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Prognostic factors in intensive care unit patients with ventilator-associated pneumonia: the role of comorbidity and clinical severity scores

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ABSTRACT

Aims: The objective of this study is to ascertain patient and other related characteristics, such as body-mass index (BMI) and comorbidities, that may be associated with prognosis in patients with ventilator-associated pneumonia (VAP) in the Anaesthesia Intensive Care Units (ICU) of Akdeniz University.

Methods: It was designed as a retrospective cohort study in which patients with a diagnosis of VAP in the ICU was included. The demographic and clinical data obtained and analysed were age, gender, comorbidities, BMI, Charlson Comorbidity Index (CCI) and the reason for admission to the ICU. The clinical severity of patients was determined by the Acute Physiology and Chronic Health Evaluation-II (APACHE II) score and the Sequential Organ Failure Assessment (SOFA) score.

Results: The study comprised of 111 patients diagnosed with VAP. The overall ICU mortality in VAP patients was 64%, and the 28-day ICU mortality was 55%. A number of factors have been identified as being independently associated with mortality in the studied cohort. These factors include increasing age, SOFA score on the day of VAP and the presence of chronic corticosteroid use.

Conclusion: VAP remains a significant problem in ICUs, and mortality is a major issue in these patients. The implementation of more effective control measures is of great importance. Among all the variables studied, age and SOFA score demonstrated the most consistent and statistically significant discriminatory power.

Keywords: Intensive care unit, mortality, ventilator associated pneumonia

INTRODUCTION

The most significant cause of nosocomial pneumonia is the use of intubation and mechanical ventilation in patients. Ventilator-associated pneumonia (VAP) is defined as pneumonia that develops 48 hours after the initiation of mechanical ventilation in intubated patients.[1] VAP is the most prevalent nosocomial infection in intensive care units (ICUs), with a consequential impact on hospital costs due to prolonged mechanical ventilation and hospitalisation.[2] The frequency of VAP is subject to variation between studies, with reported values ranging from 4.5 to 75.5 per 1.000 ventilator days.[3] The development of VAP occurs in 8% to 28% of patients receiving mechanical ventilation, with mortality ranging from 19.4% to 53%.[1,4,5] In ICUs where multiple antibiotic resistance is present, the frequency can rise to as high as 76%.[1] The initial clinical observations included fever, purulent tracheal secretions, leukocytosis, impaired pulmonary gas exchange, and the development of new pulmonary infiltrates.[6] Significant variations in the frequency of ICU may be attributable to the nature of intensive care itself and the characteristics of the personnel providing treatment services. However, despite the widespread availability of advanced healthcare facilities, the establishment of specialised ICUs, the introduction of organ support systems, and even the development of extracorporeal membrane oxygenation (ECMO) systems, the incidence of pneumonia among lung-related deaths continues to rise each year. Thus, the patient's comorbidities, acute pathologies leading to intensive care admission (e.g. burns, trauma), and organ failure caused by the pathophysiological condition (e.g. acute respiratory distress syndrome "ARDS", etc.) also influence the frequency, prognosis, mortality, and treatment processes of VAP.[7] It has been documented that elevated Acute Physiology and Chronic Health Assessment (APACHE II) scores, Sequential Organ Failure Assessment (SOFA) scores, and Charlson Comorbidity Index (CCI) scores have been shown to be associated with an increased mortality in cases of VAP.[3,8] Similarly, patients aged 75 years or older residing in nursing homes, bedridden, cachectic, with dementia or psychiatric disorders, cerebrovascular/chronic renal/ischaemic heart disease, metastatic tumours and/or lung cancer, and receiving immunosuppressive therapy have

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been shown to have a high risk of death from pneumonia.[7] Furthermore, the microbiological and pathophysiological activity characteristics of the etiological agent (multiple antibiotic resistance, cavitary and multilobular involvement, rapidly progressing pulmonary infiltrates) are also among the factors that may affect mortality.[9]

It is evident that a comprehensive understanding of prognostic risk factors associated with patients and pathogens in the development of VAP may prove effective in reducing morbidity and mortality. The objective of this study is to ascertain patient and other related characteristics, such as body-mass index (BMI) and comorbidities, that may be associated with prognosis in patients with VAP in the Anaesthesia ICUs of Akdeniz University.

METHODS

A retrospective cohort study was conducted in the 33-bed general ICUs of Akdeniz University Faculty of Medicine Hospital, Antalya, Turkiye. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee for Medical Scientific Researches at Akdeniz University (Date: 31.07.2025, Decision No: TBAEK-669). The sample consists of patients aged 18 years and older who were monitored for a minimum of 48 hours on a mechanical ventilator in the ICU between 1 March 2024 and 31 December 2024 and subsequently developed VAP with a positive tracheal aspirate culture. The data of the patients was retrieved from two distinct sources: patient observation files and a hospital information system database. Due to the retrospective nature of the study, the requirement for informed consent was waived. The investigators analysed only anonymised data. As the study was retrospective, the analyses were performed only after ethical committee approval had been obtained.

According to the 2016 ATS/IDSA guidelines, VAP is defined as pneumonia occurring 48 hours after endotracheal intubation.[6] In order to diagnose VAP in accordance with this definition, the following criteria must be met: the condition must develop at least 48 hours after intubation, and a chest X-ray must show new or progressive infiltrates. Furthermore, at least two of the following criteria must be present. The first condition is an increase in body temperature above 38°C. The second is an increase in leukocytes above 10×10^9/L or a decrease below 4×10^9/L. The third is the presence of a purulent tracheal aspirate, defined as a leukocyte count greater than 25 per high-power field (HPF). The fourth is impaired pulmonary gas exchange. In addition to the VAP clinical diagnosis mentioned above, patients with bacterial growth in tracheal aspirate culture were included in the study.[10] Tracheal aspirates were collected under aseptic conditions using sterile suction catheters and immediately transported to the microbiology laboratory. Quantitative culture techniques were performed, and a bacterial growth threshold of $\geq10^5$ colony-forming units (CFU)/ml was considered diagnostic for VAP. Microorganisms were identified, and antimicrobial susceptibility testing was performed using an automated system (VITEK 2, bioMérieux, France). Results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[6,11]

The initial admissions of patients admitted to the ICU were included in the study, with readmissions excluded from the analysis. Patients who had spent ≤48 hours in the ICU and those who had been transferred to another centre were excluded from the study. Furthermore, patients under 18 years of age, patients intubated in the acute pulmonary oedema clinic, patients with a pre-intubation diagnosis of pneumonia, patients with a VAP diagnosis not confirmed by bacterial culture of tracheal aspirate, and patients with incomplete records were excluded from the study.

The demographic and clinical data obtained and analysed include age, gender, comorbidities, BMI, CCI, coronavirus disease-19 (COVID-19) status (current and past illness), hospitalisation status in the last year and in the last 3 months, and the reason for admission to the ICU The clinical severity of patients was determined by the Acute Physiology and Chronic Health Evaluation-II (APACHE II) score (at the time of ICU) and the SOFA score (24 hours before tracheal aspiration, on the day of aspiration, and on the day of discharge). The following parameters were analysed: mechanical ventilation parameters, central venous catheterisation procedures, inspired oxygen fraction (FiO_2) administered to the patient, arterial blood gas parameters during hospitalisation (arterial partial oxygen pressure, partial carbon dioxide pressure, bicarbonate, pH, lactate), and laboratory results indicating inflammatory response (serum C-reactive protein. Furthermore, comprehensive set of data was collected for analysis, encompassing various parameters such as procalcitonin levels, leukocyte counts, treatment modalities administered for infection (antibiotic therapy), immunosuppressive treatments (steroids, chemotherapeutic agents), mechanical ventilation, and duration of ICU stays. Additionally, mortality outcomes in patients were documented for further examination. In patients monitored in the ICU, the development of sepsis, septic shock, acute kidney injury (AKI), disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS) clinical conditions was also noted, and the relationship between these clinical conditions and VAP was investigated. The definitions of sepsis and septic shock were derived from the criteria set out in "The Third International Consensus Definitions for Sepsis and Septic Shock" (Sepsis-3).[12] The 2012 Berlin criteria were used for ARDS definition,[13] KDIGO criteria for AKI definition,[14] and the British Committee for Standards in Haematology criteria for DIC definition.[15]

Outcomes

The primary outcome of the study was overall ICU mortality. The secondary outcome was 28-day ICU mortality. Identifying associated factors and their predictive role in overall ICU mortality was defined as an exploratory objective.

Statistical Analysis

The data collected in the study were recorded by the principal investigator and subsequently transferred to the statistical software package SPSS version 31 (SPSS Inc., Chicago, Illinois, USA) for analysis. The data were expressed in both categorical and quantitative forms. Continuous variables were expressed

as mean±standard deviation or median values with minimum, maximum, and interquartile range (IQR). Categorical variables were expressed as number and percentage. The determination of normal distribution was evaluated using the Kolmogorov-Smirnov test, histogram graphs, and Q-Q plot graphs. Correlation relationships between numerical data were examined using two-tailed Pearson or Spearman correlation analyses. Independent t-tests or Mann-Whitney U tests were used for pairwise comparisons of independent groups. For comparisons involving multiple independent groups, the Kruskal-Wallis H test or ANOVA test was used. Relationships between categorical variables were analysed using Pearson's Chi-square analysis or Fisher's exact test. When appropriate, the Yates correction was applied. The predictive values, marker capabilities, and cut-off values of the parameters were obtained using ROC analysis. The stepwise combination of variables in terms of mortality was evaluated using ROC analysis to control the overall mortality predictive values. Univariate and multivariate binary logistic regression was performed to determine the effects of variables on mortality. Multicollinearity assumptions were evaluated using VIF (variance inflation factor) and condition index data. VIF ≥5, and a condition index ≥15 were considered as violation of the multicollinearity issue, and variables that violated the multicollinearity assumptions were excluded from the multivariate analysis. The multivariate logistic regression analyses were carried out taking the 10 EPV (Events Per Variable) rule into account, and the number of variables was modeled in light of this principle. In our study, the type I error rate was set at 5%, and p-values <0.05 were considered statistically significant.

RESULTS

During the study period, a total of 892 patients were admitted to the Anaesthesia and Intensive Care Units of Akdeniz University. Of these patients, 27 were under the age of 18, 338 had an ICU of less than 48 hours, and 153 patients remained in the ICU for more than 48 hours without intubation. Of the 374 patients who met the inclusion criteria, 147 developed VAP, as confirmed by the presence of pathogenic microorganisms in tracheal aspirate cultures. However, 29 of these patients were excluded from the study due to incomplete data in their files, and 7 were transferred to a different centre during treatment. In consideration of the extant data and a total of 4.495 ventilator days during the study period, the incidence of VAP was 32.7 per 1.000 ventilator days. The incidence density of VAP was calculated as the number of VAP episodes per 1.000 ventilator days, in accordance with the definitions established by the National Healthcare Safety Network.[16] The flow chart of the study is shown in **Figure 1**.

The general statistical distribution characteristics of quantitative parameters (age, gender, BMI, sepsis/septic shock processes, APACHE II-SOFA-CCI scores, mechanical ventilator and length of ICU stay and inflammation markers) in patients with VAP developing in the ICU were presented in **Table 1**. The comorbidities, steroid and immunosuppressive drug use in patients with VAP are presented in **Table 2**. The mean age of the patients was 59.3±19.7 years, the median BMI value was 24 kg/m^2 (minimum-maximum: 18–41), and

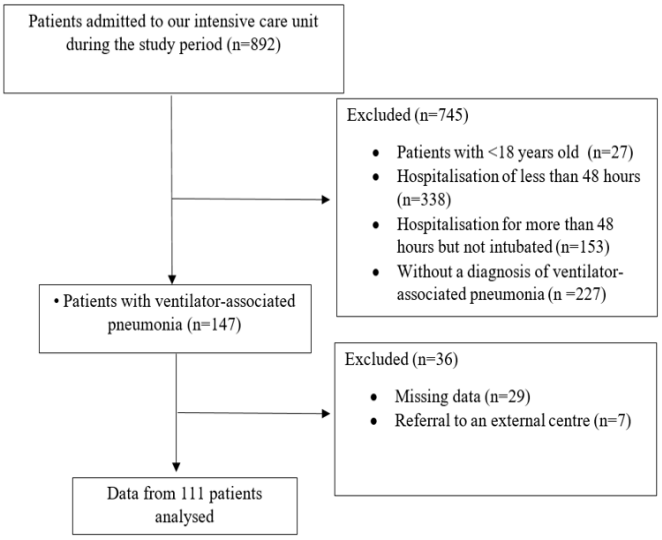


Figure 1. Flow diagram of the study

Table 1. General statistical distribution characteristics of quantitative parameters

Parameter	Minimum	Maximum	Distribution ¥
Age (years)	19	94	59.3±19.7
BMI (kg/m^2)	18	41	24 (18–41)
APACHE II	6	37	19.1±7.5
Charlson Comorbidity Index	0	21	5 (0–21)
Length of stay ICU (days)	3	127	16 (3–127)
Time from admission to infection (days)	2	60	6 (2–60)
The duration of central venous catheterisation (days)	0	16	9.3±2.5
Duration of mechanical ventilation (days)	3.0	119.0	12 (3–119)
Duration of mechanical ventilation up to nosocomial infection (days)	3	46	5 (3–46)
SOFA score 24 hours prior to VAP	3	15	7.2±2.5
SOFA on the day of VAP diagnosis	3	19	9.4±3.4
ICU discharge SOFA	0	23	12.2±6.3
Time from admission to the ICU to sepsis (days)	2	48	8 (2–48)
Time from admission to the ICU to septic shock (days)	1	58	11 (1–58)
Duration of septic shock (days)	0	15	3 (0–15)
WBC on the day of VAP diagnosis (×10^9/L)	0.02	47.87	12.5 (0.02–47.87)
CRP on the day of VAP diagnosis (mg/L)	1	471	130 (0.7–471)
PCT on the day of VAP diagnosis (µg/L)	0	100	0.8 (0–100)
Lactate on the day of VAP diagnosis (mmol/L)	0.14	10.56	1.52 (0.14–10.56)
pH on the day of VAP diagnosis	7.00	7.56	7.39 (7–7.56)
PaO_2/FiO_2 on the day of VAP diagnosis (mmhg/fraction)	35.0	425.0	167 (35–425)

Data are presented as mean±standard deviation, minimum maximum and interquartile range (IQR) or n (%). Abbreviations: ICU: Intensive care unit, APACHE II: Acute Physiological and Chronic Health Evaluation-II score, BMI: Body-mass index, SOFA: Sequential Organ Failure Assessment, VAP: Ventilator associated pneumonia, WBC: White blood cell, CRP: C-reactive protein, PCT: Procalcitonin, PaO2/FiO2: Partial oxygen pressure/ inspired oxygen fraction

Table 2. Statistical distribution characteristics of comorbid diseases and treatments in patients

		Frequency (n)	Percentage (%)
Gender	Female	39	35.1%
	Male	72	64.9%
Comorbidity	Yes	89	80.2%
	No	22	19.8%
Cardiovascular disease	Yes	40	36.0%
	No	71	64.0%
Chronic lung disease	Yes	28	25.2%
	No	83	74.8%
Diabetes mellitus	Yes	45	40.5%
	No	66	59.5%
Chronic kidney disease	Yes	12	10.8%
	No	99	89.2%
Chronic liver disease	Yes	4	3.6%
	No	107	96.4%
Cerebrovascular disease	Yes	36	32.4%
	No	75	67.6%
Solid organ malignancy	Yes	29	26.1%
	No	82	73.9%
Haematological malignancy	Yes	3	2.7%
	No	108	97.3%
Chronic corticosteroid use	Yes	32	28.8%
	No	79	71.2%
Immunosuppressive therapy	Yes	20	18.0%
	No	91	82.0%

80.2% had additional comorbidities. The most prevalent comorbid conditions identified were diabetes mellitus (40.5%), cardiovascular disease (including hypertension) (36%), cerebrovascular disease (32.4%), malignant neoplasms (26.1%), and chronic lung disease (25.2%). The CCI median value was 5 (0–21), and chronic corticosteroid use was present in 28.8% of patients. A total of 20 patients had a history of immunosuppressive therapy in the form of chemotherapy in the preceding 3 months. The majority of the sample (64.9%) consisted of male patients. The most prevalent reasons for admission to the ICU were acute respiratory failure (63%), trauma (18%), and shock (15.3%). The analysis revealed that 48.6% of the patients had a history of hospitalisation within the past 3 months, with the most common ICU admission departments being the emergency department (36%) and surgical departments (18.6%). Furthermore, 17.1% of the patients had previously experienced pneumonia due to the COVID-19. A total of 108 patients were subjected to the insertion of central venous catheters, with the mean duration of catheterisation being 9.3±2.5 days. The median time from admission to the onset of VAP was 6 days (range: 3-60 days), and the median duration of mechanical ventilation until the onset of VAP was 5 days (range: 3-46 days). Polymicrobial culture growth was observed in 61.3% of patients. During the ICU monitoring of patients with VAP, the following were detected: ARDS in 81.1% of cases, AKI in 47.7%, DIC in 18%, sepsis in 92.9%, and septic shock in 82.9% of cases. During the study period, the 28-day mortality in patients with VAP was 55%, and the overall ICU mortality was 64%. The analysis of parameters according to general ICU mortality status is presented in **Table 3, 4**. The proportion of patients with

Table 3. Comparison of quantitative parameters according to overall ICU mortality status

Parameters	General ICU outcome		Overall	p
	Mortality (n=71, 64.0%)	Survival (n=40, 36%)		
	Distribution†			
Age (years)	65.5±15.4	48.4±21.8	59.3±19.7	<0.001 [a]
BMI (kg/m^2)	24 (18-35)	24 (19-41)	24 (18-41)	0.529 [b]
APACHE II	21.2±7.3	15.5±6.3	19.1±7.5	<0.001 [a]
Charlson comorbidity index	7 (0-21)	1 (0-14)	5 (0-21)	<0.001 [b]
Length of stay ICU (days)	15 (2-127)	27 (4-114)	16 (2-127)	0.008 [b]
Time from admission to infection (days)	6 (2-46)	5 (2-60)	6 (2-60)	0.439 [b]
The duration of central venous catheterisation (days)	9.4±2.7	9.1±2.1	9.3±2.5	0.501 [a]
Duration of mechanical ventilation (days)	12 (3-119)	22.5 (3-114)	12 (3-119)	0.144 [b]
Duration of mechanical ventilation up to nosocomial infection (days)	5 (1-46)	5 (2-23)	5 (1-46)	0.208 [b]
SOFA score 24 hours prior to VAP	8.2±2.5	5.5±1.6	7.2±2.5	<0.001 [a]
SOFA on the day of VAP diagnosis	10.8±3	6.9±2.3	9.4±3.4	<0.001 [a]
Time from admission to the ICU to sepsis (days)	8 (2-48)	7.5 (2-25)	8 (2-48)	0.574 [b]
Time from admission to the ICU to septic shock (days)	10 (1-58)	12 (2-40)	11 (1-58)	0.167 [b]
Duration of septic shock (days)	3 (1-15)	2 (0-6)	3 (0-15)	0.224 [b]
WBC on the day of VAP diagnosis (×10^9/L)	14.03 (0.02-47.87)	10.87 (1.01-30.63)	12.5 (0.02-47.87)	0.127 [b]
CRP on the day of VAP diagnosis (mg/L)	127 (0.7-471)	133 (14.8-269)	130 (0.7-471)	0.564 [b]
PCT on the day of VAP diagnosis (µg/L)	1.6 (0-100)	0.4 (0.1-46.6)	0.8 (0-100)	0.062 [b]
Lactate on the day of VAP diagnosis (mmol/L)	2.07 (0.3-10.56)	1.02 (0.14-2.22)	1.52 (0.14-10.56)	<0.001 [b]
pH on the day of VAP diagnosis	7.38 (7.00-7.56)	7.40 (7.31-7.55)	7.39 (7.00-7.56)	0.042 [b]
PaO_2/FiO_2 on the day of VAP diagnosis (mmhg/fraction)	138 (35-403)	207.5 (90-425)	167 (35-425)	<0.001 [b]

†: Data are presented as mean±standard deviation, minimum maximum and interquartile range (IQR) or n (%). a: Independent t-test, b: Mann-Whitney U test. Abbreviations: ICU: Intensive care unit, APACHE II: Acute Physiological and Chronic Health Evaluation-II score, BMI: Body-mass index, SOFA: Sequential Organ Failure Assessment, VAP: Ventilator associated pneumonia, WBC: White blood cell, CRP: C-reactive protein, PCT: Procalcitonin, PaO2/FiO2: Partial oxygen pressure/ inspired oxygen fraction.

Table 4. Distributional analysis of parameters according to general ICU mortality status

		General ICU outcome			p
		Mortality (n=71, 64.0%)	Survival (n=40, 36.0%)	Overall	
Gender	Female	26 (36.62%)	13 (32.5%)	39 (35.14%)	0.662 [a]
	Male	45 (63.38%)	27 (67.5%)	72 (64.86%)	
Comorbidity	Yes	67 (94.37%)	22 (55%)	89 (80.18%)	<0.001 [a]
	No	4 (5.63%)	18 (45%)	22 (19.82%)	
Cardiovascular disease	Yes	33 (46.48%)	7 (17.5%)	40 (36.04%)	0.002 [a]
	No	38 (53.52%)	33 (82.5%)	71 (63.96%)	
Chronic lung disease	Yes	21 (29.58%)	7 (17.5%)	28 (25.23%)	0.160 [a]
	No	50 (70.42%)	33 (82.5%)	83 (74.77%)	
Diabetes mellitus	Yes	35 (49.3%)	10 (25%)	45 (40.54%)	0.012 [a]
	No	36 (50.7%)	30 (75%)	66 (59.46%)	
Chronic kidney disease	Yes	10 (14.08%)	2 (5%)	12 (10.81%)	0.206 [b]
	No	61 (85.92%)	38 (95%)	99 (89.19%)	
Chronic liver disease	Yes	4 (5.63%)	0 (0%)	4 (3.6%)	0,295 [b]
	No	67 (94.37%)	40 (100%)	107 (96.4%)	
Cerebrovascular disease	Yes	25 (35.21%)	11 (27.5%)	36 (32.43%)	0.405 [a]
	No	46 (64.79%)	29 (72.5%)	75 (67.57%)	
Solid organ malignancy	Yes	24 (33.8%)	5 (12.5%)	29 (26.13%)	0.014 [a]
	No	47 (66.2%)	35 (87.5%)	82 (73.87%)	
Haematological malignancy	Yes	3 (4.23%)	0 (0%)	3 (2.7%)	0.552 [b]
	No	68 (95.77%)	40 (100%)	108 (97.3%)	
Chronic use of corticosteroids	Yes	28 (39.44%)	4 (10%)	32 (28.83%)	0.001 [a]
	No	43 (60.56%)	36 (90%)	79 (71.17%)	
Immunosuppressive therapy	Yes	19 (26.76%)	1 (2.5%)	20 (18.02%)	0.001 [a]
	No	52 (73.24%)	39 (97.5%)	91 (81.98%)	
Polymicrobial infection	Yes	50 (70.42%)	18 (45%)	68 (61.26%)	0.008 [a]
	No	21 (29.58%)	22 (55%)	43 (38.74%)	
ARDS	Yes	64 (90.14%)	18 (45%)	82 (73.87%)	<0.001 [a]
	No	7 (9.86%)	22 (55%)	29 (26.13%)	
AKI	Yes	44 (61.97%)	9 (22.5%)	53 (47.75%)	<0.001 [a]
	No	27 (38.03%)	31 (77.5%)	58 (52.25%)	
DIC	Yes	20 (28.17%)	0 (0%)	20 (18.02%)	<0.001 [a, *]
	No	51 (71.83%)	40 (100%)	91 (81.98%)	
Sepsis	Yes	71 (100%)	32 (80%)	103 (92.79%)	<0.001 [b, *]
	No	0 (0%)	8 (20%)	8 (7.21%)	
Septic shock	Yes	70 (98.59%)	22 (55%)	92 (82.88%)	<0.001 [a]
	No	1 (1.41%)	18 (45%)	19 (17.12%)	

[a] Pearson chi-square analysis, [b] Fisher's exact test. *Yates correction had been performed. Abbreviations: ICU: Intensive care unit, ARDS: Acute respiratory distress syndrome AKI: Acute kidney injury, DIC: Disseminated intravascular coagulation

significant comorbidities and the mean age were higher in the group of patients with mortality (p<0.001, p<0.001). The median CCI value in the mortality cohort was found to be significantly higher than that in the survival cohort (p<0.001). The proportion of patients afflicted with cardiovascular disease, diabetes mellitus, and solid organ malignancy was found to be significantly higher in the cohort that exhibited mortality (p=0.002, p=0.012, p=0.014). In addition, the use of chronic corticosteroid therapy and immunosuppressive therapy was similarly higher in the mortality cohort (p<0.001, p<0.001). A comparison of the mean BMI between the two cohorts (mortality and survival) revealed no statistically significant disparities (p=0.529). SOFA scores were calculated 24 hours before tracheal aspirate culture growth, on the day of growth, and at the time of discharge from ICU. Patients who died had significantly higher scores (p<0.001). Furthermore, APACHE II scores at admission to ICU were found to be higher in the mortality cohort. The duration of treatment received by patients in intensive care prior to sepsis/septic shock, or the duration of septic shock itself, was similar between cohorts. Similarly, no significant differences were detected between cohorts in laboratory markers of

inflammation, including CRP, procalcitonin, and leukocyte count. Nevertheless, analysis of blood gas samples collected on the day of tracheal aspirate culture revealed that the mortality cohort exhibited lower pH and PaO_2/FiO_2 levels, as well as elevated lactate levels (p=0.042, p<0.001, p<0.001). The proportion of patients with polymicrobial culture growth was higher in the mortality cohort, and the proportion of patients who developed ARDS, AKI, sepsis, septic shock and DIC was also higher in the mortality cohort (p=0.008, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001). Although the duration of mechanical ventilation was comparable across the cohorts, the length of stay in the ICU was found to be greater in the mortality cohort. The following table presents a comparative analysis of parameters and comorbidities according to the duration of mechanical ventilation in patients (Table 5). The duration of mechanical ventilation did not vary with age, BMI, or CCI. However, it was found to be significantly longer in patients with cerebrovascular disease.

Univariate and multivariate logistic regression analysis was performed for the effect profiles of the parameters on overall ICU mortality (Table 6, 7). In univariate analyses, age and SOFA were found to be strongly associated with mortality. Furthermore, both APACHE II and CCI were found to be statistically significant in terms of mortality, yet their discriminatory power was found to be more limited. Patient groups with elevated mortality risk were identified as those with cardiovascular disease, diabetes mellitus, solid organ malignancy, and those receiving chronic corticosteroid and immunosuppressive treatment. Multivariate analysis revealed that age (OR 1.039, 95% CI 1.001–1.079, p=0.046),

Table 5. Comparison of quantitative parameters and comorbidities according to duration of mechanical ventilation

Parameters		Duration of mechanical ventilation (days) §			p
		0-25 quartile (%, IQR)	25-50 quartile (%, IQR)	>50 quartile (%, IQR)	
		1-7 days (n = 27)	8-11 days (n = 20)	≥12 days (n = 59)	
		Distribution†			
Age (years)		63.1±22.5	53.9±17.1	59±19.6	0.306 [a]
BMI (kg/m²)		24 (19-30)	24.5 (18-41)	23 (18-31)	0.188 [b]
APACHE II		19.4±7.8	17.3±6.7	19.7±7.6	0.448 [a]
SOFA score 24 hours prior to VAP		6.9±2.1	8.0±3.0	7.3±2.5	0.341 [a]
SOFA on the day of VAP diagnosis		9.4±3.7	10.6±3.3	9.3±3	0.283 [a]
Charlson Comorbidity Index		6 (0-21)	5.5 (0-15)	5 (0-14)	0.675 [b]
Gender	Female	13 (48.1%)	6 (30%)	20 (33.9%)	0.349 [c]
	Male	14 (51.9%)	14 (70%)	39 (66.1%)	
Comorbidity	Yes	21 (77.8%)	15 (75%)	48 (81.4%)	0.813 [c]
	No	6 (22.2%)	5 (25%)	11 (18.6%)	
Cardiovascular disease	Yes	12 (44.4%)	7 (35%)	19 (32.2%)	0.545 [c]
	No	15 (55.6%)	13 (65%)	40 (67.8%)	
Chronic lung disease	Yes	6 (22.2%)	8 (40%)	12 (20.3%)	0.20 [c]
	No	21 (77.8%)	12 (60%)	47 (79.7%)	
Diabetes mellitus	Yes	11 (40.7%)	9 (45%)	23 (39%)	0.894 [c]
	No	16 (59.3%)	11 (55%)	36 (61%)	
Chronic kidney disease	Yes	5 (18.5%)	3 (15%)	2 (3.4%)	0.031 [d, *]
	No	22 (81.5%)	17 (85%)	57 (96.6%)	
Chronic liver disease	Yes	3 (11.1%) [x]	1 (5%) [x, y]	0 (0%) [y]	0.022 [d]
	No	24 (88.9%)	19 (95%)	59 (100%)	
Cerebrovascular disease	Yes	7 (25.9%)	3 (15%)	26 (44.1%)	0.036 [c, *]
	No	20 (74.1%)	17 (85%)	33 (55.9%)	
Solid organ malignancy	Yes	8 (29.6%)	5 (25%)	15 (25.4%)	0.908 [c]
	No	19 (70.4%)	15 (75%)	44 (74.6%)	
Haematological malignancy	Yes	1 (3.7%) [x, y]	2 (10%) [x]	0 (0%) [y]	0.048 [d]
	No	26 (96.3%)	18 (90%)	59 (100%)	
Chronic use of corticosteroids	Yes	8 (29.6%)	7 (35%)	15 (25.4%)	0.702 [c]
	No	19 (70.4%)	13 (65%)	44 (74.6%)	
Immunosuppressive therapy	Yes	6 (22.2%)	5 (25%)	7 (11.9%)	0.265 [d]
	No	21 (77.8%)	15 (75%)	52 (88.1%)	

† Quantitative parameters are expressed as mean±standard deviation (SD) or quartiles [median, minimum and maximum] according to normal distribution characteristics, while qualitative parameters are expressed as frequency (n) and percentage (%). § The IMV classification was performed based on the interquartile range (IQR) percentiles according to the statistical distribution characteristics. * Although a significant difference was observed in the overall distribution, no significant difference was found between the ratios after Bonferroni correction. The proportional values are marked with (x)(y), and while no significant difference was observed between ratios containing the same letter, a significant difference was observed between ratios not containing the same letter. a One-way variance analysis (ANOVA), b Kruskal-Wallis H test, c Pearson Chi-square analysis, d Fisher's exact

Table 6. Univariate logistic regression analysis of parameters and examination of their effect profiles on overall ICU mortality

Parameters	B	Nagelkerke R^2	P	OR	CI (95%)	
					Minimum	Maximum
Age	0.049	0.227	<0.001	1.05	1.026	1.075
Gender	-0.182	0.002	0.663	0.83	0.367	1.890
BMI	-0.042	0.009	0.401	0.96	0.868	1.058
APACHE II	0.121	0.189	<0.001	1.13	1.058	1.203
SOFA on the day of VAP diagnosis	0.549	0.450	<0.001	1.73	1.399	2.144
Charlson Comorbidity Index	0.239	0.273	<0.001	1.27	1.136	1.422
Cardiovascular disease	1.410	0.117	0.003	4.09	1.600	10.475
Chronic lung disease	0.683	0.025	0.164	1.98	0.757	5.18
Diabetes mellitus	1.070	0.078	0.014	2.92	1.242	6.849
Chronic kidney disease	1.136	0.03	0.156	3.11	0.647	14.991
Chronic liver disease ¥	–	–	–	–	–	–
Cerebrovascular disease	0.360	0.009	0.406	1.43	0.614	3.345
Solid organ malignancy	1.274	0.078	0.018	3.57	1.241	10.299
Haematological malignancy ¥	–	–	–	–	–	–
Chronic use of corticosteroids	1.768	0.142	0.002	5.86	1.879	18.276
Immunosuppressive therapy	2.657	0.150	0.011	14.25	1.828	111.058

Abbreviations: OR: Odd ratio, CI: Confidence interval, ICU: Intensive care unit, APACHE II: Acute Physiological and Chronic Health Evaluation-II score, BMI: Body-mass index, SOFA: Sequential Organ Failure Assessment, VAP: Ventilator associated pneumonia. The reference category is based on the survival group. ¥ Since it did not show an appropriate distribution pattern between groups, the LR analysis assumption was not met and was excluded from the analyses

Table 7. Re-examination of the effect profiles of parameters on multivariate logistic regression analysis and overall ICU mortality within a multiple model

Nagelkerke R^2=0.614					
Parameters	B	P	OR	CI (95%)	
				Minimum	Maximum
Age (years)	0.038	0.046	1.039	1.001	1.079
Gender †	-0.328	0.603	0.720	0.209	2.478
BMI †	-0.121	0.183	0.886	0.741	1.059
SOFA on the day of VAP diagnosis	0.563	<0.001	1.756	1.357	2.272
Cardiovascular disease	0.703	0.318	2.020	0.508	8.029
Diabetes mellitus	-0.087	0.900	0.916	0.234	3.592
Chronic use of corticosteroids	1.542	0.046	4.675	1.025	21.327

Due to multicollinearity, Apache-II, Charlson comorbidity index, solid organ malignancy, and immunosuppressive treatment status were excluded from the model. The reference category is based on the survival group. † As a potential covariate, it has been included in the adjustment model. Abbreviations: OR: Odd ratio, CI: Confidence interval, BMI: Body-mass index, SOFA: Sequential Organ Failure Assessment, VAP: Ventilator associated pneumonia

SOFA score on the day of VAP diagnosis (OR 1.756, 95% CI 1.357–2.272, p<0.001), and chronic corticosteroid use (OR 4.675, 95% CI 1.025–21.327, p=0.046) were independently associated with mortality. The final model explained 61.4% of mortality (Nagelkerke R^2=0.614). However, due to multicollinearity, APACHE II, CCI, solid organ malignancy, and immunosuppressive therapy were not included in the model. The predictive properties of age, CCI, APACHE II, and SOFA values on the day of tracheal culture growth for overall ICU mortality are presented in **Table 8** and **Figure 2**. Age ≥ 48 years (95% CI: 0.617–0.833) has been shown to predict mortality with a sensitivity of 88.7% and a specificity of 57.5%. Similarly, a CCI score of 2 or higher (95% CI: 0.685-0.863) has been demonstrated to predict mortality with a sensitivity of 91.5% and a specificity of 47.5%. A SOFA score of 11 or higher (95 % CI: 0.779-0.920), calculated on the day of tracheal culture growth, has been shown to predict mortality with a high degree of specificity (97.5%). The APACHE II score, calculated at the time of admission to the ICU, has been shown to predict mortality with a sensitivity of 69% and a specificity of 70% when the score is 18 or higher (95% CI: 0.623-0.819). ROC analysis of the combined use of age, APACHE-II, SOFA values on the day of tracheal culture growth and CCI is shown in **Supplementary Figure 1**. ROC analysis of the combined use of age, APACHE II, SOFA values on the day of tracheal culture growth, CCI, and chronic corticosteroid use is shown in **Supplementary Figure 2**. Nevertheless, it should be noted that these approaches are predicated on binary

Table 8. ROC analyses and predictive properties

Parameters	AUC (95% CI)	Cut-off †	p	Sensitivity (%)	Specificity (%)
Age (years)	0.725 (0.617-0.833)	≥ 48	<0.001	88.7%	57.5%
APACHE II	0.721 (0.623-0.819)	≥18	<0.001	69.0%	70.0%
SOFA on the day of VAP diagnosis	0.849 (0.779-0.920)	≥11	<0.001	56.3%	97.5%
Charlson Comorbidity Index	0.774 (0.685-0.863)	≥2	<0.001	91.5%	47.5%

† The Youden J index was used as the basis for determining the ideal cut-off values. Abbreviations: OR: Odd ratio, CI: Confidence interval, SOFA: Sequential Organ Failure Assessment, VAP: Ventilator associated pneumonia. APACHE II: Acute Physiological and Chronic Health Evaluation-II score

variables evaluated within the same data set and are subject to optimism bias. Consequently, this result should be interpreted with caution and considered as hypothesis-generating rather than confirmatory.

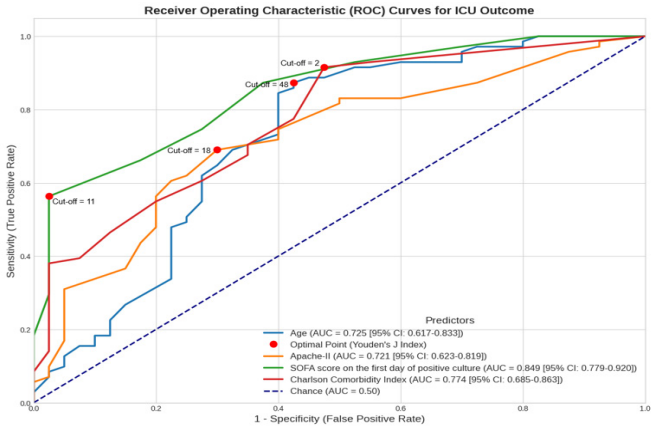
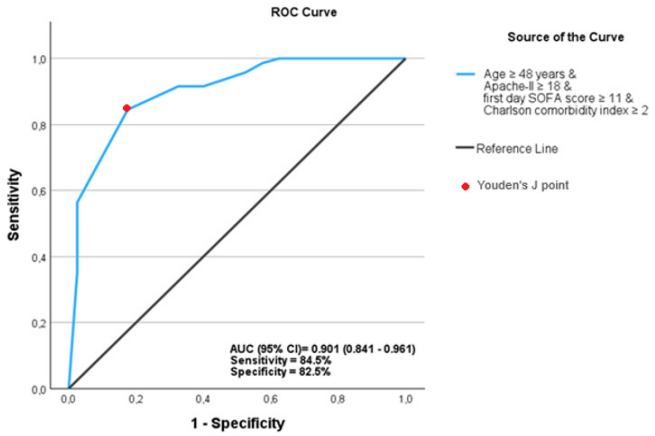
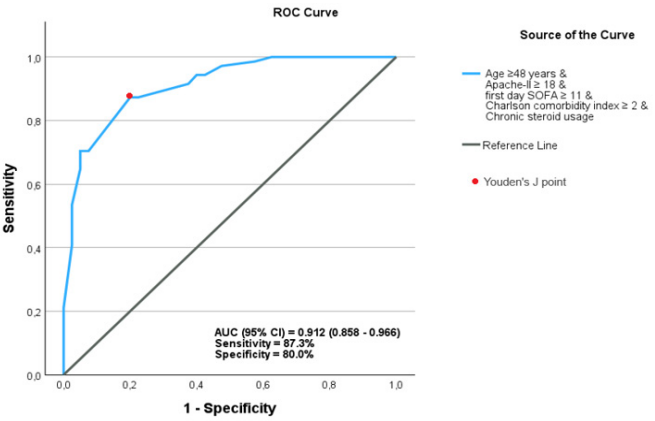


Figure 2. ROC analysis graphs for age, SOFA score on the day of tracheal culture growth, APACHE II, and Charlson Comorbidity Index.
Abbreviations: CI: Confidence interval, AUC: Area under the curve, APACHE II: Acute Physiological and Chronic Health Evaluation-II score, SOFA: Sequential Organ Failure Assessment



Supplementary Figure 1. ROC analysis of the combined use of age, APACHE II, SOFA score calculated on the day of tracheal culture growth, and CCI: the specificity for mortality increased to 84.5% and AUC to 0.901 with the combined use of variables (cut-off values obtained from ROC analysis were used).
CI: Confidence interval, AUC: Area under the curve, APACHE II: Acute Physiological and Chronic Health Evaluation-II score, SOFA: Sequential Organ Failure Assessment CCI: Charlson Comorbidity Index



Supplementary Figure 2. ROC analysis of the combined use of age, APACHE II, SOFA score calculated on the day of tracheal culture growth, CCI, and chronic corticosteroid use: The specificity for mortality increased to 87.3%, and AUC=0.912 with the combined use of variables (Cutoff values obtained from the ROC analysis were used as the basis).
CI: Confidence interval, AUC: Area under the curve, APACHE II: Acute Physiological and Chronic Health Evaluation-II score, SOFA: Sequential Organ Failure Assessment CCI: Charlson Comorbidity Index

DISCUSSION

The findings of the present study revealed that BMI had no significant effect on mortality in VAP patients. However, increased age, elevated APACHE II, SOFA, and CCI scores, the presence of concomitant cardiovascular disease, diabetes mellitus, solid organ tumours, and the use of steroid/chemotherapeutic drugs were associated with mortality in univariate analyses. The discriminatory power of APACHE II and CCI in ROC analyses remained limited in terms of mortality. Cardiovascular disease, diabetes and solid organ malignancy were found to be significant in univariate analyses, but did not remain independent predictors in multivariate analysis. Increasing age, SOFA on the day of VAP and chronic corticosteroid use are all independently associated with mortality in multivariable analyses. While an exploratory combination of age, SOFA, CCI, APACHE II, and corticosteroid use appeared to yield a high specificity (87.3%) for mortality prediction (**Supplementary Figure 2**), it should be noted that this approach is subject to optimism bias and should be interpreted as hypothesis-generating. Moreover, research has demonstrated that the duration of mechanical ventilation is independent of age, BMI, or CCI. However, it has been observed to be significantly prolonged in patients with cerebrovascular disease.

Despite the existence of various guidelines designed to prevent VAP, it remains one of the most prevalent nosocomial infections in ICUs. It is evident that VAP rates are subject to variation between hospitals, ICUs, and studies. While the incidence of VAP in North American hospitals[16] is reported to be as low as 1-2.5 cases per 1.000 ventilator-days, a multicentre study in Europe[17] reported 18.3 cases per 1.000 ventilator-days. In low-and middle-income countries, this rate is known to be higher.[18] The observed variations are hypothesised to be attributable to three main factors: firstly, variations in the definitions of VAP; secondly, differences in the application of these definitions; thirdly, the limitations of diagnostic methods. Furthermore, the incidence rates of these conditions demonstrate significant variation when considered in relation to the demographic characteristics of the population under study.[18] For instance, VAP rates of 24.5 per 1.000 ventilator days have been documented in cancer patients,[19] while a high VAP incidence of 29% has been observed in ARDS patients despite the implementation of lung-protective strategies.[20] A study conducted at a university hospital in Turkiye, which included patients from the ICU, reported an incidence of VAP of 40.9 cases per 1.000 ventilator days.[21] In a further large-scale, multi-centre study from Turkiye, the incidence of VAP was reported as 31.9 per 1.000 ventilator days.[22] In the present study, consistent with these findings, the rate was determined to be 32.7 per 1.000 ventilator days. In a recent study conducted in Ethiopia, the incidence of VAP was reported to be 45.7 per 1.000 ventilator days which is higher than the rate determined in the present study.[23] The rate we determined in our study is higher than the rate reported by Karatas et al.[24] from Turkiye (15.7/1000 ventilator days). This may be attributable to sociodemographic disparities and the sample size encompassed within the study. For instance, Karatas et al.[24] included 1152 patients, of whom only 11.1%

had malignancy. In the present study, the proportion of patients with malignancy was found to be significantly higher (solid organ malignancy: 26.1%, haematological malignancy: 2.7%). A number of studies have identified male gender as a significant independent risk factor for the development of pneumonia and VAP in patients receiving ICU.[9,25-28] Another risk factor that has been identified as a potential cause of VAP is advanced age.[29,30] A recent systematic review has indicated that the average age of patients diagnosed with VAP was 53.55 years.[28] In the present study, in accordance with the findings of preceding research, the preponderance of VAP patients was male (64.9%), with a mean age of 59.3±19.7 years.

VAP has been observed to demonstrate the highest mortality among nosocomial infections. The extant literature examining the association between VAP and mortality varies significantly in its findings, with mortality ranging from 13% to 70%.[31-35] A recent study from Turkiye reported a 30-day mortality rate of 59% in VAP patients,[36] while Hamidi et al.[9] reported a 30-day mortality of 63.2%. The findings of Bor et al.[37] revealed that the 30-day mortality was 48.2%, the ICU mortality was 67.9%, and the hospital mortality was 71.4%. In the present study, consistent with the findings of these studies, 28-day mortality was found to be 55%, and overall ICU mortality was found to be 64%. A multitude of factors have the potential to influence the mortality observed in patients diagnosed with VAP. Both community-acquired and nosocomial infections may be significantly influenced by immunosuppression. Research has indicated that corticosteroids and other immunosuppressive medications may increase the risk of infection by weakening the body's natural defence systems.[38-40] A study by But et al.[32] investigating risk factors associated with mortality in patients with VAP found that corticosteroid use was an independent risk factor for mortality. Mortality was also significantly higher in patients with solid tumours. Similarly, our study found that corticosteroid use and immunosuppressive treatment were present in 28.8% and 18% of patients, respectively, and that these conditions were risk factors for mortality. Furthermore, it was concluded that the use of corticosteroids increased the risk of death by 4.67 times, making it the most important risk factor. Additionally, logistic regression analysis showed that the mortality was higher among patients with solid organ malignancies. Many studies have proven that the severity of the disease is associated with another risk factor for mortality.[3,41-43] The present study determined that there was a significant association between mortality and the presence of an APACHE II score ≥18, a SOFA score ≥11 calculated on the day of tracheal culture growth and a CCI score ≥2. Despite the incorporation of APACHE II ≥18 and CCI ≥2 in exploratory analyses, their discriminatory capability was found to be constrained, as evidenced by the ROC analysis, with 95% confidence intervals approaching 0.5. It was also found that the combined use of these three scores amd age could predict mortality with 84.5% specificity. Furthermore, when chronic corticosteroid use is evaluated alongside these scores, specificity increases to 87.3%. Nevertheless, this approach was founded upon binary cut-offs evaluated within the same dataset and is subject to optimism bias. Consequently, this combined model should be regarded as hypothesis-generating rather than confirmatory. To the best of our knowledge, studies evaluating these parameters in conjunction with VAP are limited; however, further research is required to validate our findings. Another factor that may affect mortality in this patient group is age. However, there is no consensus on this issue. In our study, the mean patient age was 59.3±19.7 years, and we found that being over 48 years of age was an independent risk factor for mortality. Similar to our findings, Tuon et al.[44] noted that a median age of 56 years was observed in their study, and that being over 50 years of age was an independent risk factor for mortality. The 30-day and overall ICU mortality rates in that study were 57.1% and 67%, respectively, which are similar to the mortality rates observed in our study. However, some studies indicate that age is a risk factor for developing VAP, but has no effect on mortality.[37,45] Others suggest that age is not a risk factor for developing VAP, but that mortality is higher in older patients.[46,47] BMI may also be a parameter associated with mortality in VAP patients. Obesity has been linked to longer stays in the ICU and an increased risk of morbidity, but its association with mortality is unclear. This seemingly contradictory correlation between obesity and certain patient outcomes is referred to as the 'obesity paradox'. Despite an increased risk of health complications, studies have shown that obese individuals have better survival rates than non-obese individuals in certain acute conditions, such as sepsis and ARDS.[48,50] Pneumonia appears to be one of the conditions that define this paradox. Research has linked obesity to an increased risk of developing pneumonia, but it has also shown that obesity can be linked to a reduced mortality in this population.[51,52] The link between obesity and VAP is not yet well understood, as there is a lack of data on the subject. Nevertheless, studies conducted to date indicate that there is no significant difference in VAP incidence between obese and non-obese populations.[53,54] A recent large-scale United States study examining the effect of obesity on VAP found that obesity had no significant impact on the mortality of ICU patients with VAP. However, some studies have reported that obesity is associated with higher mortality among patients admitted to ICUs.[55,56] In our study, the median BMI of the patients was 24 kg/m² (range: 18–41), and we did not detect any positive or negative effect of BMI on mortality. BMI was not a significant predictor of mortality. The ROC analysis yielded no statistically significant discriminative ability, with the 95% confidence interval approaching 0.50. This finding is consistent with the findings of other studies that have reported inconsistent associations between BMI and mortality in critically ill patients. We believe that the idea that obesity confers an advantage in ICU should be further investigated in future large-scale studies.

Limitations

This study has several limitations. Firstly, it is retrospective and based on data collected from hospital databases. Secondly, due to the retrospective nature of the study, not all potential mortality-affecting factors were evaluated. Thirdly, as this study was conducted at a single centre and there was a potential of inadequate microbiological detection, our results may not reflect the true incidence of VAP. Finally, the exclusion of 29 patients with missing data and 7 patients transferred to other

centres may have influenced the study results. This should be taken into account when interpreting the findings.

CONCLUSION

VAP remains a significant problem in ICUs, and mortality is a major issue in these patients. The implementation of more effective control measures is of great importance. The findings of our study indicate that BMI does not have a significant effect on mortality in VAP patients. However, it has been identified that advanced age, high APACHE II, SOFA, and CCI scores, concomitant cardiovascular disease, diabetes mellitus, solid organ tumours, and the use of steroid/chemotherapeutic medications are associated with mortality in univariate analyses. In the present study, we identified age, SOFA score and chronic corticosteroid use as independent risk factors associated with mortality. Despite the investigation of a combined model in this study, its interpretation must be approached with caution due to its exploratory nature and the absence of external validation. Among all the variables studied, age and SOFA score demonstrated the most consistent and statistically significant discriminatory power, and may serve as more reliable indicators of mortality risk in VAP patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approved by the Ethics Committee for Medical Scientific Researches at Akdeniz University (Date: 31.07.2025, Decision No: TBAEK-669).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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