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The Relationship Between APACHE II Score and Immunological Parameters in Intensive Care Patients

Yoğun Bakım Hastalarında APACHE II Skoru ve İmmünolojik Parametreler Arasındaki İlişki

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Abstract

Introduction: In this study, the aim was to investigate the relationship between immunological parameters, specifically the fibrinogen/albumin ratio, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and the widely used acute physiology and chronic health assessment (APACHE) II scoring system in critically ill patients in the intensive care unit.

Materials and Methods: The retrospective analysis included 166 patients admitted between January 2023 and July 2023, evaluating their 28-day mortality. The patients were categorised into groups: Group M (mortality), with 53 patients and Group S (survival) with 113 patients. The immunological parameters of the patients between the groups were analyzed statistically.

Results: APACHE II score, fibrinogen, lactate, and fibrinogen/albumin ratio were identified as independent parameters associated with mortality. The ROC analysis determined the optimal cutoff points for predicting mortality for APACHE II score, fibrinogen, lactate, and fibrinogen/albumin ratio.

Conclusion: This study revealed a significant correlation between APACHE II score and immunological parameters, including fibrinogen, lactate, and fibrinogen/albumin ratio. These findings can be used to predict mortality.

Keywords: APACHE II score; immunological parameters; intensive care unit; mortality.

Özet

Giriş ve Amaç: Bu çalışmada immünolojik parametreler, özellikle fibrinojen albümin oranı, trombosit-lenfosit oranı ve nötrofil-lenfosit oranı ile kritik yoğun bakım ünitesi hastalarında yaygın olarak kullanılan akut fizyoloji ve kronik sağlık değerlendirmesi (APACHE) II skorlama sistemi arasındaki ilişkinin araştırılması amaçlandı.

Gereç ve Yöntem: Çalışmaya Ocak 2023 ile Temmuz 2023 tarihleri arasında yoğun bakım ünitesinde yatan ve 28 günlük mortaliteleri değerlendirilen 166 hasta dahil edildi. Hastalar iki gruba ayrıldı: 53 hastadan oluşan Grup M (mortalite) ve 113 hastadan oluşan Grup S (sağkalım). Gruplar arasında hastaların immünolojik parametreleri istatistiksel olarak analiz edildi.

Bulgular: APACHE II skoru, fibrinojen, laktat ve fibrinojen/albümin oranı mortaliteyle ilişkili bağımsız parametreler olarak belirlendi. ROC analizi ile APACHE II skoru, fibrinojen, laktat ve fibrinojen/albümin oranı için mortaliteyi tahmin etmeye yönelik optimal kesme noktalarını belirlendi.

Tartışma ve Sonuç: Bu çalışma APACHE II skoru ile fibrinojen, laktat ve fibrinojen/albümin oranı gibi immünolojik parametreler arasında anlamlı bir korelasyon olduğunu ortaya koydu. Bu bulgular mortaliteyi tahmin etmek için kullanılabilir.

Anahtar Kelimeler: APACHE II skoru; immünolojik parametreler; yoğun bakım ünitesi; mortalite.

Introduction

The management and prognosis of critically ill patients in intensive care units (ICUs) have long been of paramount concern in medical research (1). One widely used method for assessing the severity of illness and predicting outcomes in these patients is the APACHE II scoring system (2). The APACHE II score, which considers various physiological parameters, provides clinicians with a standardised tool to evaluate the severity of a patient's condition and guide clinical decision-making. In recent years, an increasing interest has been in understanding the relationship between immunological parameters and clinical outcomes in critically ill patients (3, 4). The immune response plays a crucial role in determining the trajectory of critical illnesses, and studying immunological markers can offer valuable insights into patient prognosis and potential therapeutic interventions (5-9). Among the emerging immunological parameters that have garnered attention are the fibrinogen/albumin ratio (FAR), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) (10). FAR is a novel indicator that reflects the balance between pro-inflammatory and anti-inflammatory responses. It integrates the levels of fibrinogen and albumin, which are implicated in the immune response and inflammatory pathways. FAR has been proposed as a potential prognostic marker in various medical conditions due to its ability to reflect the overall inflammatory state of a patient (8).

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Table 1. Patient demographics and reasons for hospitalisation

Caracteristic feature		Group S (n=113)	Group M (n=53)	*p* value
Age		73 (61-83)	74 (65-85)	0.552
Gender	Female	50 (%44.2)	24 (%45.3)	0.900
	Male	63 (%55.8)	29 (%54.7)	
BMI (kg/m^{-2})		26 (23.7-27.7)	25.8 (23.6-27.7)	0.876
Indication of admission	Respiratory failure	50 (%44.2)	20 (%37.7)	0.076
	Infection	5 (%4.4)	8 (%15.1)	
	Sepsis	6 (%5.3)	6 (%11.3)	
	Cardiac	6 (%5.3)	5 (%9.4)	
	Neurology	11 (%9.7)	4 (%7.5)	
	Postoperative	8 (%7.1)	1 (1.9)	
	Trauma	9 (%8.0)	2 (%3.8)	
	Renal	12 (%10.6)	2 (%3.8)	
	Gastrointestinal	6 (%5.3)	5 (%9.4)	
Comorbidity	No	99 (%87.6)	43 (%81.1)	0.062
	Yes	14 (%12.4)	10 (%18.9)	
Heart failure	No	88 (%77.9)	44 (%8.0)	0269
	Yes	25 (%22.1)	9 (%17.0)	
Atrial fibrillation	No	88 (%77.9)	38 (%71.7)	0.444
	Yes	25 (%22.1)	15 (%28.3)	
Coronary artery disease	No	102 (%90.3)	50 (%94.3)	0.386
	Yes	11 (%9.7)	3 (%5.7)	
Cerebrovascular disease	No	67 (%59.3)	34 (%64.2)	0.552
	Yes	46 (%40.7)	19 (%35.8)	
Diabetes mellitus	No	65 (%57.5)	31 (%58.5)	0.550
	Yes	48 (%42.5)	22 (%41.5)	
Hypertension	No	94 (%83.2)	45 (%84.9)	0.906
	Yes	19 (%16.8)	8 (%15.1)	
Chronic obstructive pulmonary disease/asthma	No	72 (%63.7)	34 (%64.2)	0.780
	Yes	41 (%36.3)	19 (%35.8)	
	Yes	89 (%78.8)	48 (%90.6)	

Data are shown as median (25-75% percentiles) or n(%). The chi-square test was applied for categorical variables, while the Mann-Whitney-U test was applied for continuous variables.

Table 2: ICU parameters of the groups

Caracteristic feature		Grup S (n=113)	Grup M (n=53)	p value
Intubation	No	51 (%45.1)	4 (%7.5)	0.001
	Yes	62 (%54.9)	49 (%92.5)	
Vasopressor	No	74 (%65.5)	18 (%34.0)	0.001
	Yes	39 (%3.,5)	35 (%66.0)	
OAB (mmHg)		80 (%65-92)	70 (58-85)	0.020
Pulse		95 (85-111)	110 (%90-117)	0.111
SpO_2 (%)		94±4	93±5	0.178
Fever		369 (36.4-37.0)	37.0 (36.5-37.3)	0.027
APACHE II		18 (12-23)	29 (27-30)	0.001
GCS		12(8-15)	9 (4-12)	0.001
Shock index		0.800 (0.660-0.980)	1.100 (0.900-1.600)	0.001

While continuous variables were expressed as mean±SD or median (25-75% percentiles), categorical variables were shown as n(%). While the Chi-square test was applied for categorical variables, the t or Mann-Whitney-U test was used for continuous variables.

The NLR and PLR are additional indicators that have gained recognition for their predictive value in assessing patient outcomes. NLR reflects the balance between neutrophils, associated with inflammation, and lymphocytes, which play a crucial role in immune regulation. PLR, on the other hand, combines platelet and lymphocyte counts to provide insights into the interplay between coagulation and immune responses (9,10). Considering the multifaceted nature of critical illnesses and the intricate interactions between immune responses and physiological parameters, investigating the potential correlations between these immunological markers and the APACHE II score holds significant promise. Such a study could shed light on how these markers might influence the prognosis of ICU patients and contribute to the refinement of predictive models (11). In this context, the present study aims to explore the relationship between APACHE II scores and immunological parameters, including the FAR, NLR, and PLR, in critically ill patients admitted to the ICU. This research contributes to understanding critical illnesses' intricate mechanisms by elucidating these potential associations. It provides clinicians with additional tools for assessing patient prognosis and tailoring therapeutic interventions.

Material and Methods

A total of 166 patients followed up in the ICU of our hospital due to various diagnoses between January 2023 and July 2023 were enrolled in the study. The patients were divided into two groups based on their 28-day mortality outcomes. Patients who died within 28 days were assigned to Group M, while those who survived were included in Group S. Patients above 18 years and referred from the emergency department or clinics were included in the study. Patients aged under 18 years were excluded from the study. Patients' demographics include age and gender, definitive diagnosis, arterial blood pressure, fingertip oxygen saturation, pleth variability index, fingertip blood glucose, fever, pulse, shock index, and serum lactate. PLR, NLR, fibrinogen, and albumin levels were recorded.

Ethical approval: The study was conducted by the Declaration of Helsinki. Ethics committee permission was obtained from the Giresun Edication and Research Hospital local ethics committee with the decision number 53593568-771-218379886 and date 19.06.2023.

Statistical analysis: Patient data were collected using IBM-SPSS Inc., version 22.0. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables' means and standard deviations (medians and percentiles) were calculated. Categorical variables were presented as counts and percentages. Parametric or non-parametric tests were used based on the normality assumption. Independent Samples-t or Mann-Whitney-U tests were employed for continuous variables, and the Chi-square test was used for categorical variables. Logistic regression analysis was conducted to identify independent risk factors associated with mortality. The receiver operating characteristic (ROC) analysis determined optimal cutoff values for variables predicting mortality.

Results

A total of 166 patients were included in the study. Among them, 53 patients experienced mortality (Group M), and 113 did not (Group S). There are no statistically significant differences between the groups for age, gender, and BMI. Similarly, medical history parameters showed no significant differences between the groups. The most common reason for admission was respiratory failure in both groups, with no significant difference (Table 1). Table 1. Patient demographics and reasons for hospitalisation Variables such as intubation rate, vasoactive agent usage, APACHE II score, shock index, and fever were significantly higher in Group M compared to Group S ($p<0.001$). Group M had lower Glasgow Coma Scale (GCS) scores and higher Organ Assessment Bias (OAB) scores ($p<0.001$, $p=0.020$) (Table 2). Table 2. ICU parameters of the groups Laboratory parameters showed significant differences between the groups. In Group M, parameters such as Hb, lymphocyte, platelet, and monocyte/albumin ratio were lower ($p<0.05$). In comparison, parameters like creatinine, prothrombin time, total bilirubin, neutrophil, fibrinogen, procalcitonin, lactate, serum blood glucose, NLR, and FAR were higher ($p<0.001$) (Table 3). Table 3. Laboratory parameter values according to groups Multivariable logistic regression analysis revealed that APACHE II, fibrinogen, lactate, and FAR were independent risk factors associated with mortality ($p<0.05$). ROC analysis identified optimal cutoff values for mortality prediction. The best cutoff values for APACHE II, fibrinogen, lactate, and FAR were determined as 25.5, 484.5, 1.85, and 159.3, respectively (Table 4, Figure 1). Table 4.

Table 3: Laboratory parameter values according to groups

Laboratory parameters	Grup S (n=113)	Grup M (n=53)	*p* value
Hb	10.1(8.8-12.2)	9.2(8.0-11.0)	0.019
Albumin (g/L)	2.90(2.54-3.30)	2.84(2.60-3.24)	0.814
Creatinin (mg/dL)	1.04(0.73-2.03)	1.54(0.92-2.44)	0.044
Prothrombin time (Seconds)	9.87(8.94-11.40)	1100(9.69-15.60)	0.001
Total bilirubin	0.52(0,35-082)	0.83(0.44-1.46)	0.001
WBC (10^9/l)	12.05(8,43-16,00)	11.40(7.53-15.04)	0.547
Neu (10^3/ml)	7.96(6.34-11.20)	10.81(9.00-14.74)	0.001
Lymp (10^3/ml)	1.02(0,71-1,45)	0.69(0.46-1.03)	0.001
Platelet (10^3 µ/L)	230(181-310)	161(114-240)	0,001
Monocyte (10^3/ml)	0.60(0.41-0.93)	0.50(0.25-0.77)	0.017
Fibrinogen	404(347-517)	680(546-860)	0.001
CRP (Mg/L)	61,5(21-172)	85(35-154)	0.159
Procalcitonin (U/L)	0.40(0,13-1.93)	1,12(0.43-4.89)	0.001
Lactate	1.40(1,10-2,0)	3.60(2.50-4.30)	0.001
Blood sugar	138(110-170)	160(131-228)	0.007
D-dimer (mg/ml)	2680(1157-6005)	2997(1265-7599)	0.389
CRP/Albumin (10^{-3})	18.99(7.50-62.81)	25.62(9.94-60.00)	0.514
Monocyte/Albumin(g)	0.19(0.15-0,31)	0.16(0.06-0.26)	0.006
Neutrophil/Lymphocyte	8.84(5,08-4.62)	16.9(11.1-28.4)	0.001
Platelet/Lymphocyte	217(150-374)	231(122-413)	0.942
Fibrinogen/Albumin	137.69(109.1-177.3)	262.39(164.5-302.8)	0.001

Variables were shown as median (25-75% percentiles). Mann-Whitney-U test was applied.

Table 4: Results of Logistic regression analysis for mortality

Risk factor	OR (%95 GA)	p value
MAP	1.009 (0.960-1,060)	0.734
Fever	0.757 (0.208-2,752)	0.673
APACHE II	1.258 (1.097-1,442)	0.001
GCS	0.855 (0.705-1,038)	0.113
Shok Index	1.098 (0.174-6,918)	0.921
Hb	0.760 (0.522-1,105)	0.150
Prothrombin Time	1.062 (0.991-1,138)	0.087
Monocyte	0.256 (0.055-1,199)	0.084
Fibrinogen	1.008 (1.003-1,014)	0.004
Lactate	3.610 (1.814-7,183)	0.001
Neutrophil/ Lymphocyte	1.001 (0.968-1,035)	0.965
Fibrinogen/Albumin	0.980 (0.967-0,993)	0.004
Intubation	2.127 (0.201-22,534)	0.531
Vasopressor	2.239 (0.423-11,855)	0.343

OR: Odd's ratio

Multivariate regression analysis of variables in patients with mortality Figure 1. ROC curve for APACHE II, Fibrinogen, Lactate and Fibrinogen/Albumin parameters in predicting mortality Table 5. Test values for independent risk factors in predicting mortality

Discussion

This study aimed to investigate the relationship between immunological parameters, namely the FAR, PLR, NLR, and a widely used prognostic

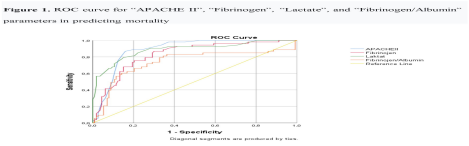

Figure 1. ROC curve for APACHE II, Fibrinogen, Lactate and Fibrinogen/Albumin parameters in predicting mortality

Table 5: Test values for independent risk factors in predicting mortality

	Cut off value	Specificity (%)	Sensitivity (%)	AUC (%95 GA)	*p* value
APACHE II	25.5	84.1	86.8	0.889 (0.839-0.939)	0.001
Fibrinogen	484.5	70.8	84.9	0.831 (0.766-0.897)	0.001
Lactate	1.85	71.7	90.6	0.887 (0.829-0.946)	0.001
Fibrinogen/Albumın	159.3	65.5	81.1	0.739 (0.645-0832)	0.001

AUC: Area under curve, CI: Confidence interval

scoring system, APACHE II. This study demonstrated that FAR predicted 28-day mortality with 65.5% sensitivity and 81.1% specificity, while APACHE II predicted 28-day mortality with 84.1% sensitivity and 86.8% specificity. Moreover, APACHE II was better than FAR in predicting mortality. Additionally, serum lactate, fibrinogen level, and APACHE II were identified as independent risk factors for mortality. Therefore, FAR calculation might be helpful to identify patients admitted to the ICU with a high risk of 28-day mortality. Our study is the first to indicate a potential relationship between immunological parameters, including the FAR and APACHE II, in critically ill patients admitted to the ICU. The analysis revealed several significant findings that shed light on the potential predictive value of these immunological parameters and their comparison with the validated APACHE II score. Vincent and Moreno highlighted that the APACHE II score is a widely used scoring system for assessing severity in intensive care patients, and high scores are associated with in-hospital mortality (12). Keegan et al. also showed that the APACHE II score is a powerful tool for evaluating prognosis in intensive care patients and that high scores are associated with poor outcomes (13). Therefore, fibrinogen can play an essential role in the cascade of inflammatory reactions. Elevated fibrinogen levels could increase the risk of long-term mortality associated with underlying diseases more than systemic organ dysfunctions (14). A recent study revealed elevated fibrinogen is associated with excessive inflammation and disease severity in COVID-19 patients (15). In our research, fibrinogen levels were high in Group M patients, and this elevation was statistically significant (p<0.001). Serum albumin is also an indicator that reflects nutrition and inflammation. FAR could reflect inflammation, immune reactions, coagulation, and nutritional states related to underlying diseases associated with long-term mortality (16). While the APACHE II scoring system has been widely accepted as a measure of illness severity, the impact of its predictions affects various aspects of patient care, such as selecting medical therapy, triaging, end-of-life care, and more. It has demonstrated accurate risk stratification for death in multiple disease states and clinical settings (6). The results of this study further confirm these insights from the literature. Our results contribute to the growing body of evidence supporting the importance of serum biomarkers in critical care. Serum biomarkers are valuable tools for early decision-making in ICU management due to their ease of obtainment. Among these biomarkers, FAR and serum albumin were possible morbidity and mortality indicators. FAR, a coagulation, nutrition, and inflammation marker, has consistently shown associations with prognostic factors in various diseases, including cancer, coronary artery disease, pulmonary-related stroke, and sepsis. Recent studies have indicated FAR's potential as a predictor for survival in advanced non-small cell lung cancer patients and advanced epithelial ovarian cancer patients, respectively (19, 20). Other studies have shown that high fibrinogen levels are linked to increased inflammation and coagulation, associated with higher risks of cardiovascular events, infections, and mortality (21). Duan et al. found that the fibrinogen-albumin ratio is related to the severity of coronary artery disease (6). These findings underscore FAR's role in predicting critical illness complexity and potential. Similarly, PLR and NLR have emerged as promising predictors of mortality in ICU patients. Higher PLR and NLR levels are associated with increased mortality risk (22). In our study, both FAR and NLR were more elevated in Group M patients, in line with the literature. This elevation was statistically significant for both values (p<0.001). The study results also indicate an association between high lactate levels and the risk of in-hospital mortality, consistent with findings from other studies in the literature. Elevated lactate levels may indicate tissue hypoxia and impaired organ function. Studies have emphasised the importance of monitoring lactate concentration in ICU patients. The comparison of FAR, PLR, and NLR with APACHE II aimed to bridge a gap in the existing literature and shed light on the potential synergy between immunological markers and clinical scoring systems. Although our study is retrospective, its

results provide valuable information about the potential of these biomarkers for additional prognostic evaluation tools. Additionally, our study contributes to the ongoing debate about scoring system utilisation in intensive care units. The dynamic nature of critically ill patient conditions necessitates objective tools for clinical decision-making, efficient resource allocation, and effective treatment strategies. Scoring systems provide a structured framework for assessing patient status, comparing outcomes, and establishing a database for future research.

Study limitations: However, this study has several limitations. Significant limitations include a relatively small number of patients, single-centre conduct, retrospective nature, and a lack of exploration of other relevant immunological factors. Nonetheless, being the first retrospective study on this topic in the literature is a strength. Our results will guide further comprehensive studies with larger patient cohorts.

Conclusion

This study highlights the potential prognostic value of serum biomarkers FAR, PLR and NLR in critically ill patients admitted to the ICU. By comparing these immunological parameters with the validated APACHE II score, our findings are a stepping stone to a more comprehensive approach to prognostic evaluation. These markers could complement existing scoring systems, improving our ability to predict outcomes and improve patient care in the demanding intensive care environment.

Ethical consent: Ethics committee permission was obtained from the Giresun Training and Reseache Hospital local ethics committee with the decision number 53593568-771-218379886 and date 19.06.2023.

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