronic Health Evaluation (APACHE II, III, and IV), the Simplified Acute Physiology Score (SAPS II and SAPS 3), and the Mortality Probability Model (MPM II and III)—are typically calculated upon ICU admission to estimate baseline mortality risk. In contrast, organ dysfunction scores, including the Sequential Organ Failure Assessment (SOFA), Multiple Organ Dysfunction Score (MODS), and Logistic Organ Dysfunction System (LODS), are designed for serial assessment, allowing for the evaluation of the progression of organ failure during the ICU stay.[1]

Several studies have investigated the performance of general ICU severity and organ dysfunction scores in patients with hematologic diseases, particularly hematologic malignancies, yielding heterogeneous results. While some studies have demonstrated acceptable discrimination of APACHE II, SAPS II, and SOFA scores in this population, others have reported reduced predictive accuracy compared to mixed ICU cohorts. Importantly, most prognostic models were developed and validated in general ICU populations, where hematologic patients are often underrepresented, and disease-specific factors—such as immunosuppression, treatment-related toxicity, and prolonged organ dysfunction—are not adequately captured. Consequently, the applicability and reliability of these models in critically ill hematologic patients remain uncertain.[2-5]

Moreover, most available data originate from general ICUs in high-income countries, with limited evidence from dedicated hematology ICUs or from low- and middle-income healthcare settings.[3,4] Dedicated hematology ICUs may differ substantially from general ICUs in terms of admission criteria, patient case-mix, timing of ICU referral, and intensity of hematologic support, all of which may influence the performance of prognostic scoring systems. The scarcity of data from such specialized units represents a relevant gap in the literature.

In recent years, increasing attention has been directed toward the prognostic value of dynamic changes in organ dysfunction scores. In particular, trends in SOFA scores during the first days of ICU admission have been shown to outperform single admission values in predicting mortality in heterogeneous ICU populations. However, data specifically evaluating early SOFA trajectories in critically ill hematologic patients remain limited.[3,5] Given the high prevalence of evolving multiorgan failure and the complexity of treatment decisions in this population, understanding whether early changes in SOFA scores provide meaningful prognostic information is of considerable clinical importance.

Therefore, in the present study, we aimed to address these gaps by evaluating prognostic factors associated with ICU mortality in critically ill hematologic patients admitted to a dedicated hematology ICU at a university hospital. Specifically, we assessed the predictive performance of APACHE II, SAPS II, and SOFA scores and investigated the prognostic significance of early changes in these scores between ICU day 1 and day 3.

Materials and Methods

Study Design and Setting

This retrospective study was conducted in the hematology ICU of Gazi Hospital, a tertiary care referral center in Ankara. This unit, exclusively dedicated to patients with hematologic diseases requiring intensive care support, has a capacity of 4 beds and admits approximately 100-150 patients annually.

Patient Population

Adult patients (≥18 years) with hematologic diseases admitted to the hematology ICU between January 1, 2018, and December 31, 2019, were eligible for inclusion. Patients with an ICU stay of less than 24 hours or with missing data were excluded. For patients with multiple ICU admissions, only the data from the first admission were analyzed.

Data Collection

Demographic characteristics, underlying hematologic diagnoses, disease status (newly diagnosed, remission, relapsed or progressive disease, or terminal stage), history of hematopoietic stem cell transplantation (HSCT), and recent chemotherapy were recorded. Reasons for ICU admission, source of admission, laboratory variables required to calculate severity scores, and clinical outcomes were extracted from electronic medical records. APACHE II, SAPS II, and SOFA scores were calculated at 24 and 72 hours after ICU admission, and changes in scores over time were analyzed.

Ethical Consideration

This study was approved by the Gazi University Faculty of Medicine Clinical Research Ethics Committee (Approval Number: 545, Date: 14.06.2021).

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as medians and interquartile ranges (1st-3rd quartiles), and categorical variables as counts and percentages. Patients were categorized as survivors or non-survivors based on ICU outcome. Continuous variables were compared using the Mann–Whitney U test, and categorical variables using the chi-square or Fisher's exact test, as appropriate. Variables significant in univariate analyses were entered into multivariate logistic regression models to identify independent predictors of ICU mortality. Receiver operating characteristic (ROC) curve analysis was used to evaluate the prognostic performance of scoring systems, with area under the curve (AUC), optimal cut-off values, sensitivity, and specificity reported. A p-value <0.05 was considered statistically significant.

Results

Study Population

During the study period, 187 patients were admitted to the hematology ICU. After excluding repeated admissions (n=48), ICU stays shorter than 24 hours (n=28), and cases with missing data (n=4), a total of 107 patients were included in the final analysis. The ICU mortality rate was 40.2% (n=43).

Baseline demographic characteristics, hematologic diagnoses, comorbidities, and admission features are summarized in Table 1. Survivors and non-survivors did not differ significantly in terms of age, sex, or comorbidity burden. However, non-survivors had a significantly longer interval between hospital admission and ICU transfer (p=0.001). Additionally, non-survivors were more frequently admitted from the hematology ward (p=0.001), had a higher prevalence of allogeneic hematopoietic stem cell transplantation (HSCT) (p=0.024), and were more commonly admitted due to respiratory failure (p=0.016) and neurological deterioration (p=0.013).

Acute Illness Severity and Organ Dysfunction Scores at Day 1 and Day 3 in the ICU

APACHE II, SAPS II, and SOFA scores calculated at 24 and 72 hours after ICU admission are presented in Table 2. At both time points, non-survivors had significantly higher scores across all three scoring systems compared to survivors (all p<0.001).

Dynamic Changes in Acute Illness Severity and Organ Dysfunction Scores

Dynamic changes in severity scores between ICU day 1 and day 3 were analyzed in 75 patients who survived beyond 72 hours. An increase in APACHE II, SAPS II, or SOFA scores during this period was significantly associated with ICU mortality. Survivors demonstrated a significant reduction in all three scores, whereas non-survivors exhibited persistently elevated or increasing scores. Median changes in APACHE II, SAPS II, and SOFA scores differed significantly between the two groups (Table 2), indicating that early score trajectories provided additional prognostic information beyond baseline values.

Prognostic Performance of Acute Illness Severity and Organ Dysfunction Scores

Receiver operating characteristic (ROC) curve analyses demonstrated good discriminatory performance of APACHE II, SAPS II, and SOFA scores at both ICU day 1 and day 3 (Figs. 1–3). For all scoring systems, day 3 values showed higher predictive accuracy than admission values. Cut-off values, sensitivities, specificities, and area under the curve (AUC) are summarized in Table 3. Among all evaluated parameters, the SOFA score at day 3 demonstrated the highest prognostic accuracy for ICU mortality.

Dynamic changes in severity scores between day 1 and day 3 were also prognostically relevant. Failure to de-

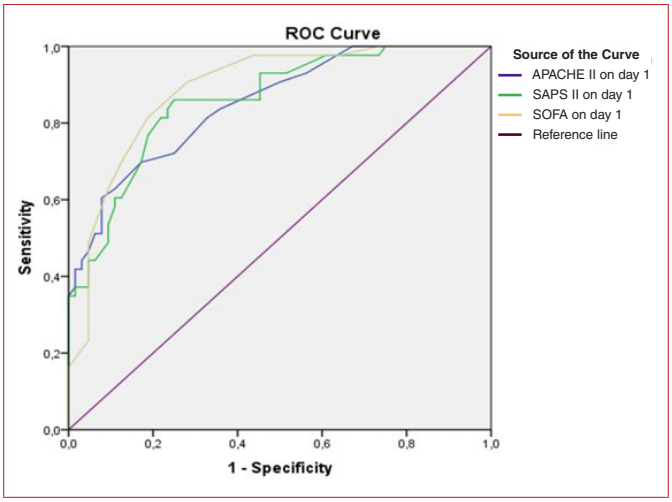

Figure 1. ROC curves for APACHE II, SAPS II, and SOFA scores on Day 1.

Table 1. Baseline characteristics of critically Ill hematologic patients

Characteristics	All patients (n=107)	Survivors (n=64)	Non-Survivors (n=43)	p
Age (years)*	62 (53-70)	62 (55-69.75)	61 (42-70)	0.442
Gender, male, n (%)	69 (64.5)	42 (65.6)	27 (62.8)	0.764
Days from hospital to ICU admission*	5 (0-18)	1 (0-15)	14 (4-28)	0.001
ICU length of stay (days)*	4 (2-7)	4 (2.25-6)	4 (2-9)	0.895
Hospital length of stay (days)*	21 (14-42)	21 (14-41.5)	23 (12-42)	0.824
Comorbidities, n (%)				
Hypertension	35 (32.7)	18 (28.1)	17 (39.5)	0.217
Diabetes mellitus	22 (20.6)	15 (23.4)	7 (16.3)	0.369
Cardiovascular disease	18 (16.8)	11 (17.2)	7 (16.3)	0.902
Chronic Kidney disease	18 (16.8)	11 (17.2)	7 (16.3)	0.902
COPD/Asthma	11 (10.3)	6 (9.4)	5 (11.6)	0.753
Solid cancer	9 (8.4)	4 (6.3)	5 (11.6)	0.480
Hematologic disease, n (%)				
Multiple myeloma	34 (31.8)	27 (42.2)	7 (16.3)	0.005
Non-Hodgkin lymphoma	22 (20.6)	10 (15.6)	12 (27.9)	0.123
Acute myeloid leukemia	20 (18.7)	9 (14.1)	11 (25.6)	0.134
Acute lymphoblastic leukemia	9 (8.4)	4 (6.3)	5 (11.6)	0.480
Other hematologic diseases**	22 (20.6)	15 (23.4)	7 (16.3)	0.10
Disease status, n (%)				
Relapse/Progressive	43 (40.2)	21 (32.8)	22 (51.2)	0.058
Newly diagnosed	37 (34.6)	26 (40.6)	11 (25.6)	0.109
Complete/Partial response	25 (23.4)	16 (25)	9 (20.9)	0.626
Terminal stage	2 (1.9)	1 (1.6)	1 (2.3)	0.563
Chemotherapy in the Last 30 days	77 (72)	48 (75)	29 (67.4)	0.393
Hematopoietic stem cell transplantation (HSCT), n (%)				
All HSCT	47 (43.9)	25 (39.1)	22 (51.2)	0.216
Allogeneic HSCT	30 (28)	13 (20.3)	17 (39.5)	0.024
Autologous HSCT	22 (20.6)	14 (21.9)	8 (18.6)	0.682
Graft versus host disease, n (%)	17 (15.9)	7 (10.9)	10 (23.3)	0.087
Admission from, n (%)				
Admission from the hematology ward	61 (57)	28 (43.8)	33 (76.7)	0.001
Admission from the emergency room	30 (28)	27 (42.2)	3 (7)	0.0001
Admission from the bone marrow transplant unit	13 (12.1)	6 (9.4)	7 (16.3)	0.284
Other clinics	3 (2.7)	3 (4.8)	0	1.00
Reasons for admission, n (%)				
Respiratory failure	73 (68.2)	38 (59.4)	35 (81.4)	0.016
Sepsis	58 (54.2)	33 (51.6)	25 (58.1)	0.503
Hemodynamic instability	36 (33.6)	24 (37.5)	12 (27.9)	0.303
Neurological deterioration	12 (11.2)	3 (4.7)	9 (20.9)	0.013
Post-Arrest care	11 (10.3)	3 (4.7)	8 (18.6)	0.026
Postoperative monitoring	2 (1.9)	2 (3.1)	0	0.515
Metabolic	3 (2.8)	2 (3.1)	1 (2.3)	1.00
GI/Hepatic	2 (1.9)	2 (3.1)	0	1.00
Other	4 (3.6)	3 (4.8)	1 (2.3)	0.425

Median (1st-3rd quartiles), n = number, % = percentage. **Other Hematological Diseases: essential thrombocytosis (4), aplastic anemia (5), myelofibrosis (4), immune thrombocytopenic purpura (3), autoimmune hemolytic anemia (4), and polycythemia vera (2).

Table 2. Acute illness severity and organ dysfunction scores on day 1 and day 3, and change in scores between day 1 and day 3 in critically Ill hematologic patients

Scores	All patients (n=107)	Survivors (n=64)	Non-Survivors (n=43)	p
Day 1 APACHE II	23 (19-29)	20.5 (17-23.75)	30 (23-40)	0.0001
Day 1 SAPS II	49 (40-69)	42 (37.25-49.75)	68 (54-94)	0.0001
Day 1 SOFA	8 (6-11)	6 (4-8)	11 (9-14)	0.0001
Scores	**All Patients (n=75)**	**Survivors (n=48)**	**Non-Survivors (n=27)**	
Day 3 APACHE II	21 (15-27)	17 (13.25-20.75)	31 (25-37)	0.0001
Day 3 SAPS II	49 (36-62)	39.5 (34-48.5)	70 (56-84)	0.0001
Day 3 SOFA	7 (4-12)	5 (4-6.75)	14 (10-15)	0.0001
Change in scores between day 1 and day 3				
APACHE II decreased, n (%)	45 (60)	34 (70.8)	11 (40.7)	0.003
APACHE II increased, n (%)	21 (28)	7 (14.6)	14 (51.8)	
APACHE II unchanged, n (%)	9 (12)	7 (14.6)	2 (7.4)	
Δ APACHE II*	-2.0 (-5.0-2.0)	-2.0 (-5.0-0.0)	0.0 (-4.0-5.0)	0.006
SAPS II decreased, n (%)	36 (48)	31 (64.5)	5 (18.5)	0.0001
SAPS II increased, n (%)	23 (30.6)	5 (10.4)	18 (66.6)	
SAPS II unchanged, n (%)	16 (21.3)	12 (25)	4 (14.8)	
Δ SAPS II*	0.0 (-8.0-3.0)	-5.5 (-8.0-0.0)	3.0 (0.0-12.0)	0.0001
SOFA decreased, n (%)	35 (46.6)	32 (66.6)	3 (11)	0.0001
SOFA increased, n (%)	23 (30.6)	6 (12.5)	17 (62.9)	
SOFA unchanged, n (%)	17 (22.6)	10 (20.8)	7 (25.9)	
Δ SOFA*	0.0 (-1.0-1.0)	-1.0 (-2.0-0.0)	1.0 (0.0-4.0)	0.0001

Median (1st-3rd quartiles), n = number, % = percentage. APACHE II: Acute Physiology and Chronic Health Evaluation II, SAPS II: Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment, Δ: Difference between day 3 score and day 1 score.

Table 3. AUC, Cut-off, sensitivity, and specificity values of ROC curves for APACHE II, SAPS II, and SOFA scores on Day 1, Day 3, and changes between these days

Variable	Cut-off	AUC	p	95% CI (Lower)	95% CI (Upper)	Sensitivity (%)	Specificity (%)
Day 1 APACHE II	22.5	0.850	0.0001	0.779	0.922	81.4	67.2
Day 1 SAPS II	52.5	0.859	0.0001	0.789	0.929	81.4	78.1
Day 1 SOFA	8.5	0.888	0.0001	0.826	0.950	81.4	81.2
Day 3 APACHE II	22.5	0.946	0.0001	0.894	0.997	92.6	89.6
Day 3 SAPS II	49.5	0.946	0.0001	0.899	0.992	92.6	81.2
Day 3 SOFA	8.5	0.958	0.0001	0.910	1.000	96.3	93.7
Δ APACHE II	-1.5	0.692	0.006	0.562	0.822	63.0	62.5
Δ SAPS II	-0.5	0.800	0.0001	0.683	0.916	81.5	64.6
Δ SOFA	-0.5	0.845	0.0001	0.750	0.941	88.9	66.7

AUC: Area Under the Curve, CI: Confidence Interval, APACHE II: Acute Physiology and Chronic Health Evaluation II, SAPS II: Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment, Δ: Difference between day 3 score and day 1 score.

crease APACHE II, SAPS II, or SOFA scores was associated with increased mortality, with changes in SOFA score providing the strongest discrimination.

Multivariate Analysis

In multivariate logistic regression analysis incorporating clinically relevant variables and severity scores, the

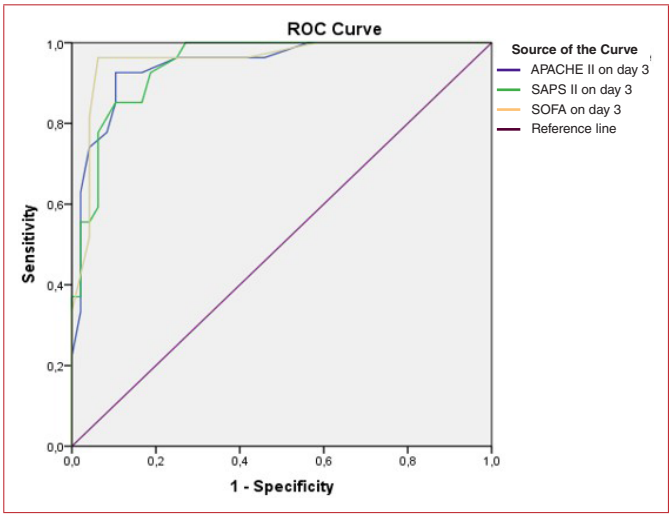

Figure 2. ROC curves for APACHE II, SAPS II, and SOFA scores on day 3.

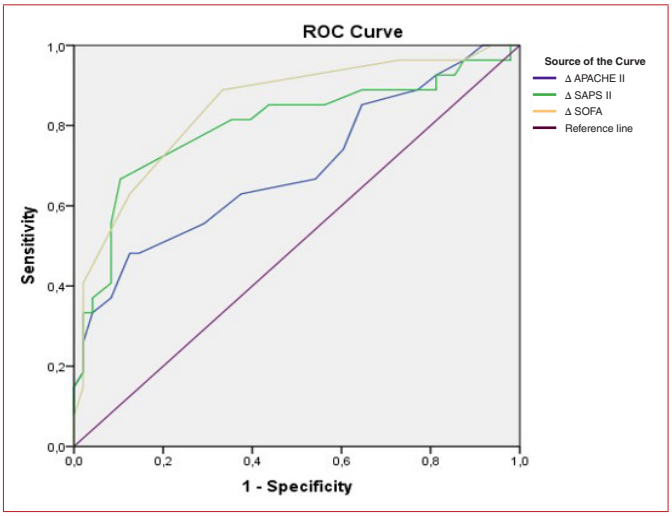

Figure 3. ROC curves of changes between day 1 and day 3 in APACHE II, SAPS II, and SOFA scores.

Table 4. Independent risk factors for ICU mortality in critically ill hematologic patients

Variable	Wald	p	OR	95% CI (Lower)	95% CI (Upper)
Pre-ICU hospital stay	1.080	0.299	1.049	0.959	1.148
Admission from the hematology ward	2.258	0.133	5.512	0.595	51.083
Presence of allogeneic HSCT	0.799	0.372	2.719	0.303	24.378
Day 3 SOFA	14.121	0.001	2.042	1.407	2.962
Respiratory failure on admission	1.008	0.315	3.017	0.349	26.049

ICU: Intensive Care Unit, HSCT: Hematopoietic Stem Cell Transplantation, SOFA: Sequential Organ Failure Assessment, MV: Mechanical Ventilation, OR: Odds Ratio, CI: Confidence Interval.

SOFA score at ICU day 3 emerged as the strongest independent predictor of ICU mortality (OR 2.042, 95% CI 1.407-2.962, p=0.001) (Table 4).

Discussion

Historically, ICU admission of patients with hematologic diseases, particularly those with hematologic malignancies, was approached with caution due to poor reported outcomes. However, advances in hematologic-oncologic therapies, supportive care, and critical care practices have led to increased ICU utilization and improved survival in this population. Nevertheless, mortality rates among critically ill hematologic patients remain substantially higher than those observed in the general ICU population, particularly among patients with hematologic malignancies who require invasive mechanical ventilation, vasopressor support, renal replacement therapy, or those with allogeneic hematopoietic stem cell transplantation (HSCT).[6-9] In this context, accurate and dynamic prognostic assessment remains essential to guide clinical decision-making.

Previous studies have identified numerous factors associated with mortality in critically ill hematologic patients, including disease-related characteristics, treatment history, organ support requirements, and laboratory abnormalities.[10-15] However, the prognostic relevance of several of these variables—such as age, neutropenia, disease type, and disease status—has been shown to vary over time.[16,17] In contrast, the severity of acute illness, the extent of organ dysfunction at ICU admission, and, importantly, their evolution during the ICU stay have consistently remained robust predictors of outcome.[18-21]

Acute illness severity and organ dysfunction scores have been extensively studied in both general ICU and hematologic populations. Higher APACHE II, SAPS II, and SOFA scores at ICU admission are associated with increased mortality in both populations. Numerous

studies in general ICU cohorts have also demonstrated that serial SOFA measurements and early score trajectories outperform single admission values in predicting mortality. Similar findings have been reported in hematologic populations, where persistent or worsening organ dysfunction is strongly associated with poor outcomes.[21-31]

Our results align with this body of evidence. In the present study, higher APACHE II, SAPS II, and SOFA scores at ICU admission and on day 3 were significantly associated with ICU mortality. More importantly, early dynamic changes in these scores—particularly between day 1 and day 3—provided additional prognostic information. Survivors demonstrated significant reductions in severity scores, whereas non-survivors exhibited persistently elevated or worsening scores, highlighting the clinical relevance of early responses to intensive care support.

Among all evaluated parameters, the SOFA score on ICU day 3 emerged as the strongest independent predictor of ICU mortality in multivariate analysis, demonstrating excellent discriminatory performance. This finding underscores that ongoing organ dysfunction and its reversibility, rather than baseline disease characteristics or admission severity alone, are the principal drivers of outcomes in critically ill hematologic patients. Compared with APACHE II and SAPS II, the SOFA score showed superior prognostic accuracy, likely because it captures the dynamic burden of organ failure and response to therapy over time.

These findings have important clinical implications. Dynamic SOFA assessment may support early identification of high-risk patients, facilitate timely reassessment of treatment goals, and aid in shared decision-making with patients and families. Rather than using admission scores as a basis for ICU triage or treatment limitations, an approach that incorporates short-term ICU trials with serial reassessments of organ dysfunction may be more appropriate for this complex population.

An additional strength of this study lies in its setting. Most data on prognostic scoring systems in critically ill hematologic patients originate from general ICUs in high-income countries. Our results from a dedicated hematology ICU in a university hospital provide valuable insights into the performance of these scores in a specialized care environment, where admission practices, supportive strategies, and hematologic management may differ substantially from those in general ICUs.

Several limitations should be acknowledged. This was a single-center study with a relatively small sample size, which may limit generalizability. The retrospective design precludes the assessment of how real-time use of severity scores influenced clinical decision-making. Additionally, disease-specific and treatment-related factors were not incorporated into the prognostic models. Despite these limitations, the study provides valuable data from a dedicated hematology ICU and reinforces the prognostic importance of dynamic organ dysfunction assessment.

In conclusion, although APACHE II, SAPS II, and SOFA scores are all useful for prognostication in critically ill hematologic patients, dynamic evaluation—particularly the SOFA score on ICU day 3—offers the most accurate prediction of ICU mortality. These findings support routine serial assessment of organ dysfunction and emphasize that ICU outcomes in this population are primarily driven by the severity and reversibility of organ failure rather than by underlying hematologic disease characteristics.

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ORIGINAL INVESTIGATION

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Comparison of the Relationship Between SIMV and PRVC Ventilatory Modes on the Incidence of Asynchrony in Mechanically Ventilated Patients in the Intensive Care Unit: A Randomized Outcome-Assessor-Blinded Study

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Abstract

Aim: Patient–ventilator asynchrony (PVA), commonly occurring in mechanically ventilated patients, is a significant issue that contributes to increased discomfort, prolonged ventilation, and higher mortality rates. Among various ventilatory modes, Synchronized Intermittent Mandatory Ventilation (SIMV) and Pressure Regulated Volume Control (PRVC) are frequently used, yet their comparative effects on PVA remain unclear. This study aims to evaluate and compare the relationship between SIMV and PRVC ventilatory modes and the type and incidence of asynchrony in trauma patients in the ICU.

Study Design: This randomized, outcome-assessor-blinded clinical trial enrolled 100 mechanically ventilated trauma patients in the ICU of a hospital in southern Iran. Patients were randomly assigned to either SIMV or PRVC mode (n=50 in each group). Asynchrony was assessed over a span of 72 hours using standard waveform analysis. The overall incidence of asynchrony was chosen as the primary outcome, while specific types of asynchrony were considered secondary outcomes. Statistical analyses, including t-tests, chi-square tests, and ANOVA, were performed, with a significance level set at $p<0.05$.

Results: Asynchrony was observed in 63% of the patients. Trigger asynchrony was the most prevalent type, affecting 37% of patients. There were no statistically significant associations between the incidence of asynchrony and patient age, gender, or ventilation mode ($p>0.05$). The rates and distribution of asynchrony were similar for both SIMV and PRVC modes.

Conclusions: The significant occurrence of PVA underscores the need for careful, individualized adjustments to ventilator settings. The comparable results obtained with SIMV and PRVC modes suggest that optimizing trigger sensitivity may reduce the impact of mode selection, thus diminishing its importance in clinical decision-making.

Keywords: Intensive care unit; Mechanical ventilation; Patient–ventilator asynchrony; Pressure regulated volume control; Randomized clinical trial; Synchronized intermittent mandatory ventilation; Trigger asynchrony.

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Introduction

In critical care, one of the most essential supportive techniques is mechanical ventilation, which assists patients who are unable to receive sufficient oxygen or eliminate carbon dioxide due to respiratory failure.[1] This therapy is designed to temporarily take over the patient's breathing, allowing the respiratory system to rest and heal, while simultaneously providing oxygen and alleviating some of the pressure on the respiratory muscles.[2] Unfortunately, one of the most significant factors influencing the effectiveness of mechanical ventilation is patient-ventilator asynchrony.

Mechanical ventilation modes reflect technological advancements in flexibility. Synchronized Intermittent Mandatory Ventilation (SIMV) was developed in the 1970s to facilitate patient weaning and quickly became the most common ventilation mode, used in 90.2% of hospitals by the 1980s.[3,4] SIMV combines and synchronizes mandatory and spontaneous breaths. To enhance the clinician's experience, Pressure Regulated Volume Control (PRVC) is a dual-control mode that dynamically adjusts inspiratory pressure to achieve the target tidal volume, adapting to the patient's ventilation needs and lung mechanics with each breath.[5,6]

Patient-ventilator asynchrony is defined as a mismatch between the patient's spontaneous breathing and the ventilator's function. This can occur during the initial phase of breathing, the airflow phase, or the final phase of exhalation.[7] Among critically ill patients receiving mechanical ventilation, the reported prevalence of asynchrony ranges from 10% to 80%.[8] The variation in prevalence is due to differences in assessment methods and the patient populations studied. Data suggest that 25-47% of patients experience severe asynchrony, with an index exceeding 10%.[9]

The clinical implications of patient-ventilator asynchrony are considerable and concerning. Asynchrony can lead to additional strain on the patient's respiratory muscles, increased oxygen consumption, discomfort, anxiety, sleep disturbances, and a greater need for sedation to manage the patient.[10] More severe consequences include prolonged mechanical ventilation, extended ICU stays, ventilator-associated pneumonia, ventilator-induced lung injury, and diaphragm dysfunction—all of which contribute to extended time on mechanical ventilation. Asynchrony also significantly increases patient mortality, particularly in severe cases, with mortality rates as high as 67%, compared to 14% in patients without severe asynchrony.[11]

Several factors contribute to asynchrony, which can be categorized into two broad groups. In terms of device-related issues, the ventilator mode, trigger sensitivity, flow rate, flow rate pattern, and timing of the respiratory cycle are key factors.[12,13] Regarding patient-related factors, the level of consciousness, depth of sedation, comorbid conditions (such as pneumonia and sepsis), smoking history, and medications that exacerbate asynchrony are also important considerations.[14] Research shows that appropriate sedation and the use of certain medications, such as dexmedetomidine, can effectively reduce asynchrony rates.[15]

Few studies have explored the clinical significance of patient-ventilator asynchrony in the southern region of Iran. Therefore, the aim of this study is to determine the degree and type of patient-ventilator asynchrony in this population. Identifying these patterns can form the basis for improving care quality, reducing complications and the duration of mechanical ventilation, and ultimately enhancing patient outcomes.

Materials and Methods

Study Design

This study was a randomized, outcome-assessor-blinded, single-center clinical trial conducted in the intensive care unit (ICU) of a hospital in southern Iran. The goal was to assess the impact of two ventilatory modes—PRVC and SIMV—on patient-ventilator asynchrony in mechanically ventilated multiple trauma patients within the first 72 hours of their care. The study was designed as a parallel-group superiority trial with a 1:1 allocation ratio. The research adhered to the Declaration of Helsinki (2013) and was granted ethical approval from Ethics Committee of Hormozgan University of Medical Sciences (Approval Number: IR.HUMS.REC.1402.054, Date: 31.08.2022). It was also registered in the Iranian Registry of Clinical Trials (ID: IRCT20230702058640N1).

Participant Selection and Enrollment

Of the 105 trauma patients requiring mechanical ventilation, five patients (4.8%) were excluded from randomization due to hemodynamic instability with high-dose vasopressors (n=3) and active pneumothorax (n=2). One hundred patients provided informed consent, and all

were randomly assigned to either the SIMV group (n=50) or the PRVC group (n=50), with a 1:1 allocation ratio.

Inclusion criteria were: trauma ICU patients requiring invasive mechanical ventilation, aged 15-70 years, and with explicit informed consent from the patient or their legal representative.

Exclusion criteria included: hemodynamic instability defined as high-dose vasopressor therapy or a mean arterial pressure of less than 65 mmHg; active pneumothorax; chronic lung diseases (e.g., COPD, severe asthma, pulmonary fibrosis); significant pulmonary contusion or large-scale chest trauma (e.g., flail chest or multiple rib fractures affecting respiratory mechanics); the need for severe or massive fluid resuscitation; open abdomen trauma; death; extubation; withdrawal from the study before completion; review of the patient's records; any type of resuscitation in the last 24 hours; study withdrawal; or issues with the mechanical ventilator.

Ventilator settings and patient management were overseen by intensivists and third-year or higher anesthesiology residents, all with at least 1 year of experience with ventilators. Before the study began, all staff underwent training on the study protocol during educational workshops designed specifically for this purpose (Fig. 1).

Sample Size Calculation

The sample size was calculated to detect a clinically meaningful 10% difference in the mean Asynchrony Index (AI, as a continuous variable), with a standard deviation of 15%. The calculation used the formula for comparing two means, a type I error (α) of 0.05, and a statistical power of 80%, based on the reference methodology by Thille et al.,[16] which is widely accepted for patient-ventilator asynchrony studies. After accounting for a 10% dropout rate, the final sample size was determined to be 50 patients per group, for a total of 100 patients.

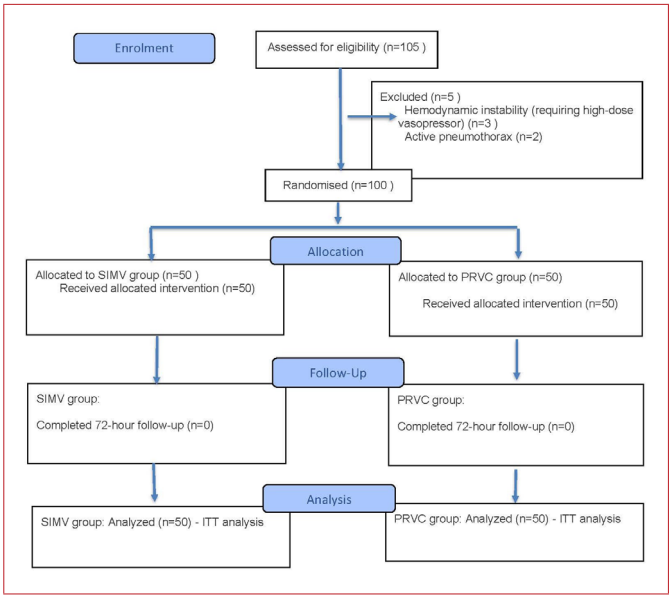

Figure 1. CONSORT 2025 flow diagram.

Randomization, Allocation, and Blinding

An independent statistician performed block randomization with block sizes of 4 and 6, using the Random Allocation Software and stratifying by Injury Severity Score (ISS < 25 vs. ≥ 25). An ICU nurse, who was not involved in the patient's care, opened sealed, opaque, consecutively numbered envelopes to ensure allocation concealment after eligibility was confirmed.

Outcome evaluators and data analysts were blinded to group allocation. Treating clinicians could not be blinded due to the nature of the intervention but were excluded from outcome assessment. Patients were also unaware of their allocation due to sedation and mechanical ventilation.

Interventions

Participants were equipped with standard endotracheal tubes (7.5-8 mm for males; 7-7.5 mm for females) prior to being connected to an Evita 4 mechanical ventilator.

The standard mechanical ventilation parameters were set within the following ranges: 10-15 breaths/min, a tidal volume of 6 mL/kg body weight per breath, 5 cm H2O PEEP, 10 cm H2O pressure support, 2-3 L/min trigger sensitivity, FiO2 adjusted to maintain peripheral oxygen saturation (SpO2) ≥ 92%, and an inspiratory-to-expiratory (I:E) ratio of 1:2 to 1:3.

For the SIMV group, the volume-controlled SIMV mode was used, while the volume-controlled PRVC mode was used for the PRVC group, with an additional upper pressure limit of 35 cm H2O. All other ventilatory settings were as previously described.

No changes were made to the ventilatory settings unless clinically indicated by conditions such as hypoxemia, acidosis, hemodynamic instability, or hypercapnia. Adherence to these conditions was recorded.

All patients received a continuous intravenous midazolam infusion at a rate of 0.06 to 0.15 mg/kg/hr, adjusted as needed to maintain a Richmond Agitation-Sedation Scale (RASS) score of –2 to –3. Fentanyl was adminis-

tered either as a continuous infusion or as needed boluses (1 mcg/kg/hr) for pain control. No neuromuscular blocking agents were used. Average infusion rates and total drug amounts were similar between the SIMV and PRVC groups for both drugs (all comparisons, $p>0.05$).

Study Outcomes

The overall level of patient-ventilator asynchrony and the Asynchrony Index (AI) were assessed during the first three days of mechanical ventilation (MV) using the formula for AI = (number of asynchronous breaths / total number of breaths) × 100. This was the primary measure of patient-ventilator asynchrony (AI) and served as the Primary Outcome of the study.

For the Secondary Outcome, variables were assessed based on the type of asynchrony, classified in accordance with the Consensus Nomenclature:

Trigger Asynchrony: Triggering inefficiency, auto-triggering, and trigger delay.

Asynchrony of Flow/Channel or Vt: Volume asynchrony, target-volumetric consistency, and PRVC-related asynchrony.

Premature or Over-Delayed-Cycling Asynchrony: Asynchrony due to early or delayed cycling of breaths.

Study-specific checklists were used to report mechanical ventilation complications, document instances of barotrauma and hemodynamic instability, identify peak airway pressures > 40 cm H_2O, and record severe asynchrony episodes (AI ≥ 30%).

Data Collection and Asynchrony Detection

Once Institutional Review Board (IRB) approval was granted and informed consent was obtained, clinical and demographic data—including age, sex, and initial ventilator settings—were collected. Asynchrony detection was performed through intermittent waveform sampling, with three 30-minute time slices selected randomly each day (0-24 hours, 24-48 hours, and 48-72 hours), providing 90 minutes of analysis per day. Waveforms were obtained from Respina P1 ventilators (Saadat Co., Tehran, Iran) with a 12.1-inch display monitor resolution of 1280×800. The pressure-time and flow-time waveforms were analyzed with a sweep speed of 10-15 mm/s.

Each breath in the 30-minute file was analyzed breath-by-breath by one of three intensivists with at least five years of experience interpreting ventilator waveforms. No detection software was used to support the analysis. The average number of breaths analyzed per 30-minute recording was 612±78. This study relied on a clearly definable limit. A single observer evaluated each recording to determine inter-observer agreement (kappa), with no defined agreement required. Continuous 24-hour monitoring was performed without interruption.

Asynchrony Classification Criteria

Asynchrony types were classified according to standardized definitions:

Trigger Asynchrony: Including ineffective triggering (visible patient inspiratory effort without ventilator response), auto-triggering (ventilator-initiated breath without patient effort), and double-triggering (two ventilator cycles triggered by a single patient effort), as defined by Blanch et al.[17] and Bruni et al.[18]

Premature/Delayed Cycling: Early termination of mechanical inspiration before the completion of the patient's inspiratory effort (premature cycling) or prolonged mechanical inspiration beyond the patient's neural inspiratory time (delayed cycling), identified by persistent inspiratory flow at the end of the mechanical breath or active expiratory muscle recruitment.[18]

Flow Asynchrony: A mismatch between the patient's inspiratory flow demand and the delivered flow, identified by a concave deformity in the pressure-time waveform during inspiration or a scooped appearance of the flow-time curve.[17,18]

Combined/Multiple Asynchronies: The simultaneous occurrence of two or more asynchrony types within the same breath or recording period.

Each breath was categorized into one of these types based on visual waveform patterns. Due to study design limitations, subtypes within trigger asynchrony (e.g., differentiating ineffective from auto-triggering) were not separately quantified.

Statistical Analysis

Data analysis was performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Quantitative variables with normal distributions were analyzed and compared using independent t-tests. Variables that did not conform to normality were analyzed and compared using Mann-Whitney U tests. Qualitative variables were compared using chi-square and Fisher's exact tests.

Primary outcomes were compared using independent t-tests and repeated-measures ANOVA with Bonferroni post hoc corrections. A p-value of <0.05 was considered statistically significant and used for subsequent analyses.

Intention-to-treat principles were followed during the analytic phase. Listwise deletion was applied for missing data rates of less than 5%, and datasets with higher rates underwent sensitivity analysis. Subgroup analysis was performed based on trauma severity, Injury Severity Score (ISS), age, and time periods.

Use of Artificial Intelligence

The only AI-assisted technology used in this study was for improving the clarity and readability of the manuscript, specifically for editing and grammar checks. All scientific content, including data analysis, interpretation, and conclusions, remains the original work of the authors.

Results

Demographic and Other Descriptive Findings

This study enrolled 100 patients on mechanical ventilation. Of the participants, 65 (65%) were male, and 35 (35%) were female (Table 1), indicating a higher prevalence of males. The SIMV mode of ventilation was the most commonly used, employed in 51 patients (51%), while PRVC was used in 49 patients (49%) (Table 2).

Analysis of asynchrony revealed that 63 patients (63%) experienced patient-ventilator asynchrony, while the remaining 37 patients (37%) did not experience any asynchrony during the entire observation period. This finding highlights a substantial occurrence of asynchrony among mechanically ventilated patients. Among the types of asynchrony, the most common was trigger asynchrony, observed in 37 patients. This was followed, in relative order, by premature/delayed cycling, flow asynchrony, and combined multiple concurrent asynchronies (trigger and cycling) (Table 2).

Main Findings

Age was not significantly associated with the occurrence of patient-ventilator asynchrony. The mean age of patients without asynchrony was 34.57±11.03 years (n=37), compared to 34.90±14.04 years in patients with

Table 2. Frequency distribution of study variables and asynchrony types

Variables	n (%)
Study variables	
Gender	
Male	65 (65)
Female	35 (35)
Ventilation mode	
SIMV	51 (51)
PRVC	49 (49)
Asynchrony presence	
No asynchrony	37 (37)
Asynchrony	63 (63)
Asynchrony types (among all patients, n=100)	
Trigger asynchrony	37 (37)
Premature/Delayed cycling	8 (8)
Flow asynchrony (TARGET)	6 (6)
Combined trigger and flow asynchrony	7 (7)
Combined trigger and cycling asynchrony	2 (2)
Multiple concurrent asynchronies (≥3 types)	5 (5)
No asynchrony	37 (37)

SIMV: Synchronized intermittent mandatory ventilation; PRVC: Pressure regulated volume control.

Table 1. Demographic and clinical characteristics of study patients

Variables	Total patients (n=100)	Without asynchrony (n=37)	With asynchrony (n=63)	p
Age (years) Mean±SD	-	57.34±11.03	34.90±14.04	0.72
Gender, n (%)				0.68
Male	65 (65)	25 (67.5)	40 (63.5)	
Female	35 (35)	12 (32.5)	23 (36.5)	
Ventilation mode, n (%)				0.37
SIMV	51 (51)	21 (56.7)	30 (47.6)	
PRVC	49 (49)	16 (43.3)	33 (52.4)	

SD: Standard deviation; SIMV: Synchronized intermittent mandatory ventilation; PRVC: Pressure regulated volume control.

asynchrony (n=63). There was no statistically significant difference between the two groups (p=0.72), indicating that age does not influence the likelihood of experiencing asynchrony.

In terms of gender distribution, 25 (38.5%) of the asynchrony-free males and 40 (61.5%) of the asynchrony-free females were in the asynchrony-ventilated population. Among females, 12 (34.3%) of the asynchrony-free females were in the asynchrony-ventilated population, while 23 (65.7%) of the females with asynchrony were in the asynchrony-ventilated group. Although both males and females had a higher number of patients with asynchrony, the difference was not significant (p>0.05), suggesting that gender is not a defining characteristic of asynchrony (Table 3).

Regarding ventilation modes, 33 patients with asynchrony (67.3% of the cohort) were on PRVC, while 30 patients (58.8%) were on SIMV mode. These figures suggest that the implementation of SIMV showed comparable asynchrony, and statistical testing revealed no substantial differences (p>0.05). Therefore, the type of ventilatory mode does not appear to significantly influence the incidence of asynchrony.

When analyzing the distribution of asynchrony types across gender, interesting patterns emerged. For males, the most dominant type of asynchrony was trigger asynchrony, with 22 cases (59.5% of males with asynchrony). A comparable pattern was observed for females, where trigger asynchrony accounted for 15 cases (40.5% of females with asynchrony). Other types of asynchrony, such as premature/delayed cycling, target, and combined multiple concurrent asynchronies (trigger and cycling), were less common, with similar distributions across genders. Statistical analysis revealed no significant differences in the distribution of these asynchrony types by gender (p>0.05).

Asynchrony distribution by ventilation mode showed that under PRVC ventilation, trigger asynchrony was the most prevalent, affecting 20 patients (54.1% of PRVC patients with asynchrony). This asynchrony type was also the most prevalent in SIMV mode, affecting 17 patients (45.9% of SIMV patients with asynchrony). Other asynchrony types, including premature/delayed cycling, target, and combined multiple concurrent asynchronies (trigger and cycling), were evenly distributed across the two ventilation modes. The differences between the two modes in terms of asynchrony type distribution were not significant (p=0.1) (Table 4).

This study shows that trigger asynchrony was the most frequent type of asynchrony across all study cohorts, regardless of gender or ventilation mode. This suggests that more focused attention should be given to optimizing trigger sensitivity settings and limits on the ventilator apparatus. Additionally, the absence of significant differences across demographic factors (age, gender, and

Table 3. Asynchrony presence by study variables

Variables	Without asynchrony n (%)	With asynchrony n (%)	p
Gender			**0.68**
Male	25 (67.5%)	40 (63.5%)	
Female	12 (32.5%)	23 (36.5%)	
Ventilation mode			**0.37**
SIMV	21 (56.7%)	30 (47.6%)	
PRVC	16 (43.3%)	33 (52.4%)	

SIMV: Synchronized intermittent mandatory ventilation; PRVC: Pressure regulated volume control.

Table 4. Asynchrony type distribution by study variables

Variables	Premature/ Delayed cycling	Flow asynchrony	Trigger asynchrony	Combined trigger & Flow	Combined trigger & Cycling	Multiple concurrent (≥3 types)	p
Gender							**0.57**
Male	4 (66.6%)	5 (83.3%)	22 (59.5%)	5 (71.4%)	2 (100%)	2 (40%)	
Female	2 (33.4%)	1 (16.7%)	15 (40.5%)	2 (28.6%)	0 (0%)	3 (60%)	
Ventilation mode							**0.1**
SIMV	1 (16.6%)	6 (100%)	17 (45.9%)	3 (42.8%)	1 (50%)	2 (40%)	
PRVC	5 (83.4%)	0 (0%)	20 (54.1%)	4 (57.2%)	1 (50%)	3 (60%)	

SIMV: Synchronized Intermittent Mandatory Ventilation; PRVC: Pressure Regulated Volume Control.

mode of ventilation) indicates that these variables had little impact on asynchrony. Furthermore, all asynchrony types within the studied cohorts showed statistically insignificant differences. A more striking finding was the degree of asynchrony observed in 63% of patients, underscoring the need for careful and active surveillance of asynchrony throughout patient care.

Discussion

In this study, 100 patients on mechanical ventilation were evaluated, and asynchrony was found in 63% of the patients, with the most prevalent form being trigger asynchrony, observed in 37 patients. This was not significantly correlated with the patients' age, sex, or the type of ventilation used (SIMV or PRVC). These findings align with existing literature, although there are differences in asynchrony prevalence, the dominant type of asynchrony, factors influencing asynchrony, and the resulting clinical outcomes.

Blanch et al.,[17] the first prospective study to utilize 24-hour monitoring alongside Better Care software, set the stage for follow-up research. They documented a high prevalence of patient-ventilator asynchrony (PVA) across all hours, with a predominance of ineffective expiratory efforts (IEE), a type of trigger asynchrony. Most notably, they revealed the association between high AI and ICU mortality ($p<0.05$). Our results are consistent in terms of prevalence (>50%), the predominance of trigger asynchrony, and the lack of effect of ventilation mode, although we did not assess mortality. This study continues to be the gold standard for defining AI and continuous monitoring.

In a pediatric population, Mortamet et al.[19] documented that 27% of ventilation time was spent in asynchrony, predominantly due to trigger delays and cycling-off errors. While the population differs, their findings regarding ventilator-free days and the emphasis on trigger events align with ours. Our study demonstrates that PVA occurs across the entire age spectrum and is largely independent of demographic characteristics, a conclusion supported by our findings in the adult population.

In their review of 62 studies, Bruni et al.[18] highlighted the variation in research methods, particularly in the definition of AI. Ineffective efforts and double-triggering were the most common types, and relationships with MV duration, patient comfort, and sleep were identified. However, the relationship with mortality remained unspecified (causal vs. associative). This review aligns with our findings that ventilation mode has no significant effect on asynchrony and emphasizes the need for standardization. Our reported prevalence of 63% is within the upper range of reported values (up to 80%).

Sousa et al.[20,21] (2019, protocol; 2020, results - EPISYNC) conducted a study with a design similar to ours (Better Care, entire MV duration) and reported a median AI of 5.1%, with 22% of patients having AI≥10%. The AI range was predicted by intrinsic PEEP and intrinsic SAPS3 (disease severity), while compliance and airway resistance were not. Assisted modes showed greater asynchrony, which was associated with extubation failure (33% vs. 6%, $p=0.01$) but not with mortality. This study is our closest counterpart: it lacks association with age, gender, or mode; shows the predominance of trigger asynchrony; utilizes continuous monitoring; and assesses clinical outcomes. The difference in prevalence (63% vs. 22% with AI≥10%) can be attributed to differences in the AI calculation (entire duration vs. specific hours) and the definition of "asynchrony presence."

Kyo et al.[15] conducted a meta-analysis of 16 studies and found low-quality evidence linking longer mechanical ventilation (MV) (5.16 days) with increased ICU mortality (OR=2.73) and hospital mortality (OR=1.94) in patients with an Asynchrony Index (AI) ≥10%. The use of pressure-targeted modes, tidal volume adjustment, and sedation with dexmedetomidine were shown to reduce the prevalence of adverse events (PVA). This supports the importance of monitoring and post hoc interventions, in line with our emphasis on optimizing trigger sensitivity. Although no intervention was performed in our study, the lack of a mode effect is consistent with the reduction of PVA observed during pressure-cycled ventilation (PCV) in other studies.

Zhou et al.[14] analyzed PVA in a cohort of 676 patients, the largest to date, reporting a 24% prevalence, with double triggering (13%) and flow starvation (10%) as the most common types of PVA. Risk factors included smoking, pneumonia, sepsis, and ARDS. Use of pressure-targeted ventilation was associated with a reduction in PVA, and a higher PVA count was linked to longer mechanical ventilation duration and fewer hospital-free days. While our study reported a lower prevalence of PVA, these findings align with ours. Although we did not study underlying disease factors, the lack of a mode effect in SIMV/PRVC

ventilation supports Zhou's findings in VC-SIMV. The predominance of trigger/cycle-related events and their reduction with PCV, in correlation with worse outcomes, is consistent with our observations.

There are several limitations in this study that must be acknowledged. The single-center design limits the generalizability of the results. Additionally, the lack of systematic collection of baseline clinical characteristics, such as Injury Severity Score (ISS), APACHE II, height, weight, and arterial blood gas values, limits our understanding of baseline group comparability. This represents a significant methodological gap that should be addressed in future multicenter studies.

We also note that asynchrony was assessed using intermittent sampling of 30-minute periods (90 minutes total over 24 hours), rather than continuous sampling, which may lead to an underestimation of asynchrony. Furthermore, the absence of esophageal pressure monitoring prevented the precise identification of ineffective patient-ventilator interactions. The assessment by a single observer within predefined time periods, without establishing inter-rater reliability, may introduce bias in interpretation.

Another limitation is that asynchrony subtypes were captured as whole categories rather than separately, which likely affects the depth of the comparative analysis with more recent literature. Additionally, certain clinical outcomes (e.g., time on mechanical ventilation, ICU length of stay, and mortality) were not captured, preventing an assessment of the potential clinical impact of asynchrony. Future studies should address continuous monitoring, establish an agreed-upon protocol for baseline data collection, and track clinical outcomes more comprehensively.

Conclusion

In this randomized, outcome-assessor-blinded study, 63% of mechanically ventilated patients experienced patient-ventilator asynchrony, with trigger asynchrony being the most common type. There was no significant relationship between asynchrony and patient age, gender, or ventilation mode (SIMV or PRVC), indicating comparable performance between the two modes. Given the high frequency of asynchrony, we advocate for dynamic, individualized adjustments to trigger sensitivity, enhanced educational efforts to support the recognition of asynchrony patterns, and further research to explore the clinical implications of the corrective actions outlined in this study.

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

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Prognostic Factors in Patients with Lung Cancer in the Intensive Care Unit: A Retrospective Single-Center Study

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Abstract

Aim: Patients diagnosed with lung cancer may require intensive care due to sudden and severe clinical events; however, early survival outcomes vary widely. In this context, we investigated ICU mortality and analyzed admission-specific clinical characteristics associated with death in a healthcare setting where access to intensive care is not limited by predefined admission criteria.

Study Design: The study population consisted of adult individuals with lung cancer who required intensive care from 2018 to 2022. Patient demographics, cancer-related features, indications for ICU admission, illness severity indices, requirements for organ-supportive therapies, and clinical outcomes were systematically evaluated. Associations between baseline variables and ICU mortality were examined using multivariable logistic regression analysis.

Results: The study cohort comprised 351 critically ill patients with lung cancer. The median age was 66 years, and ICU mortality occurred in 76% of cases. The presence of metastatic disease independently increased the risk of death (OR 2.32, 95% CI 1.26–4.26). In contrast, patients admitted due to hypercapnic respiratory failure demonstrated a significantly lower mortality risk (OR 0.36, 95% CI 0.17–0.75). Higher illness severity scores were consistently associated with unfavorable outcomes.

Conclusions: Despite significant advances in intensive care medicine, short-term outcomes for lung cancer patients admitted to the ICU remain unfavorable. Disease burden, reflected by metastatic status and severity scores, strongly influences outcomes, whereas patients admitted with hypercapnic respiratory failure demonstrate a more favorable prognosis.

Keywords: Intensive care unit; Lung cancer; Mortality; Respiratory failure; SOFA score.

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Introduction

Lung cancer imposes a significant global health burden, with many patients eventually requiring intensive care due to life-threatening respiratory deterioration or complications arising from advanced disease.[1,2] Despite substantial progress in oncologic diagnostics and treatment strategies, many patients continue to develop severe, life-threatening conditions that necessitate intensive care support. These complications most commonly include respiratory failure, septic shock, and acute neurologic deterioration, all of which are associated with a high risk of short-term mortality.[3–6] With the increasing incidence of metastatic lung cancer and the complex-

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ity of its management, identifying factors linked to poor outcomes in ICU settings has become a critical focus for clinicians and researchers alike.

Advances in cancer treatment strategies over the past few decades have been accompanied by measurable improvements in survival among patients with solid malignancies.[7] Enhanced critical care and oncologic management have led to better ICU survival rates among cancer patients, with mortality rates for those with solid tumors now approaching those observed in patients without malignancy.[7,8] Nevertheless, individuals with lung cancer continue to experience poorer outcomes following ICU admission compared to patients with other solid malignancies.[9] ICU mortality has been reported as ranging from 28% to 47% in previous studies.[4–6,10] In some studies, mortality rates exceed 70%.[11,12] This high mortality rate highlights the importance of identifying prognostic factors that influence ICU outcomes in this population. Understanding variables such as metastatic disease, the severity of respiratory failure, and the need for early invasive interventions may help clinicians make timely and appropriate decisions regarding life-sustaining treatments.

A major unresolved issue in the care of critically ill cancer patients is the lack of standardized frameworks to guide ICU admission decisions in those with advanced disease. Intensivists and oncologists often approach these decisions from different clinical perspectives.[13] Earlier studies suggest that unfavorable ICU outcomes among cancer patients are influenced by factors such as patient age, the extent of acute physiological derangement, the need for ventilatory support, and the burden of organ failure at admission.[4–6,14,15] In Türkiye, ICU admission policies are relatively liberal, with no legal or institutional restrictions on life-sustaining therapies. Unlike in North America and Europe, where guidelines for end-of-life decisions and the limitation of futile treatments are well established, such practices are less clearly defined in Türkiye.[16,17] As a result, critically ill patients with advanced lung cancer are increasingly treated in intensive care settings, where prolonged life-sustaining interventions may be implemented despite limited anticipated benefit. The objective of this study was to investigate ICU mortality in lung cancer patients and identify clinical factors present at admission that are associated with mortality in a system without restrictions on ICU access.

Materials and Methods

This retrospective analysis was conducted in a respiratory disease-focused ICU with a capacity of 23 beds, serving as a tertiary referral center for patients with severe pulmonary disorders, including lung cancer. The study was approved by the University of Health Sciences Türkiye, Dr. Suat Seren Chest Disease and Thoracic Surgery Teaching and Research Hospital Clinical Research Ethics Committee (Approval Number: 2023/29-38, Date: 06.06.2023). Given the retrospective nature of the study and the use of anonymized data, the requirement for informed consent was waived.

Patients

Adult patients with a histopathological diagnosis of lung cancer who required intensive care during the study period were evaluated for inclusion. Patients were eligible if their ICU length of stay exceeded 24 hours and if all predefined clinical variables and outcome measures were available for analysis.

Patients who died within the first 24 hours, those admitted immediately following oncologic surgery, individuals with a lung cancer diagnosis exceeding five years, and cases with incomplete records were excluded. The flow of patient selection is presented in Figure 1. During the study period, pulmonologists referred patients from hospital wards or the emergency department when intensive care support was deemed necessary, and the attending intensivist determined eligibility for ICU admission. Ad-

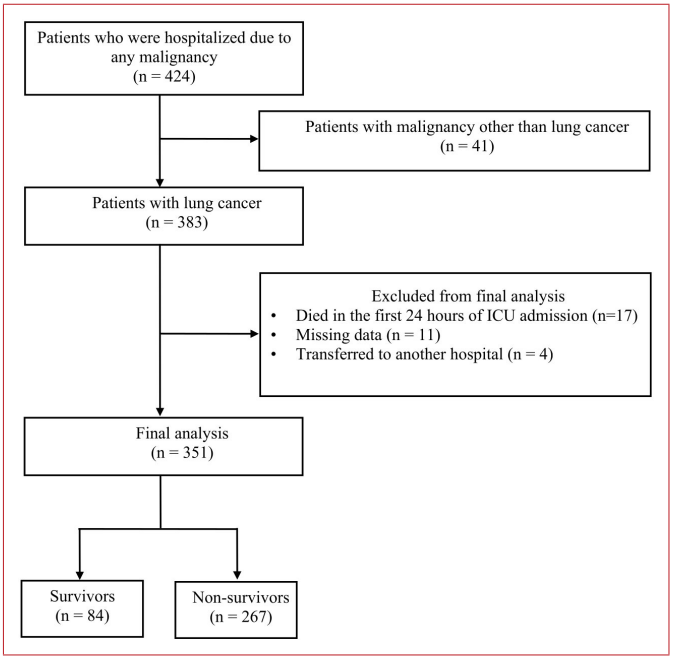

Figure 1. Flowchart of patient selection process.

mission was generally unrestricted, except in cases where the patient or their legal representative declined intensive care.

Data Collection

For each patient, demographic and clinical characteristics were obtained, including age, gender, comorbid conditions, histological subtype of lung cancer, presence of metastatic disease, prior chemotherapy or radiotherapy, and documented treatment response.

Additional variables included the primary reason for ICU admission, respiratory status at presentation, disease severity scores, as well as the requirement for vasopressor therapy and renal replacement therapy (RRT). ICU admission diagnoses were categorized into eight groups:

1. Hypoxemic respiratory failure ($PaO_2 < 60$ mmHg)
2. Hypercapnic respiratory failure ($PaCO_2 > 45$ mmHg)
3. Septic shock
4. Acute neurological impairment
5. Post–cardiopulmonary resuscitation (CPR)
6. Neutropenic fever
7. Hemoptysis
8. Acute kidney injury

Since "do not resuscitate" (DNR) or "do not intubate" (DNI) directives are not legally recognized in Türkiye, all cancer patients experiencing cardiac arrest received full basic and advanced life support. When multiple clinical problems were present at admission, the condition judged to be the predominant cause for ICU referral was recorded as the principal reason.

Statistical Analysis

Data analysis was performed using SPSS version 26.0 (IBM, Armonk, NY, USA). Continuous variables are summarized using median and interquartile range values, whereas categorical variables are described as absolute numbers and percentages. Comparisons between survivor and non-survivor groups were made using non-parametric statistical tests or chi-square analysis, as appropriate. To determine factors independently associated with ICU mortality, variables meeting a predefined threshold in univariable analysis ($p<0.20$) were incorporated into an adjusted logistic regression model. Results are presented as odds ratios with 95% confidence intervals, and statistical significance was defined as $p<0.05$.

Results

The analysis included 351 patients, with a median age of 66 years (IQR 59–71), and the majority of the cohort was male (309 patients, 88%). Among pre-existing conditions, hypertension was the most frequently observed comorbidity, followed by diabetes mellitus and chronic obstructive pulmonary disease, with prevalences of 25.4%, 22.8%, and 21.1%, respectively. Approximately half of the patients had metastatic disease; squamous cell carcinoma (42.2%) and adenocarcinoma (39.9%) were the most common histological types of lung cancer. Among the study population, 199 patients (56.7%) had not received chemotherapy at the time of ICU admission. This subgroup included newly diagnosed patients awaiting treatment initiation, patients with poor performance status who were not eligible for systemic therapy, and patients receiving only palliative or supportive care. The leading reason for ICU admission was hypoxemia (37.9%), followed by post-CPR (16.2%) and hypercapnia (15.7%). Detailed demographic information is presented in Table 1.

More than three-quarters of the patients (n=267, 76%) experienced mortality during their ICU stay. Survivors were more likely to be admitted for hypercapnic respiratory failure (38.1%) compared to non-survivors (8.6%) ($p<0.001$). Non-survivors were more frequently admitted for hypoxemic respiratory failure (40.4%) compared to survivors (29.8%) ($p<0.001$). The APACHE II scores were markedly higher in non-survivors (median 24, IQR 20–30) than in survivors (median 18, IQR 14–22) ($p<0.001$).

Ventilatory support requirements within the first 24 hours of ICU admission differed significantly according to survival status (Table 2). Non-invasive mechanical ventilation (NIMV) was more frequently used among survivors compared to non-survivors (50.0% vs. 23.6%, $p<0.001$). The use of invasive mechanical ventilation was significantly more frequent among patients who did not survive compared to survivors (67.0% vs. 29.8%, $p<0.001$). Similarly, vasopressor therapy was administered more often in non-survivors (39.7%) than in survivors (14.3%, $p<0.001$). These findings were consistent with greater organ dysfunction at ICU admission, as reflected by higher SOFA scores in non-survivors (median 5, IQR 3–8) compared to survivors (median 3, IQR 2–4; $p<0.001$) (Table 2).

After adjustment in the multivariable logistic regression model, metastatic cancer remained the dominant predictor of ICU mortality, increasing the odds of death by

Table 1. Demographic features of patients

Variable	All patients (n=351)	Survivors (n=84)	Non-survivors (n=267)	p
Age, median (IQR), years	66 (59–71)	66 (58–71)	66 (60–72)	0.577
Gender, male, n (%)	309 (88)	72 (85.7)	237 (88.8)	0.453
BMI, median (IQR), kg/m²	23.8 (21.2–26.2)	24.0 (20.8–27.6)	23.8 (21.3–26.0)	0.559
Smoking status, n (%)				
Non-smoker	12 (3.4)	7 (8.3)	5 (1.9)	0.655
Active smoker	107 (30.5)	24 (28.6)	83 (31.1)	
Ex-smoker	227 (64.7)	56 (66.7)	171 (64.0)	
Smoking duration, median (IQR), pack-years	45 (40–50)	40 (35–50)	45 (40–50)	0.750
Comorbid diseases, n (%)				
COPD	74 (21.1)	29 (34.5)	45 (16.8)	0.001
DM	80 (22.8)	26 (30.9)	54 (20.2)	0.041
Hypertension	89 (25.4)	25 (29.8)	64 (24.0)	0.287
CAD	45 (12.8)	13 (15.5)	32 (12.0)	0.404
CHF	23 (6.6)	7 (8.3)	16 (6.0)	0.450
Other malignancy	13 (3.7)	2 (2.4)	11 (4.1)	0.462
Number of comorbidities	1 (0–1)	0 (0–1)	1 (0–2)	0.014
Histological type, n (%)				
Small cell carcinoma	44 (12.5)	11 (13.1)	33 (12.4)	0.679
Squamous cell carcinoma	148 (42.2)	36 (42.9)	112 (41.9)	
Adenocarcinoma	140 (39.9)	35 (41.7)	105 (39.3)	
Other	19 (5.4)	2 (2.3)	17 (6.4)	
Metastasis status, n (%)				
Non-metastatic	180 (51.3)	60 (71.4)	120 (44.9)	<0.001
Metastatic	171 (48.7)	24 (28.6)	147 (55.1)	
Radiotherapy				
No radiotherapy	198 (56.4)	48 (57.1)	150 (56.2)	0.642
Thoracic	98 (27.9)	25 (29.8)	73 (27.3)	
Cranial	33 (9.4)	5 (6.0)	28 (10.5)	
Bone	22 (6.3)	6 (7.1)	16 (6.0)	
Chemotherapy				
No chemotherapy	199 (56.7)	46 (54.8)	153 (57.3)	0.709
Less than 1 month*	73 (20.8)	19 (22.6)	54 (20.2)	
1–3 months*	38 (10.8)	9 (10.7)	29 (10.9)	
8–12 months*	20 (5.7)	3 (3.6)	17 (6.4)	
More than 12 months*	21 (6.0)	7 (8.3)	14 (5.2)	
Response to treatment, n (%)				
No treatment evolution	237 (67.5)	47 (56.0)	190 (71.2)	<0.001
Progression	72 (20.5)	12 (14.3)	60 (22.5)	
Stable	33 (9.4)	19 (22.6)	14 (5.2)	
Regression	9 (2.6)	6 (7.1)	3 (1.1)	

BMI: Body Mass Index; CAD: Coronary Artery Disease; CHF: Chronic Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; DM: Diabetes Mellitus; IQR: Interquartile Range; *Time interval between the last chemotherapy session and ICU admission.

Table 2. Clinical characteristics of patients

Variable	All patients (n=351)	Survivors (n=84)	Non-survivors (n=267)	p
Cause of ICU admission, n (%)				
Hypoxemia	133 (37.9)	25 (29.8)	108 (40.4)	<0.001
Hypercapnia	55 (15.7)	32 (38.1)	23 (8.6)	
Septic shock	32 (9.1)	6 (7.1)	26 (9.7)	
Neurologic disturbance	22 (6.3)	5 (6.0)	17 (6.4)	
Post-CPR	57 (16.2)	4 (4.8)	53 (19.9)	
Neutropenic fever	17 (4.8)	2 (2.4)	15 (5.6)	
Hemoptysis	14 (4.0)	4 (4.8)	10 (3.7)	
Acute kidney injury	21 (6.0)	6 (7.1)	15 (5.6)	
APACHE-2 score	23 (17–28)	18 (14–22)	24 (20–30)	<0.001
Respiratory status on 1st day of ICU, n (%)				
O^2 support only	42 (12.0)	17 (20.2)	25 (9.4)	<0.001
NIMV	105 (29.9)	42 (50.0)	63 (23.6)	
IMV	204 (58.1)	25 (29.8)	179 (67.0)	
Vasopressor use on 1st day of ICU, n (%)	118 (33.6)	12 (14.3)	106 (39.7)	<0.001
RRT on 1st day of ICU, n (%)	23 (6.6)	2 (2.4)	21 (7.9)	0.076
SOFA score on 1st day of ICU, median (IQR)	4 (3–7)	3 (2–4)	5 (3–8)	<0.001
LOS of ICU, median (IQR), days	8 (4–15)	7 (4–13)	8 (3–16)	0.994

APACHE: Acute Physiology and Chronic Health Evaluation; CPR: Cardiopulmonary Resuscitation; ICU: Intensive Care Unit; IMV: Invasive Mechanical Ventilation; IQR: Interquartile Range; LOS: Length of Stay; NIMV: Non-invasive Mechanical Ventilation; RRT: Renal Replacement Therapy; SOFA: Sequential Organ Failure Assessment

more than twofold (OR 2.32, 95% CI 1.26–4.26; p=0.007). Severity-of-illness scores also demonstrated independent prognostic value, with incremental increases in APACHE II and SOFA scores associated with a higher mortality risk (OR 1.09, 95% CI 1.03 – 1.16; p=0.002 and OR 1.21, 95% CI 1.03 – 1.42; p=0.024, respectively). Conversely, patients admitted with hypercapnic respiratory failure had a significantly reduced risk of ICU mortality (OR 0.36, 95% CI 0.17–0.75; p=0.006). Post-CPR status was not independently related to mortality in the adjusted model (Table 3).

Table 3. Multivariate analysis for ICU mortality

Variable	OR (95% CI)	p
Age	1.03 (0.99–1.06)	0.109
Number of comorbidities	1.04 (0.87–1.27)	0.445
Metastatic cancer	2.32 (1.26–4.26)	0.007
APACHE-2 score	1.09 (1.03–1.16)	0.002
SOFA score on the 1st day of ICU	1.21 (1.03–1.42)	0.024
Hypercapnic respiratory failure	0.36 (0.17–0.75)	0.006
Post-CPR	1.36 (0.42–4.42)	0.612

APACHE: Acute Physiology and Chronic Health Evaluation; CPR: Cardiopulmonary Resuscitation; ICU: Intensive Care Unit; OR: Odds Ratio; SOFA: Sequential Organ Failure Assessment.

Discussion

This investigation aimed to identify clinical determinants associated with ICU mortality in patients with lung cancer who required intensive care. Our analysis revealed a notably high mortality rate, reflecting the challenges inherent in treating critically ill individuals with advanced malignancy. The findings demonstrate that metastatic involvement, greater illness severity, and early organ dysfunction significantly contribute to adverse outcomes. These observations offer valuable insights that may assist clinicians in making informed decisions when managing lung cancer patients in the ICU.

The most striking finding of this study was the exceptionally high ICU mortality among lung cancer patients: three out of every four individuals did not survive their ICU stay, where end-of-life decisions and limitations of life-sustaining treatment are not routinely applied. Prior studies have consistently reported unfavorable outcomes

among lung cancer patients admitted to the ICU, although mortality rates vary considerably across different cohorts. Qian et al.[5] documented a 28-day mortality rate of 30.6% in a single-center cohort, while Puxty et al.[6] observed that 41.5% of lung cancer patients admitted to ICUs in a nationwide study died during their ICU stay. Earlier studies have reported even higher mortality rates—Boussat et al.[12] noted ICU mortality reaching 67.5% in the early 2000s. The ICU mortality observed in this cohort was notably higher than that reported in earlier studies, with only 23.9% of patients surviving to ICU discharge. The absence of established end-of-life decision-making processes may have substantially contributed to the elevated mortality rate observed in this population. Another notable characteristic of our population was the high proportion of post-cardiopulmonary resuscitation (post-CPR) admissions. Following hypoxemic respiratory failure, post-CPR status represented the second most frequent reason for ICU admission, accounting for 16.2% of the cohort—substantially higher than the rates reported in earlier studies (1.3% in Chen et al.,[3] 2% in Barth et al.,[4] and 7.3% in Puxty et al.[6]). Because DNR orders are not legally permitted in Türkiye, all patients, including those with advanced cancer, undergo full resuscitative efforts when cardiac arrest occurs. Outcomes for cancer patients after CPR are known to be poor. A meta-analysis reported that only 6.2% survived following CPR.[18] In our study, survival following CPR was similarly low, with only 4 of 57 post-CPR patients (7%) living beyond the event. The exclusion of postoperative patients—who are known to have lower mortality—may offer an additional explanation for the relatively high mortality rate observed in our study.[15]

In our cohort, metastatic disease at the time of ICU admission emerged as the strongest predictor of ICU mortality. Patients with metastasis had a 2.3-fold higher likelihood of dying in the ICU compared with those without metastatic involvement. This observation aligns with earlier work identifying metastasis as a major determinant of poor outcomes. Park et al.[15] demonstrated that cancer stage was the most influential clinical factor associated with ICU mortality among lung cancer patients, while Qian et al.[5] found that metastatic disease increased 28-day mortality risk by 1.7 times. The severity of acute illness also played a key role. Patients who did not survive had significantly higher APACHE II and SOFA scores upon admission compared to survivors. Similar findings have been noted across previous studies. Namendys-Silva et al.[19] reported that the APACHE II score independently predicted mortality with an odds ratio of 1.92, and Song et al.[20] showed that a SOFA score above 10 increased the risk of death nearly tenfold.

NIMV has been shown to confer important clinical benefits in patients with hypercapnic respiratory failure, notably by decreasing the need for invasive mechanical ventilation (IMV) and improving survival outcomes.[21] In contrast, IMV has repeatedly been reported as a strong predictor of mortality in patients with lung cancer.[4,5] Our results indicate that hypercapnic respiratory failure as the primary reason for ICU admission was associated with a lower risk of mortality, independent of other clinical factors. The relative reversibility of this condition and the applicability of noninvasive respiratory support may partly explain this favorable outcome.

Several limitations of this study should be considered. First, the retrospective design and the use of data from a single tertiary care center may limit the generalizability of the findings to other institutions and patient populations. Additionally, the use of electronic medical records and retrospective data collection restricted our ability to adjust for certain unrecorded confounders, including the timing of ICU referral and specific oncologic management decisions. Another limitation is the absence of follow-up information beyond the ICU stay; long-term outcomes, such as post-discharge quality of life, were not evaluated, although such data would provide important insight into the broader consequences of critical illness in this population. The study lacked detailed information on cancer-directed therapies—such as chemotherapy, immunotherapy, or targeted treatments—which may have influenced both the severity of illness at admission and overall survival in the ICU. Finally, standardized performance status or frailty measures (e.g., ECOG, Karnofsky, or clinical frailty scale) were not consistently available due to the retrospective design and therefore could not be analyzed, which may have influenced the interpretation of outcomes.

Conclusion

Our study highlights the high mortality rate among ICU patients with lung cancer, with metastatic disease and disease severity serving as significant prognostic factors. Early recognition of these factors and careful consideration of the potential benefits and limitations of ICU interventions are crucial for optimizing patient care.

Ethics Committee Approval: Ethics committee approval was

obtained from University of Health Sciences, Dr. Suat Seren Chest Disease and Thoracic Surgery Teaching and Research Hospital Clinical Research Ethics Committee (Approval Number: 2023/29-38, Date: 06.06.2023).

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ORIGINAL INVESTIGATION

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Ultrasound-Based Rectus Femoris and Parasternal Intercostal Muscle Thickness and Weaning Outcomes in Critically Ill Patients

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Abstract

Aim: To investigate the association between ultrasound-derived rectus femoris and parasternal intercostal muscle thickness and weaning outcomes in mechanically ventilated, critically ill patients, as well as their relationship with post-extubation non-invasive mechanical ventilation requirements and 28-day mortality.

Study Design: This prospective observational study included 69 mechanically ventilated adult patients undergoing spontaneous breathing trials in a medical intensive care unit. Demographic characteristics, clinical severity scores (modified Nutrition Risk in the Critically Ill [modified NUTRIC] score, Acute Physiology and Chronic Health Evaluation II [APACHE II], Sequential Organ Failure Assessment [SOFA], and Clinical Frailty Scale [CFS]), and ultrasonographic measurements of rectus femoris and parasternal intercostal muscle thickness were obtained at the 30th minute of the spontaneous breathing trial. Patients were classified into weaning success or failure groups based on the absence or presence of reintubation or death within seven days after extubation.

Results: The mean rectus femoris thickness was 6.93±2.31 mm in the weaning success group and 5.96±2.41 mm in the weaning failure group ($p>0.05$). Parasternal intercostal muscle thickness was 4.49±1.25 mm and 4.18±1.48 mm in the respective groups ($p>0.05$). Muscle thickness was not associated with weaning success; however, both rectus femoris and parasternal intercostal muscle thicknesses were significantly lower in non-survivors compared with survivors at 28 days. Reduced rectus femoris thickness was also associated with an increased requirement for post-extubation non-invasive mechanical ventilation. In addition, higher modified NUTRIC scores were associated with both weaning failure and 28-day mortality.

Conclusions: Ultrasound-based muscle thickness alone was not associated with weaning success; however, reduced rectus femoris and parasternal intercostal muscle thickness were associated with 28-day mortality and an increased requirement for post-extubation non-invasive mechanical ventilation. These findings suggest that ultrasound-based muscle assessment may provide useful prognostic insights for risk stratification in critically ill patients. Further multicenter studies are needed to validate standardized cut-off values and enhance clinical applicability.

Keywords: Critical illness; mechanical ventilation; mNUTRIC score; muscle thickness; parasternal intercostal; rectus femoris; sarcopenia; ultrasonography; weaning.

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Introduction

Liberation from mechanical ventilation represents a pivotal transition in the management of critically ill patients; however, failure to achieve successful discontinuation remains common, occurring in nearly one-quarter of cases, depending on the study population and the definitions used.[1,2] Unsuccessful weaning is associated with prolonged intensive care unit (ICU) stay, increased complications, and substantial mortality.[3] Although multiple physiological determinants influence weaning outcomes, respiratory muscle function and overall skeletal muscle integrity are among the most critical factors.[4]

ICU-acquired weakness and sarcopenia develop early during critical illness as a consequence of systemic inflammation, immobility, suboptimal nutrition, and multiorgan dysfunction.[5] These processes contribute to the rapid loss of both peripheral and respiratory muscle mass, frequently resulting in diaphragmatic dysfunction and subsequent difficulty in achieving ventilator independence.[6] Traditional indices such as the rapid shallow breathing index (RSBI) provide only modest predictive accuracy.[7] In contrast, diaphragm ultrasonography, despite its increasing use, remains limited by operator dependency, technical variability, and inconsistent cutoff values across heterogeneous ICU cohorts.[8]

Consequently, attention has shifted toward the evaluation of peripheral and accessory respiratory muscles. The rectus femoris is a major locomotor muscle that is highly susceptible to systemic muscle wasting, whereas the parasternal intercostals contribute directly to inspiratory effort and may reflect respiratory load. Both muscle groups can be assessed reproducibly at the bedside using ultrasonography. Previous research has shown associations between rectus femoris thickness and cross-sectional area and muscle strength, prolonged mechanical ventilation, and mortality.[9,10] Similarly, increased parasternal intercostal activity has been linked to diaphragmatic dysfunction and adverse respiratory outcomes.[11]

Ultrasound-based muscle evaluation provides a practical, repeatable, and radiation-free alternative to imaging modalities such as computed tomography and magnetic resonance imaging, while also offering patient-specific information relevant to clinical decision-making.[12] Beyond quantifying muscle mass, ultrasonography may improve early risk stratification in mechanically ventilated patients.

Based on this rationale, we hypothesized that reduced peripheral and respiratory muscle thickness would be associated with weaning difficulty and adverse short-term outcomes. Accordingly, this study aimed to investigate the association between rectus femoris and parasternal intercostal muscle thickness and weaning success, post-extubation non-invasive mechanical ventilation requirements, and 28-day mortality among critically ill patients receiving mechanical ventilation.

Materials and Methods

Study Design and Patient Population

This prospective observational study included all intubated adults (≥18 years) admitted to the Medical Intensive Care Unit (ICU) of Marmara University School of Medicine between August 2024 and May 2025. In mechanically ventilated patients with an inspired oxygen fraction (FiO_2)<50%, positive end-expiratory pressure (PEEP)≤5 cmH_2O, no vasopressor requirement or norepinephrine<0.2 $\mu g/kg/min$, and a rapid shallow breathing index (RSBI)<105, daily spontaneous breathing trials (SBTs) were performed to assess readiness for liberation from mechanical ventilation.

Weaning Protocol

Eligible patients underwent spontaneous breathing trials using either pressure support ventilation with a pressure support of 7 cmH_2O and a positive end-expiratory pressure of 5 cmH_2O, or a T-piece system delivering supplemental oxygen without pressure support. Each spontaneous breathing trial was conducted for 30 minutes. The choice of spontaneous breathing trial modality was left to the discretion of the treating clinician, based on patient characteristics and clinical judgment, as both approaches are routinely used in daily practice and recommended by current weaning guidelines. Patients who fulfilled the predefined spontaneous breathing trial success criteria were extubated and considered weaned.

Successful weaning was defined according to established criteria: extubation without death or reintubation within the subsequent 7 days (regardless of whether post-extubation non-invasive ventilation was applied), or discharge from the ICU without invasive mechanical ventilation within 7 days, whichever occurred first. This standardized definition ensured consistency in outcome assessment and allowed reliable comparison with prior studies.[13]

Patients were categorized into weaning success and weaning failure groups based on the occurrence of reintubation or death within 7 days after extubation.

Post-extubation non-invasive mechanical ventilation (NIMV) was initiated in patients who developed signs of respiratory distress after extubation, including increased work of breathing, tachypnea, hypercapnia, or hypoxemia despite conventional oxygen therapy.

Ultrasound Assessment

Ultrasound measurements of rectus femoris and parasternal intercostal muscle thickness were obtained at the 30th minute of the spontaneous breathing trial. All examinations were performed using an Esaote MyLab™ Seven device by a single intensivist with formal certification in critical care ultrasonography, more than five years of experience, and active involvement in ultrasound training programs, thereby ensuring consistency and minimizing interobserver variability. Measurements were performed with patients in the supine position and with the head of the bed elevated to approximately 30°. For rectus femoris assessment, the lower extremities were positioned in passive extension and neutral rotation. A high-frequency linear transducer (7–13 MHz) was used for all measurements, and care was taken to avoid excessive probe pressure to prevent muscle compression. Measurements were obtained on the right side only for both the rectus femoris and parasternal intercostal muscles to enhance procedural standardization and feasibility in the critical care setting.

All ultrasound measurements were obtained during the spontaneous breathing trial under standardized ventilatory conditions. At the time of ultrasonographic assessment, patients were either breathing through a T-piece without pressure support or receiving pressure support ventilation with a pressure support level of 7 cmH_2O and a positive end-expiratory pressure of 5 cmH_2O, in accordance with the study protocol. All patients met the predefined criteria for spontaneous breathing trials, including an inspired oxygen fraction below 50%.

Rectus Femoris Measurement

A straight line was drawn between the anterior inferior iliac spine (AIIS) and the superior border of the patella. Using a high-frequency linear transducer in B-mode, measurements were obtained at the midpoint of this line. Each measurement was performed three times, and the mean value was recorded.[14]

Parasternal Intercostal Measurement

The probe was positioned at the right second intercostal space, 6–8 cm lateral to the sternal border. With a high-frequency linear transducer held longitudinally in B-mode, parasternal thickness was measured at the thickest point of the mid-portion of the muscle. Each measurement was repeated three times, and the average value was used for analysis.[15]

Sample Size and Power Analysis

Prior to data collection, an a priori power analysis was performed using G*Power (version 3.1.9.7). The calculation was based on the primary comparison between patients with weaning success and weaning failure in terms of rectus femoris muscle thickness. Assuming a two-sided α of 0.05, 80% power, and a moderate effect size (Cohen's d=0.5), the required sample size was estimated to be 55 participants, assuming approximately equal group allocation. In the absence of well-established reference values for this population, a moderate effect size was selected a priori as a pragmatic assumption for sample size estimation. To account for potential exclusions and missing data, a higher enrollment target was planned. The final analyzable cohort consisted of 69 patients, exceeding the minimum requirement and maintaining at least 80% statistical power for the primary comparison.

Variables Assessed

The following parameters were collected: demographic variables (age, sex), comorbidities, body mass index (BMI), Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores assessed at ICU admission and at the time of weaning; modified Nutrition Risk in the Critically Ill (modified NUTRIC) score and Clinical Frailty Scale (CFS) assessed at ICU admission; Charlson Comorbidity Index; reason for ICU admission; rectus femoris and parasternal intercostal muscle thickness; serum albumin level at hospital admission; ICU length of stay; 28-day mortality; requirement for post-extubation NIMV or high-flow nasal cannula (HFNC); and weaning outcome.

Severity and nutritional risk scores were calculated according to previously validated definitions.[16,17,19]

Sepsis was defined as sepsis present at ICU admission, in accordance with the Sepsis-3 criteria, i.e., suspected or documented infection accompanied by an acute increase of ≥2 points in the SOFA score.[18]

Frailty was assessed using the CFS, a 9-point scale that

evaluates baseline functional status prior to acute illness, with higher scores indicating greater frailty, as originally described by Rockwood et al.[20]

The primary outcome of the study was weaning success or failure. Secondary outcomes included post-extubation non-invasive ventilation requirement and 28-day mortality.

Twenty-eight-day mortality was defined as death from any cause occurring within 28 days following extubation. Mortality data were obtained from the hospital electronic medical record system and, when applicable, verified using the national death registry.

Eligibility Criteria

Patients were eligible for inclusion if they were admitted to the Medical Intensive Care Unit of Marmara University School of Medicine, were aged ≥18 years, and had received invasive mechanical ventilation for at least 24 hours. Patients were excluded if they had been intubated for more than 24 hours prior to ICU admission, experienced self-extubation, received neuromuscular blocking agents during the ICU stay, declined participation, had a history of endotracheal intubation within the preceding 6 months, or had a tracheostomy in place before or performed during the study period. The process of patient screening, enrollment, and exclusion is summarized in the flow diagram presented in Figure 1.

Ethics Approval

This study was approved by the Marmara University School of Medicine Clinical Research Ethics Committee (Approval Number: 09.2024.749; Date: 19.07.2024). Written informed consent was obtained from the legally authorized representatives of all included patients. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

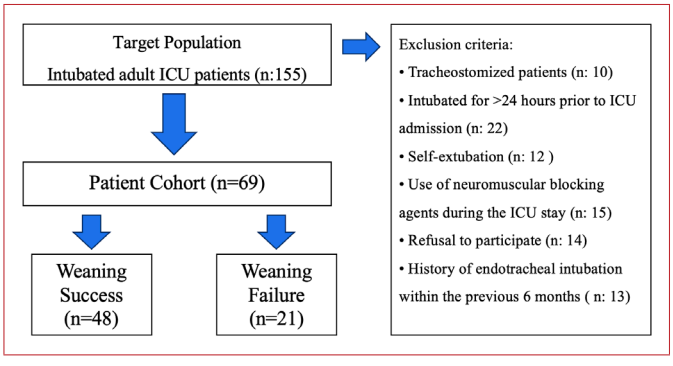

Figure 1. Flow diagram of the study enrollment process.

Statistical Analysis

All statistical analyses, data management, visualization, and reporting were performed using R software (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria). The R6 package was used to create reusable object-oriented structures that supported modular and flexible analytical workflows, rstatix facilitated the streamlined execution of statistical tests, and flextable was used to generate publication-ready summary tables formatted according to journal standards.

Numerical variables were first assessed for normality using the Shapiro–Wilk test, after which appropriate statistical methods were selected based on distributional characteristics. For normally distributed variables, comparisons between two groups were performed using the independent-samples t-test, and one-way analysis of variance (ANOVA) was used for comparisons involving more than two groups. For non-normally distributed variables, the Wilcoxon rank-sum test was used for two-group comparisons, and the Kruskal–Wallis test was used for comparisons involving more than two groups.

Categorical variables were analyzed using Pearson's chi-square test when expected cell counts were ≥5; otherwise, Fisher's exact test was applied.

Correlation analyses were conducted to evaluate associations between continuous variables. Pearson's correlation coefficient was used for normally distributed variables with linear relationships, whereas Spearman's rank correlation coefficient or Kendall's tau was preferred for non-normal distributions, monotonic associations, or small sample sizes (<30).

RESULTS

A total of 69 patients were included in the analysis, of whom 41 (59.4%) were male, with a median age of 73 years (IQR: 66–79). The most common comorbidities were hypertension (49.3%), diabetes mellitus (37.7%), and chronic obstructive pulmonary disease (COPD) (26.1%). Pulmonary causes constituted the leading reason for ICU admission (62.3%) and included acute exacerbation of COPD, community-acquired pneumonia, hospital-acquired pneumonia, acute respiratory distress syndrome, and other acute respiratory conditions. Postoperative conditions accounted for 17.4% of admissions, while cardiovascular diseases represented 10.1%. COPD was recorded both as a comorbidity and, when applica-

ble, as the primary reason for ICU admission, and was additionally reported as a separate category because of its clinical relevance and high prevalence in the study population. The median ICU length of stay was 13 days (IQR: 8–23). Baseline demographic, clinical, and ultrasonographic characteristics stratified by weaning outcome are summarized in Table 1.

Following spontaneous breathing trials and subsequent extubation, patients were monitored for 7 days. During this period, 21 patients (30.4%) experienced weaning failure, whereas 48 patients (69.6%) were successfully weaned. At 28 days following extubation, 24 patients (34.8%) had died, while 45 patients (65.2%) remained alive. Twenty-eight-day mortality was assessed as a secondary outcome and was defined independently of weaning success or failure.

The mean rectus femoris muscle thickness in the overall cohort was 6.63±2.37 mm. Rectus femoris thickness did not differ significantly between patients with successful and failed weaning (6.93±2.31 mm vs. 5.96±2.41 mm, respectively; p=0.116). Similarly, parasternal intercostal muscle thickness was comparable between the weaning success and failure groups (4.49±1.25 mm vs. 4.18±1.48 mm, respectively; p=0.369). These findings indicate that static measurements of peripheral and accessory respiratory muscle thickness were not associated with short-term weaning outcomes (Table 1).

In contrast, both rectus femoris and parasternal intercostal muscle thickness were significantly lower in non-survivors compared with survivors at 28 days. Mean parasternal intercostal muscle thickness was 4.65±1.35 mm in survivors and 3.92±1.13 mm in non-survivors (p=0.027). Likewise, rectus femoris muscle thickness was significantly reduced in non-survivors compared with survivors (5.50±1.62 mm vs. 7.24±2.49 mm, respectively; p=0.003). These results are presented in Table 2.

Table 1. Baseline demographic, clinical, and ultrasonographic characteristics of the study population according to weaning outcome

	All patients (n=69)	Weaning success (n=48)	Weaning failure (n=21)	p
Demographic and baseline clinical characteristics				
Age, years, median (IQR)	73 (66–79)	72 (65–78)	75 (67–81)	0.258
Male sex, n (%)	41 (59.4)	27 (56.3)	14 (66.7)	0.41
BMI, mean±SD	24.7±4.2	24.6±4.1	24.9±4.3	0.43
Reasons for ICU admission, n (%)				
Pulmonary cause of ICU admission	43 (62.3)	30 (62.5)	13 (61.9)	0.85
Sepsis at ICU admission	12 (17.4)	7 (14.6)	5 (23.8)	0.36
Comorbidities, n (%)				
Malignancy	16 (23.2)	9 (18.8)	7 (33.3)	0.18
Chronic obstructive pulmonary disease (COPD)	18 (26.1)	12 (25.0)	6 (28.6)	0.72
Chronic kidney disease	11 (15.9)	7 (14.6)	4 (19.0)	0.63
Severity, frailty, and nutritional risk scores				
SOFA score, median (IQR)	6 (3–8)	5 (3–6.25)	8 (6–10)	0.006
APACHE II score, median (IQR)	12 (9–20)	12 (7–16.25)	19 (12–30)	0.006
Modified NUTRIC score, median (IQR)	4 (3–6)	4 (3–5)	6 (5–7)	<0.001
Clinical Frailty Scale score, median (IQR)	6 (4–7)	5 (3–7)	6 (4–7)	0.19
Charlson Comorbidity Index, median (IQR)	6 (4–8)	6 (3.75–8)	6 (4–8)	0.53
ICU course and ultrasonographic measurements				
ICU length of stay, days, mean±SD	15.9±9.6	15.3±8.9	16.9±10.7	0.60
Rectus femoris thickness, mm, mean±SD	6.63±2.37	6.93±2.31	5.96±2.41	0.116
Parasternal intercostal thickness, mm, mean±SD	4.40±1.32	4.49±1.25	4.18±1.48	0.369

BMI: body mass index; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II; COPD: Chronic obstructive pulmonary disease; NUTRIC: Nutrition Risk in the Critically Ill; ICU: intensive care unit.

Table 2. Relationship between muscle thickness and 28-day mortality

	All patients (n=69)	Survivors (n=45)	Non-survivors (n=24)	p
Parasternal intercostal muscle thickness, mm, mean±SD	4.40±1.32	4.65±1.35	3.92±1.13	0.027
Rectus femoris muscle thickness, mm, mean±SD	6.63±2.37	7.24±2.49	5.50±1.62	0.003

RF: rectus femoris; PI: parasternal intercostal.

Correlation analyses further characterized the relationships between muscle thickness and clinical variables. Parasternal intercostal muscle thickness demonstrated a weak positive correlation with body mass index (ρ=0.328, p=0.006) and weak negative correlations with frailty score (ρ=–0.287, p=0.017) and 28-day mortality (ρ=–0.261, p=0.031). No significant association was observed between parasternal intercostal muscle thickness and the modified NUTRIC score. Rectus femoris muscle thickness showed a moderate positive correlation with body mass index (ρ=0.418, p<0.001) and a moderate negative correlation with frailty score (ρ=–0.392, p=0.001). In addition, rectus femoris thickness demonstrated a weak negative correlation with 28-day mortality (ρ=–0.334, p=0.005). No significant correlations were observed between rectus femoris thickness and ICU length of stay, hospital length of stay, SOFA score, APACHE II score, or Charlson Comorbidity Index. Correlation analyses are summarized in Table 3.

Post-extubation non-invasive mechanical ventilation was required in a subset of patients following weaning. Rectus femoris muscle thickness was significantly lower in patients who required post-extubation NIMV compared with those who did not (5.60±2.11 mm vs. 6.97±2.37 mm, respectively; p=0.037). In contrast, parasternal intercostal muscle thickness did not differ significantly between patients who required NIMV and those who did not (4.23±0.87 mm vs. 4.45±1.44 mm, respectively; p=0.566). These findings are shown in Table 4. High-flow nasal cannula was used as post-extubation respiratory support in a limited number of patients; however, due to the small sample size, these patients were not analyzed as a separate subgroup.

Table 3. Correlation between muscle thickness and clinical parameters

Parameter	Parasternal intercostal thickness (r)	p	Rectus femoris thickness (r)	p
ICU length of stay, days	-0.102	0.404	-0.105	0.388
SOFA score	0.027	0.825	-0.065	0.594
Charlson Comorbidity Index	-0.213	0.079	-0.146	0.231
Body mass index	0.328	0.006	0.418	<0.001
Modified NUTRIC score	-0.167	0.169	-0.230	0.057
APACHE II score at weaning	0.029	0.811	-0.177	0.145
APACHE II score at admission	0.021	0.845	-0.026	0.830
Clinical Frailty Scale score	-0.287	0.017	-0.392	0.001
28-day mortality	-0.261	0.031	-0.334	0.005

SOFA: Sequential Organ Failure Assessment; BMI: body mass index; APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU: intensive care unit , mNUTRIC: modified Nutrition Risk in the Critically Ill score; RF: rectus femoris; PI: parasternal intercostal.

Table 4. Relationship between muscle thickness measurements and post-weaning NIMV requirement

	All patients (n=69)	No NIMV requirement (n=52)	NIMV requirement (n=17)	p
Parasternal intercostal muscle thickness, mm, mean±SD	4.40±1.32	4.45±1.44	4.23±0.87	0.566
Rectus femoris muscle thickness, mm, mean±SD	6.63±2.37	6.97±2.37	5.60±2.11	0.037

RF: rectus femoris; PI: parasternal intercostal; NIMV: non-invasive mechanical ventilation.

Discussion

In this prospective observational study, we investigated whether ultrasound-derived measurements of rectus femoris and parasternal intercostal muscle thickness were associated with weaning outcomes and short-term prognosis in mechanically ventilated, critically ill patients. Our results demonstrate that, while static muscle thickness measurements were not predictive of weaning success, reduced rectus femoris thickness was significantly associated with both an increased requirement for post-extubation NIMV and higher 28-day mortality. These findings suggest that peripheral and accessory respiratory muscle depletion, detectable through bedside ultrasonography, reflects global physiological vulnerability rather than immediate weaning performance.

Weaning failure remains a multifactorial clinical challenge, affecting approximately one-quarter of critically ill patients despite the implementation of structured weaning protocols.[1–3,13] Among the physiological determinants of weaning outcomes, respiratory muscle dysfunction, particularly ventilator-induced diaphragmatic atrophy, is well recognized.[4,6,8] However, diaphragm ultrasonography is limited by operator dependency, technical variability, and the absence of universally accepted cutoff values.[8] These limitations have led to increasing interest in alternative ultrasound-based indices that may better reflect overall muscle health and physiological reserve.

ICU-acquired weakness and sarcopenia develop rapidly during critical illness as a consequence of systemic inflammation, immobility, and inadequate nutritional intake.[5,10] Muscle mass loss may exceed 20% within the first week of ICU admission.[10] This loss affects both locomotor and respiratory muscles and contributes to impaired ventilatory mechanics and persistent respiratory insufficiency.[9–11] The rectus femoris, as a large and metabolically active locomotor muscle, has been proposed as a reliable surrogate marker of global muscle wasting.[14] In contrast, the parasternal intercostal muscles contribute directly to inspiratory effort and may become increasingly recruited when diaphragmatic function is compromised.[11,15]

In our cohort, neither rectus femoris nor parasternal intercostal muscle thickness discriminated between successful and failed weaning. This finding is consistent with previous studies demonstrating that single, static muscle measurements have limited predictive value for extubation readiness.[21,22] Weaning and extubation outcomes are influenced by multiple factors beyond muscle mass, including airway protection, secretion clearance, cardiovascular reserve, and the occurrence of unexpected post-extubation complications, none of which are captured by static ultrasound measurements alone.

The very low mean rectus femoris thickness observed in our study population (6.63 mm), which is substantially below the sarcopenia screening thresholds reported in prior studies (typically 11–16 mm depending on age and sex), likely reflects the advanced age and substantial disease burden of our cohort.[14–21] Furthermore, thickness-based assessments may underestimate the true extent of muscle atrophy compared with cross-sectional area measurements and may not fully reflect functional impairment or contractile capacity.[23,24] These methodological considerations may partly explain why static muscle thickness failed to differentiate weaning success from failure.

Similarly, static parasternal intercostal muscle thickness was not associated with weaning outcomes or post-extubation NIMV requirement in our cohort. Previous investigations suggest that dynamic parasternal measurements, particularly the thickening fraction, are more closely linked to respiratory load and adverse outcomes than static thickness alone.[15,25] The parasternal muscles are small, anatomically constrained by rib shadowing, and lack validated reference values, all of which may limit the sensitivity of static measurements. Dynamic indices may therefore offer superior prognostic value and warrant further investigation.[26]

In contrast to weaning outcomes, both rectus femoris and parasternal intercostal muscle thickness demonstrated significant inverse associations with 28-day mortality. These findings align with extensive literature identifying skeletal muscle mass as a robust predictor of mortality in critically ill patients.[10,14,23] Muscle depletion reflects global catabolism, systemic inflammation, and metabolic exhaustion, which collectively reduce physiological reserve and impair the ability to adapt to acute stressors.[26] In this context, ultrasound-based muscle assessment may serve as a practical bedside tool for the early identification of high-risk patients, particularly older adults who are more susceptible to sarcopenia-related adverse outcomes.

A clinically meaningful finding of our study was the association between reduced rectus femoris thickness and an increased post-extubation NIMV requirement.

Non-invasive mechanical ventilation has been shown to reduce the risk of post-extubation respiratory failure in selected patients.[27,28] This is particularly relevant for those with advanced age, comorbidities, high illness severity, or respiratory muscle impairment.[29,30] In our cohort, diminished rectus femoris thickness may reflect generalized muscle weakness, reduced cough effectiveness, and limited respiratory reserve, thereby explaining the increased reliance on NIMV following extubation.

To further explore this observation, we performed a secondary analysis in which post-extubation NIMV requirement was reclassified as a form of weaning difficulty. This approach revealed stronger associations between muscle weakness and adverse outcomes, suggesting that NIMV requirement may represent an intermediate phenotype between successful weaning and overt weaning failure. Although the Weaning according to a New Definition (WIND) classification does not define NIMV use as weaning failure unless reintubation or death occurs within seven days,[13] accumulating evidence indicates that patients requiring NIMV after extubation remain at increased risk of clinical deterioration.[31,32] Future studies should evaluate whether incorporating post-extubation NIMV requirement into weaning outcome definitions improves prognostic stratification and clinical decision-making.

Limitations

This study has several limitations. It was conducted at a single center, which may limit the generalizability of the findings. Ultrasound assessments were performed at a single time point and did not include dynamic measurements such as diaphragm or parasternal intercostal thickening fractions. In addition, receiver operating characteristic analyses and cutoff values were not determined, as the study was not designed to derive or validate diagnostic thresholds. Given the relatively small sample size and limited number of outcome events, such analyses would carry a substantial risk of overfitting and have limited external validity. Finally, the duration of invasive mechanical ventilation was not systematically recorded and therefore could not be included in the analysis.

Conclusion

Although rectus femoris and parasternal intercostal muscle thickness did not predict weaning success, reduced rectus femoris thickness was associated with an increased requirement for post-extubation non-invasive mechanical ventilation, and both muscle groups demonstrated significant negative associations with 28-day mortality. These findings suggest that ultrasound-based skeletal muscle assessment may provide valuable prognostic information in critically ill patients beyond conventional weaning outcomes. Incorporating post-extubation non-invasive mechanical ventilation requirement into the evaluation of weaning outcomes may improve risk stratification. Future multicenter studies are warranted to validate these findings and establish standardized cutoff values and dynamic muscle indices to enhance clinical applicability.

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Cranial Nerve Involvement and Thalamic Lesions in West Nile Virus Encephalitis in a Kidney Transplant Recipient: Implications for Diagnosis and Prevention

Faruk Yildiz,[1] Volkan Inal[2]

To the Editor,

We read with great interest the case report by Gorgulu et al.,[1] titled "West Nile Virus Encephalitis in a Kidney Transplant Patient," published in the *Journal of Critical and Intensive Care* 2025;16(3):138–141. The authors describe a rare case of West Nile virus (WNV) encephalitis in an immunosuppressed kidney transplant recipient who presented with fever, altered mental status, and progressive neurological deterioration. This report contributes significantly to the Turkish intensive care literature by illustrating the diagnostic challenges in immunosuppressed patients and the high mortality risk of neuroinvasive WNV disease.[1]

The most notable feature of this case is the simultaneous presence of bilateral thalamic lesions and contrast enhancement in the cisternal segments of the right trigeminal nerve and bilateral oculomotor nerves on MRI. While thalamic and basal ganglia hyperintensities are well recognized in WNV encephalitis, their combination with cranial nerve involvement—particularly of the trigeminal and oculomotor nerves—is rarely highlighted in the imaging literature. Although cranial nerve neuropathies (e.g., facial or abducens) have been reported in neuroinvasive WNV,[2] the specific pattern of cisternal enhancement involving the trigeminal and oculomotor nerves, alongside thalamic lesions, appears to be uncommon. In immunosuppressed hosts, this pattern may reflect meningoencephalitis with perineural spread and could serve as a highly suggestive radiological marker of WNV infection. This observation warrants validation in larger multicenter case series of immunocompromised patients.

Additionally, the occurrence of infection 36 months after transplantation further supports the possibility of donor-derived or transfusion-transmitted WNV.[3] Türkiye experienced its largest WNV outbreak in 2024, with 51 cases reported in a multicenter series and a case fatality rate of 17.6% (all fatal cases involved advanced age and comorbidities).[4] Given Türkiye's endemic status and the increasing number of cases reported across Europe, routine WNV screening for organ donors and recipients remains nonstandard.[3,4] This case highlights the urgent need for a practical diagnostic algorithm: WNV PCR in cere-

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brospinal fluid should be routinely included in the meningoencephalitis panel for all immunosuppressed patients presenting with fever and altered consciousness, irrespective of season, and should be accompanied by prompt reduction of immunosuppression when indicated.[5]

We commend the authors for this insightful and unusual case report. Their findings emphasize the importance of reviewing WNV screening protocols in transplant centers and raising awareness of atypical radiological patterns in neuroinvasive viral infections among immunosuppressed patients. Multicenter prospective studies are necessary to enhance both diagnostic and preventive strategies.

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