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Evaluation of the clinical course of acute phase reactants and associated factors in geriatric patients followed up in icu due to community- and hospital-acquired pneumonia

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ABSTRACT

Aims: Advancing age leads to numerous physiopathological changes, particularly in the respiratory system. Moreover, biomarkers and acute phase reactants are affected by age-related inflammation and cellular and humoral immunity changes. Our aim in this study was to evaluate the age-related course of acute phase reactants in community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) patients and to assess its relationship with independent intra-intensive unit (ICU) mortality.

Methods: Patients followed up in ICU due to CAP and HAP were evaluated retrospectively. Patients were divided into four groups in terms of age: (I) 18-64 years, (II) 65-75 years, (III) 76-90 years, and (IV) 91+ years. Acute phase reactants were measured at ICU admission and at 72 hours after admission.

Results: A total of 549 patients comprising 389 CAP and 160 HAP patients were included in the study. Mean age was 73 (range, 22-99) years and 33% of the participants were female. Age and gender were similar between the two groups. On laboratory examination, neutrophil count (NE), C-reactive protein (CRP), procalcitonin (PCT), CRP and PCT were significantly higher in the HAP group than in the CAP group. The rate of intra-ICU independent mortality was significantly higher in HAP patients than in CAP patients (24.4% vs 11.6, p<0.001). All laboratory parameters except for lymphocyte count (LY) on admission were similar between the groups.

Conclusion: The response of LY to advancing age was greater than the response of other inflammatory acute phase reactants. In patients with severe pneumonia, serial measurement of WBC, CRP, PCT, and NE may be useful in predicting short-term intra-ICU mortality.

Keywords: Age, community-acquired pneumonia, course of acute phase reactants, hospital-acquired pneumonia

INTRODUCTION

Community-acquired pneumonia (CAP) occurs at any time of life, while hospital-acquired pneumonia (HAP) develops 48 hours after hospital admission or within 48 hours of discharge. Both CAP and HAP are serious infectious diseases associated with significant mortality and morbidity. In both conditions, the risk of mortality and morbidity increases particularly in intensive care unit (ICU) patients due to the implementation of respiratory support therapies such as high-flow nasal oxygen (HFNO), noninvasive mechanical ventilation (NIMV), and invasive mechanical ventilation (IMV). In CAP and HAP patients, numerous scoring systems are used for the diagnosis, treatment, and mortality prediction.[1,2]

Acute phase reactants and biomarkers are inflammatory markers whose serum levels increase and decrease in response to several clinical conditions such as chronic diseases, fever, anorexia, sepsis, septic shock, and bacteremia. These markers are commonly used in CAP and HAP patients, particularly for the diagnosis and as markers of clinical variability and pneumonia severity. Procalcitonin (PCT), C-reactive protein (CRP), white blood cell count (WBC), neutrophil count (NE), and lymphocyte count (LY) are acute phase reactants frequently used in clinical practice. Of these, WBC, NE, and LY are simple parameters that are easily and routinely measured in complete blood count (CBC). In a previous study using CURB-65 (confusion, serum urea nitrogen level, respiratory rate, blood pressure and age ≥65 years), CRP levels were found to correlate with CURB-65 scores in patients with non-Coronavirus Disease 2019 (COVID-19) pneumonia. In CAP patients, the sensitivity and specificity of CRP are reported to be 40-90% as opposed to 38-91% for PCT.[3-5] In pneumonia patients, clinical improvement and change occur within 48 to 72 hours, while clinical stabilization begins

within 48 hours. The diagnosis and treatment planning are guided by serial and sequential measurements. There are several studies on the use of acute phase reactants such as CRP and PCT in predicting mortality and prognosis.[6,7]

With advancing age, numerous physiopathological changes occur in the respiratory system, particularly in elastic recoil pressure, lung compliance, and respiratory muscle strength. Due to these changes, the frequency of pneumonia is typically higher in the geriatric age group compared to the younger population. Moreover, in the advanced age group, pneumonia may have an atypical clinical course due to the increased incidence of comorbidities and age-related changes, resulting in higher mortality and morbidity. On the other hand, biomarkers and acute phase reactants are known to be affected by the inflammation and cellular and humoral immunity changes occurring with advanced age. The age-related variation and cut-off values of acute phase reactants in patients over 65 years old with CAP and HAP requiring intensive care due to severe pneumonia have not been clearly defined in the literature. Compared with studies in patients under 65, few studies have focused on the geriatric age group. The association of acute phase reactants with intensive care-specific independent mortality in elderly patients with pneumonia, in relation to disease severity, has been evaluated in only a limited number of studies.[8-11] In clinical practice, it is essential to define the age-related trajectory of acute phase reactants and their role in predicting clinical prognosis in geriatric patients with severe community- and hospital-acquired pneumonia. Therefore, our aim in this study was to evaluate the age-related course of acute phase reactants in CAP and HAP patients and to assess its relationship with independent intra-ICU mortality.

METHODS

This study was conducted with the approval of the Scientific Researches Ethics Committee of the Ankara Atatürk Sanatorium Training and Research Hospital (Date: 14.02.2024, Decision No: 2024 BÇEK/8). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This retrospective study included patients with CAP and HAP who were admitted to our intensive care unit between 2021 and 2023. CAP was defined as pneumonia occurring in the community setting, whereas HAP was defined as pneumonia developing at least 48 hours after hospital admission or following discharge. All the patients met the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) ICU admission criteria. Major criteria were defined as the need for mechanical ventilation and septic shock requiring vasopressor support. Minor criteria were specified as radiologically confirmed multilobar infiltrates, confusion, hypothermia and hypotension requiring fluid resuscitation, thrombocytopenia, leukopenia, uremia, a respiratory rate ≥30 breaths per minute, and an arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio ≤250 on arterial blood gas analysis. According to the ATS and IDSA criteria, patients with one major criterion or at least three minor criteria were included in the study. Patients presenting with relevant respiratory symptoms and undergoing clinical, radiological, and microbiological evaluations for diagnostic purposes were included in the study. Moreover, all the patients included in the study received an appropriate diagnosis of CAP or HAP, underwent clinical treatment, and were followed up according to national and international guidelines.[12-14] All the patients were evaluated for independent intra-ICU mortality and prognosis using the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system and the Sequential Organ Failure Assessment (SOFA) within the first 72 hours after ICU admission.[15] Patients included in the study were divided into four groups in terms of age: (I) 18-64 years, (II) 65-75 years, (III) 76-90 years, and (IV) 91+ years. CURB-65 was used to assess the severity of CAP and the Clinical Pulmonary Infection Score (CPIS) was calculated retrospectively for HAP.[12-14] Patients aged under 18 years, pregnant women, patients hospitalized due to diagnoses other than pneumonia or due to malignancy, collagen tissue diseases, and hematological diseases were excluded from the study.

WBC, NE, LY, CRP, and PCT values were recorded in all patients during ICU admission and at 72 hours after admission. Hemoglobin (Hgb) level measured at ICU admission was evaluated for each patient. Normal ranges of WBC, Hgb, NE, and LY (photometric method) were accepted as 4.6-10.2 $\times10^3/\mu L$, 12-16 g/dl, 2-7 $\times10^3/\mu L$, and 0.8-4 $\times10^3/\mu L$, respectively. Normal ranges of CRP, and PCT were accepted as 0-5 mg/L, and <0.25 ng/ml, respectively. CRP was measured using the turbidimetric assay and PCT was measured using the immunoassay method.

Statistical Analysis

Data were analyzed using SPSS for Windows version 21.0 (Armonk, NY: IBM Corp.). Categorical variables were expressed as frequencies (n) and percentages (%). Normal distribution of continuous variables was assessed by Kolmogorov-Smirnov test and histograms. Normally distributed continuous parameters were compared using Student's t-test or One-Way Analysis of Variance (ANOVA), while parameters with nonnormal distribution were analyzed by Mann-Whitney U test or Kruskal-Wallis test. Categorical variables were compared by Chi-square or Fisher's Exact test as appropriate. The accuracy of different laboratory parameters to predict 72-h mortality was evaluated by receiver operating characteristic (ROC) analysis. The accuracy of the tests was measured by the area under the ROC curve (AUC), in which an AUC close to 1 represents a perfect diagnostic test and an AUC of 0.5 represents a worthless test. A p value of <0.05 was considered significant.

RESULTS

A total of 549 patients comprising 389 (70.85%) CAP patients and 160 (29.15%) HAP patients were included in the study. Mean age was 73 years in CAP patients and 72 years in HAP patients (p=0.693). Comorbidities were present in 68.4% of CAP patients and in 70.6% of HAP patients (p=0.605). The rate of independent intra-ICU mortality was 11.6% in CAP patients and 24.4% in HAP patients and a significant difference was observed between the two groups (p<0.001). Both APACHE II and SOFA scores were significantly different between the two groups (p<0.001 for both). **Table 1** presents the demographic and clinical characteristics of the patients.

Table 1. Demographic and clinical characteristics

Variables	CAP (n=389)		HAP (n=160)		p
Gender					
Female, n (%)	129 (33.2)		52 (32.5)		
Male, n (%)	260 (66.8)		108 (67.5)		0.881
Variables	**CAP (n=389) median (min-max)**		**HAP (n=160) median (min-max)**		**p**
Age (years)	73 (22-99)		72 (25-93)		0.693
CURB-65 score	3 (3-5)				
CPIS			9.1±1.3		
APACHE II score	15 (10-30)		24 (10-30)		<0.001
SOFA score	5 (2-20)		10 (3-20)		<0.001
Variables	**CAP (n=389)**		**HAP (n=160)**		**p**
	No, n (%)	**Yes, n (%)**	**No, n (%)**	**Yes, n (%)**	
Intra-ICU mortality	344 (88.4)	45 (11.6)	121 (75.6)	39 (24.4)	< 0.001
Chronic illness	123 (31.6)	266 (68.4)	47 (29.4)	113 (70.6)	0.605
COPD	223 (57.3)	166 (42.7)	100 (62.5)	60 (37.5)	0.263
Neurological disorder	353 (90.7)	36 (9.3)	141 (88.1)	19 (11.9)	0.353
DM	318 (81.7)	71 (18.3)	130 (81.3)	30 (18.7)	0.891
Hypertension	305 (78.4)	84 (21.6)	102 (63.7)	58 (36.3)	< 0.001
CAD	344 (88.4)	45 (11.6)	128 (80)	32 (20)	0.010
Heart failure	362 (93.1)	27 (6.9)	137 (85.6)	23 (14.4)	0.006
AF	373 (95.9)	16 (4.1)	149 (93.1)	11 (6.9)	0.174

CAP: Community-acquired pneumonia, HAP: Hospital-acquired pneumonia, CURB-65: (Confusion, uremia, elevated respiratory rate, hypotension, and age ≥65), CPIS: Clinical pulmonary infection score, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: The Sequential Organ Failure Assessment, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CAD: Coronary artery disease, AF: Atrial fibrillation

Table 2 presents mean serum levels of laboratory parameters (acute phase reactants and biomarkers) measured in the study. Of these, serum levels of NE at admission, CRP at admission and at 72 hours, and PCT at admission and 72 hours were significantly different between the two groups (p=0.034, p=0.001, p=0.001, p<0.001, p<0.001, respectively).

Table 2. Laboratory parameters

Variables	CAP (n=389) median (min-max)	HAP (n=160) median (min-max)	p
WBC (µL) on admission	11000 (500-72550)	12500 (1900-38000)	0.074
WBC (µL) on 72nd hour	9900 (600-70000)	9850 (2400-45900)	0.255
LY (µL) on admission	850 (100-29010)	830 (120-6990)	0.627
LY (µL) on 72th hour	920 (80-45640)	840 (140-9300)	0.180
NE (µL) on admission	9290 (10-54410)	10760 (830-36300)	0.034
NE (µL) on 72th hour	8120 (30-50000)	8080 (2080-43790)	0.158
CRP (mg/L) on admission	69.20 (1.41-524)	98.56 (2.3-520)	0.001
CRP (mg/L) on 72th hour	66 (0.09-717)	90.18 (0.57-425)	0.001
PCT (ng/ml) on admission	0.16 (0.1-100)	0.345 (0.02-100)	<0.001
PCT (ng/ml) on 72th hour	0.11 (0.01-100)	0.38 (0.016-84.32)	<0.001

CAP: Community-acquired pneumonia, HAP: Hospital-acquired pneumonia, Min: Minimum, Max: Maximum, WBC: White blood cell count, LY: Lymphocyte count, NE: Neutrophil count, CRP: C-reactive protein, PCT: Procalcitonin

Independent predictors of intra-ICU mortality were found to be statistically significant in the overall patient population, including age, type of pneumonia (CAP and HAP), APACHE II and SOFA scores, CURB-65 score in CAP and CPIS in HAP, comorbidities such as COPD, neurological disorders, and DM (p=0.044, p<0.001, p<0.001, p<0.001, p<0.001, p=0.011 p=0.003, and p=0.021, respectively). WBC, NE, CRP, and PCT levels measured at admission and at 72 hours were statistically significant for predicting mortality (p<0.05). **Table 3** presents the association between laboratory parameters and mortality status in patients with and without mortality. Of note, WBC, CRP, NE, and PCT were statistically significant for predicting mortality at a cut-off value of >15.1, >93.72, >10.73, and >0.66, respectively (**Figure**). Serum levels of 72-h LY were significantly different among the four age

Table 3. Association between laboratory parameters and intra-ICU mortality

Variables	Without mortality (n=465) median (min-max)	With mortality (n=84) median (min-max)	p
WBC (µL) on admission	10800 (500-72550)	15250 (1000-38000)	<0.001
WBC (µL) on 72th hour	9500 (600-70000)	10700 (3600-51500)	0.017
LY (µL) on admission	860 (100-19500)	810 (140-29010)	0.587
LY (µL) on 72th hour	880 (100-15000)	820 (80-45640)	0.230
NE (µL) on admission	9260 (10-54410)	12130 (720-36300)	0.003
NE (µL) on 72th hour	7900 (30-50000)	9500 (3000-33990)	0.007
CRP (mg/L) on admission	74.01 (1.41-520)	124.35 (3.14-524)	<0.001
CRP (mg/L) on 72th hour	69.30 (0.09-717)	127.34 (7.3-463)	<0.001
PCT (ng/ml)on admission	0.16 (0.01-100)	0.95 (0.03-100)	<0.001
PCT (ng/ml) on 72th hour	0.12 (0.01-75)	1.52 (0.016-100)	<0.001

ICU: Intensive care unit, Min: Minimum, Max: Maximum, WBC: White blood cell count, LY: Lymphocyte count, NE: Neutrophil count, CRP: C-reactive protein, PCT: Procalcitonin

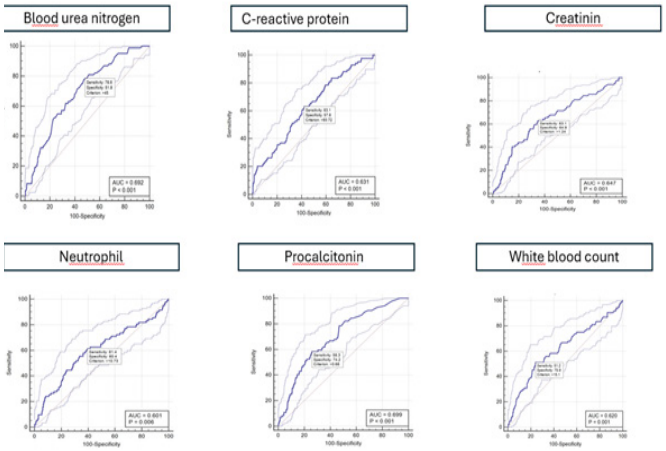

Figure. Receiver operating characteristic curve for blood urea nitrogen, C-reactive protein, creatinine, neutrophil, procalcitonin, white blood cell count to predict intra-ICU independent mortality
AUC: Area under the curve, ICU: Intensive care unit

groups (p=0.014). **Table 4** presents the laboratory parameters for age groups.

DISCUSSION

The present retrospective study evaluated geriatric patients with severe CAP and HAP and found that the rate of independent intra-ICU mortality was significantly higher in HAP patients. Similarly, both baseline and 72-h WBC, CRP, PCT, and NE levels were significantly higher in HAP patients with mortality. It was also found that the decrease in 72-h LY levels became more prominent with advanced agewith advancing age.

In the literature, geriatric patients are defined as those aged 65 years and older. Individuals aged 65-74 are considered young-old, those 75-84 as middle-old, and those 85 years and above as oldest-old. In the literature, elderly patients with acute respiratory failure in intensive care have been evaluated across different age groups. It has been demonstrated in the literature that intensive care unit admissions have increased among patients over the age of 85.[16-18] Therefore, in our study, patients were categorized into age-based groups of 18-64, 65-75, 76-90, and ≥91 years.

In individuals aged over 65, a number of changes occur in individual cells and in whole organs, leading to functional losses and physiopathological changes. Especially in the lungs, changes occur in compliance, resistance, respiratory muscle strength, gas exchange, ventilation/perfusion ratio, mucociliary transport, and cough reflex. In geriatric patients, pneumonia is the most common reason for ICU and hospital admission. In such patients, both the incidence of comorbidities and the rate of pneumonia-related mortality increase with advancing age.[8-10] Moreover, such patients have an increased need for ICU admission particularly due to acute respiratory failure. It has also been reported that the need for mechanical ventilation increases by 10 times in individuals aged over 85 compared to individuals aged 55.[19] Studies evaluating patients with severe CAP have reported in-hospital and 28-day independent mortality rates as 9.3% and 14-21%, respectively.[20,21] In a study evaluating patients with CAP, it was found that the in-hospital mortality rate in patients aged over 90 years was significantly higher than in patients aged 65-69 years.[22,23] In a study evaluating geriatric patients, the in-hospital mortality rate was 43.5% in HAP patients and 19.6% in CAP patients.[24] Studies conducted in HAP patients have reported that the mortality rate in HAP patients is higher than in CAP patients due to disease severity. Additionally, the statistically significant difference in cardiovascular comorbidities among the pneumonia groups observed in our study was considered to be associated with an increased mortality rate. In our study, the rate of independent intra-ICU mortality was 11.2% in CAP patients and 24.4% in HAP patients. As suggested in the literature, this difference could be attributed to the greater disease severity in HAP. On the other hand, previous studies have reported a relatively higher mortality rate in HAP due to higher patient age and the greater disease severity.[22-24] Likewise, mean age of our patients with mortality was higher in the HAP group than in the CAP group.

In lower respiratory tract infections such as HAP and CAP, changes occur in inflammatory acute phase reactants due to a number of factors including immune response, inflammatory cytokines, and inflammatory processes.[1] Moreover, with advancing age, changes occur in cellular and humoral immunity. To date, no reference values have been defined for serum levels of acute phase reactants in the elderly compared to the young population. Therefore, it is difficult to establish reference values due to comorbidities, physiopathological alterations, and functional losses.[25] CRP, PCT, WBC, NE, and LY are acute phase reactants frequently used in clinical practice.

Table 4. Laboratory parameters in different age groups

Variables	Group I (n=163) median (min-max)	Group II (n=170) median (min-max)	Group III (n=199) median (min-max)	Group IV (n=17) median (min-max)	p
WBC (µL) on admission	10880 (1000-36600)	12050 (1400-72550)	11400 (1900-37700)	8200 (500-30900)	0.249
WBC (µL) on 72nd hour	9400 (1600-45900)	9700 (600-70000)	10150 (2400-51500)	8700 (700-24500)	0.639
LY (µL) on admission,	900 (100-7420)	850 (110-16520)	800 (120-29010)	520 (400-6990)	0.136
LY (µL) on 72th hour,)	1000 (150-9300)	790 (190-21870)	860 (80-45640)	750 (230-6680)	0.014
NE (µL) on admission,	9430 (720-33790)	9960 (830-54410)	9500 (1450-35680)	6450 (10-29510)	0.407
NE (µL) on 72th hour,	7770 (1180-43790)	8000 (1970-50000)	8370 (1080-34970)	7330 (30-22720)	0.703
CRP (mg/L) on admission	71.51 (2-524)	69.12 (3-480)	96.90 (1.41-520)	66.08 (5.46-290)	0.090
CRP (mg/L) on 72th hour	63 (1.43-425)	66.38 (1-330)	82.29 (0.09-717)	84.94 (7.12-251)	0.105
PCT (ng/ml) on admission	0.2 (0.01-100)	0.215 (0.01-98.330)	0.26 (0.01-100)	0.16 (0.02-11.58)	0.765
PCT (ng/ml) on 72th hour	0.11 (0.01-100)	0.2 (0.01-54)	0.13 (0.016-100)	0.24 (0.04-10.72)	0.500

Group I: 18-64 years, Group II: 65-75 years, Group III: 76-90 years, Group IV: 91+ years, Min: Minimum, Max: Maximum, WBC: White blood cell count, LY: Lymphocyte count, NE: Neutrophil count, CRP: C-reactive protein, PCT: Procalcitonin

A study conducted in CAP patients aged over 65 who were followed up in ICU reported that the roles of leukocytosis, CRP, and PCT in early diagnosis and prognosis prediction were limited.[18] Another study evaluated a geriatric group with CAP and showed that WBC and PCT were higher and LY levels were lower in the group with in-hospital mortality than in other groups.[26] Studies conducted in pneumonia patients aged over 65 have suggested that the severity of leukocytosis or leukopenia is consistent with the severity of the disease. Another study evaluated geriatric patients with severe CAP and showed that both WBC and NE were higher and LY was lower in the group with poor prognosis. In the same study, the lower LY value was associated with immunosuppression and impaired regulation of the immune system, whereas the higher WBC and NE values were attributed to multiple organ dysfunction and injury to organ parenchymal cells due to severe infection.[27,28] In studies evaluating CAP patients aged over 80 and 90 years, CRP, PCT, WBC, and NE were higher and LY was lower in patients with mortality.[29] Literature suggests that serial measurement of serum CRP and PCT levels is essential for monitoring the prognosis in CAP patients followed up in ICU. It is also proposed that clinical and laboratory evaluation of pneumonia patients should be performed within 48-72 hours, except in cases with clinical worsening and resistant infection.[2,12,13] In our study, inflammatory acute phase reactants were measured both at ICU admission and at 72 hours. Our findings indicated that WBC, CRP, PCT, and NE were significant predictors of independent intra-ICU mortality, which was consistent with the findings of numerous studies in the literature. In the literature, there are varying cut-off values reported for WBC, CRP, PCT, and NE.[18,26-30] The cut-off values in our study were determined based on the values obtained at ICU admission and we did not find any significant difference among the age groups with regard to WBC, CRP, PCT, and NE. A number of studies have proposed that it is difficult to establish a reference range for most of the inflammatory acute phase reactants due to the aging process.[25] Similarly, our findings indicated that appropriate reference values should be established to determine age-specific cut-off values for the inflammatory acute phase reactants to be used in predicting independent mortality in severe pneumonia patients followed up in ICU. Unlike many studies in the literature, our study showed that LY was statistically insignificant in predicting independent intra-ICU mortality. It was also revealed that the decrease in the 72-h LY with advancing age was statistically more significant than the decrease in other acute phase reactants. These findings suggest that the response of LY to advancing age in patients followed up in ICU, regardless of the type of pneumonia, is greater than the response of WBC, PCT,CRP, and NE.

Limitations

Our study had several limitations. First, it was a retrospective and single-center study and evaluated severe and critical pneumonia patients only. Second, it only evaluated independent, and hence non-specific, intra-ICU mortality. Third, acute phase reactants were only measured at admission and at 72 hours. Finally, medical treatments that could affect serum levels of inflammatory acute phase reactants could not be evaluated due to the retrospective nature of our study.

CONCLUSION

Overall, our findings indicated that serum levels of LY, one of the inflammatory acute phase reactants, decreased with advancing age on the third day after admission in patients with severe pneumonia. Additionally, the response of LY to advancing age was greater than the response of other inflammatory acute phase reactants. Further multicenter, prospective studies with a larger number of cases are needed to determine the benefits of LY in clinical practice in elderly patients with severe pneumonia. Our findings also suggested that in patients with severe pneumonia, serial measurement of WBC, CRP, PCT, and NE may be useful in predicting short-term mortality. Multicenter and prospective studies are required to determine age-specific reference and cut-off values for the acute phase reactants to be used in predicting mortality in geriatric patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Scientific Researches Ethics Committee of the Ankara Atatürk Sanatorium Training and Research Hospital (Date: 14.02.2024, Decision No: 2024 BÇEK/8).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained. This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

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

Financial Disclosure

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

Author Contributions

Designing the Study: DH; Analyzing the Data: DH; Writing the Manuscript: DH; Literature search: DH, EBÇ, MD, SS, HS; Conceptualization of Study Design: DH, EBÇ, MD, SS, HS; Data Collection: SS, MD, EBÇ, SS, GED, DH; Interpretation: SS, MD, EBÇ, SS, GED, DH.

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