

# Evaluation of the factors affecting long-term mortality in geriatric patients followed up in intensive care unit due to hospital-acquired pneumonia

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## Abstract

Aging is a normal physiological process involving changes in the respiratory system, thereby causing an increased incidence of pulmonary infections such as hospital-acquired pneumonia (HAP). The primary aim of this study was to investigate the role of acute-phase reactants and inflammation-based biomarkers in predicting 90-day mortality in patients aged over 65 years who were hospitalized in the intensive care unit (ICU) due to HAP. Clinical records of patients aged  $\geq 65$  years who were diagnosed as having HAP and were followed up in ICU were retrospectively evaluated. One hundred and fifteen ICU patients (67.8% male, mean age  $76.81 \pm 7.480$  years) were studied. Ninety-day mortality occurred in 43 (37.4%) patients. Red cell distribution (RDW, %), mean platelet volume (MPV, f/L), white blood cell count (WBC,  $10^3/\mu\text{L}$ ), C-reactive protein (CRP, mg/L), and procalcitonin (PCT, ng/mL) median values were 18.2 (13.7–35.6), 7.42 (5.66–11.2), 14.3 (3.21–40), 9.58 (0.12–32), 0.41 (0.05–100) in the group with 90-day mortality. In the Receiver Operator Characteristics Curve analysis, a WBC value  $18.2 \times 10^3/\mu\text{L}$  predicted 90-day independent mortality with a sensitivity of 90.70% and specificity of 31.94% ( $P = .029$ ). The results indicated that serum WBC level can be used for predicting long-term mortality and prognosis in HAP patients aged over 65 years. High WBC value was statistically significant in predicting 90-day independent mortality ( $P < .05$ ).

**Abbreviations:** % = percentages, ALB = albumin, APACHE II = acute physiology and chronic evaluation, CAP = community-acquired Pneumonia, CBC = complete blood count, CRP = C-reactive Protein, DM = diabetes mellitus, HAP = hospital-acquired Pneumonia, HCAP = health care-associated pneumonia, ICU = intensive care unit, MPV = mean platelet volume, PCT = procalcitonin, RDW = red cell distribution, VAP = ventilator-associated Pneumonia, WBC = white blood cell.

**Keywords:** geriatric, inflammation-based biomarkers, intensive care unit, mortality, pneumonia

## 1. Introduction

Patients aged 65 and over make up the majority of hospitalized patients. They tend to have more comorbid chronic diseases and disability and require age-appropriate management to reduce the risk of adverse events during hospitalization.<sup>[1]</sup> Underlying health conditions, malnutrition, and greater disease severity contribute to increased rates of hospital-acquired (or nosocomial) infections in older patients. The incidence of pneumonia and its associated mortality both increase with age, and pneumonia is a common and serious condition in patients aged 65 and over.<sup>[1]</sup>

Hospital-acquired pneumonia (HAP) is a form of pneumonia that occurs within 48 hours after hospital admission or 48 hours after discharge from the hospital. HAP is associated with high morbidity and mortality, particularly in patients in

the intensive care unit (ICU).<sup>[2]</sup> A previous study evaluated a cohort of geriatric patients with pneumonia, suggesting that the serum levels of the white blood cell count (WBC), lymphocyte count, C-reactive protein (CRP), and albumin (ALB) could be used for predicting mortality.<sup>[3,4]</sup> Another study evaluated geriatric HAP patients and reported that CRP and procalcitonin (PCT) had no significant prognostic value.<sup>[5]</sup> In contrast, some other studies have presented different findings regarding the prognostic value of CRP and PCT in geriatric patients with pneumonia.<sup>[6,7]</sup> Here, a previous study evaluated HAP patients, showing that serum ALB level was associated with mortality and decreased as an acute-phase reactant. The authors also noted that in the geriatric group, a low ALB level at hospital admission was associated with high mortality.<sup>[8,9]</sup> Red cell distribution width (RDW) and mean platelet volume (MPV) are routine complete blood count (CBC) parameters.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration (as revised in 2013) and its later amendments or comparable ethical standards.

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How to cite this article: Aydemir S, Hoşgün D. Evaluation of the factors affecting long-term mortality in geriatric patients followed up in intensive care unit due to hospital-acquired pneumonia. *Medicine* 2022;101:38(e30645).

Received: 12 May 2022 / Received in final form: 17 August 2022 / Accepted: 18 August 2022

<http://dx.doi.org/10.1097/MD.00000000000030645>

A study conducted on sepsis suggested that RDW and MPV could be used in risk assessment systems for predicting 28-day mortality.<sup>[10]</sup>

To the best of our knowledge, there is little documentation of HAP in the geriatric population. In particular, data on the use of WBC, ALB, CRP, PCT, RDW, and MPV in predicting mortality are contradictory and highly limited. The primary aim of the current study was to investigate the role of acute-phase reactants and inflammation-based biomarkers in predicting 90-day independent mortality in patients aged 65 years or older who were hospitalized in the ICU because of HAP. Our secondary aim was to evaluate the effect of hospital and ICU admissions within the 90-day number of emergency room admissions, the referring clinic (emergency department or chest diseases clinic), clinical risk factors, and durations of hospital and ICU stay on mortality.

## 2. Materials and Methods

### 2.1. Study design

This retrospective observational study was conducted in the 20-bed Intensive Care Clinic of Atatürk Chest Diseases and Chest Surgery Education and Research Hospital (medical center), Department of Anesthesiology and Reanimation, between January 2016 and March 2021. Ethics committee approval with the protocol code of 2012-KAEH-15/2445 was granted prior to the start of the study.

HAP is pneumonia that occurs 48 hours or more after admission and did not appear to be incubating at the time of admission. Definitive diagnosis of HAP is a form of pneumonia that occurs within 48 hours after hospital admission or 48 hours after discharge from the hospital.

### 2.2. Patients and methods

The clinical records of patients over the age of 65 who were admitted to the ICU with the diagnosis of HAP and who were diagnosed with HAP during their stay in the ICU were evaluated retrospectively. All patients were diagnosed, followed up, and treated according to international guidelines for HAP.<sup>[2]</sup> Only patients who met the Infectious Diseases Society of America/American Thoracic Society consensus criteria for ICU admission,<sup>[11]</sup> underwent laboratory tests including CBC, ALB, CRP, and PCT and microbiological sampling, and were followed up for their 90-day independent mortality were included.

Microbiological samples were obtained within the first 1 hours of ICU admission and the blood laboratory values within the first 24 hours after the admission of the patients to the ICU were analyzed retrospectively. While the laboratory values of the patients were recorded, if steroids were administered within the first 24 hours of ICU hospitalization, the values before steroid administration were included in the study.

Sputum specimens containing  $\geq 25$  polymorph nuclear leukocytes and fewer than 10 epithelial cells per low power field were considered acceptable. Patients were deemed culture positive if semi-quantitative cultures of sputum, blood, and urine were 10<sup>4</sup>, 10<sup>3</sup>, and 10<sup>5</sup> U/mL, respectively.<sup>[2,11]</sup> The posterior-anterior chest X-rays obtained on ICU admission were retrospectively evaluated by a specialist pulmonologist. The Acute Physiology and Chronic Evaluation (APACHE II) score was calculated within the first 24 hours of ICU admission.<sup>[12]</sup> Hospital and ICU admissions and the number of emergency room admissions within the 90-day, the referring clinic (emergency department or chest diseases clinic), ICU records, and the durations of hospital and ICU stay were retrospectively reviewed.

Exclusion criteria in the study were: being under 65 years old, diagnosed with community-acquired pneumonia (CAP), diagnosed with healthcare-associated pneumonia (HCAP),

diagnosed with aspiration pneumonia, diagnosed with ventilator-associated pneumonia (VAP), having a history of connective tissue disease, having a history of malignancy and hematological disease, having a clinical frailty score greater than 4, using methylprednisolone within 1 week and missing data on controlled parameters. In addition, patients with a history of iron, vitamin B12 and folic acid supplementation in the last 3 months were not included in the study, as they affected the parameters of the CBC.

Normal ranges of WBC, hemoglobin, platelet, RDW, and MPV values were 4.6 to 10.2  $\times 10^3/\mu\text{L}$ , 12 to 16 g/dL, 142 to 424  $\times 10^3/\mu\text{L}$ , 11.6% to 17.2%, and 7.8 to 11 fL, respectively. Normal ranges of CRP, and ALB values were 0 to 5 mg/L and 3.5 to 7.2 mg/L, respectively. A PCT concentration of  $\geq 0.5$  ng/mL was considered indicating a low risk for and concentration of  $>2$  ng/mL as indicating high risk for infection. CRP and ALB levels were measured using the turbid metric assay on a Beckman Coulter AU5800 auto-analyzer (Beckman Coulter Inc. CA), PCT was measured using the immunoassay method on the Siemens ADVIA Centaur XP analyzer, and blood parameters were measured using the photometric method on a Mindray BC-6800 auto-hematology analyzer.

### 2.3. Statistical analysis

The data were analyzed using SPSS for Windows version 23.0 (Armonk, NY: IBM Corp.). Categorical variables were expressed as frequencies and percentages (%), and continuous variables were expressed as the mean, standard deviation, and minimum–maximum values. After checking the conformity of measurable data with normal distribution with the single sample Shapiro–Wilk test, Student *t* test was used for comparisons between groups for those with normal distribution and more than 2 variables were compared using a one-way ANOVA test. The Mann–Whitney *U* test was used to evaluate the data that did not fit the normal distribution.

Pearson  $\chi^2$  test and Kolmogorov Smirnov 2 sample tests were used for qualitative data. Receiver operator characteristics curve analysis was used in the evaluation of diagnostic tests. Arithmetic mean  $\pm$  standard deviation and Median (Min–Max) values were given for descriptive statistics. The limit of significance for all statistics was chosen as 2-sided *P* < .05.

## 3. Results

The 115 patients included in the study comprised 78 (67.8%) men and 37 (32.2) women, with a mean age of 76.81  $\pm$  7.480 years (Fig. 1). 90-day mortality occurred in 43 (37.4%) patients. Table 1 presents the demographic and clinical characteristics of the patients.

Multivariate logistic regression analysis was not performed because the number of data that was significant as a 90-day mortality factor was low. When the available data were analyzed by

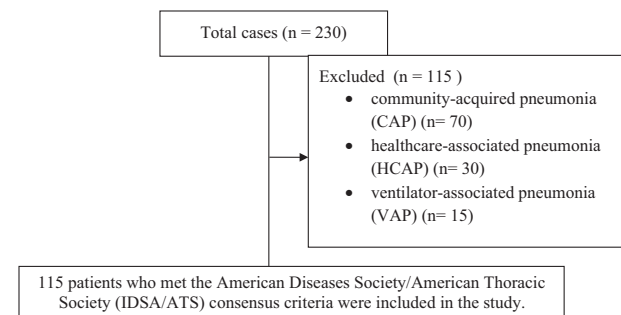


Figure 1. Flow charts of the patients.

**Table 1**  
**Demographic and clinical characteristics.**

Variables	n = 115	Mortality		P value
		No (n:72)	Yes (n:43)	
Age (yr) (median/IQR)	77 [65–93]	74 [65–90]	77 [66–93]	.076
Gender (male/female)	78/37	51/21	27/16	.374
APACHE II (median/IQR)	26 [13–54]	27 [13–42]	25 [16–54]	.794
ICU stay (d) (median/IQR)	19 [1–96]	19.5 [5–96]	16 [1–48]	.673
Hospital stay (d) (median/IQR)	27 [7–146]	26 [9–126]	28 [7–146]	.553
Number of emergency room admissions (median/IQR)	4 [0–22]	4.5 [0–20]	3 [0–22]	.725
Hospital admission within the 90-d (n%)	96(83.5%)	58 (80.5%)	38 (88.4%)	.442
ICU admission within the last 90-d (n%)	56 (48.7%)	33 (45.8%)	23 (53.5%)	.429
Comorbidities (n%)	102 (88.7%)	65 (90.2%)	37 (86%)	.488
HT (n%)	51 (44.3%)	34 (47.2%)	17 (39.5%)	.422
DM (n%)	21 (18.3%)	15 (20.8%)	6 (14%)	.356
CHF (n%)	34 (29.6%)	22 (30.6%)	12 (27.9%)	.764
COPD (n%)	78 (67.8%)	50 (69.4%)	28 (65.1%)	.631
CAD (n%)	33 (28.7%)	20 (27.8%)	13 (30.2%)	.778
CKD (n%)	14 (12.2%)	8 (11.1%)	6 (14.0%)	.652
CVD (n%)	36 (31.3%)	22 (30.6%)	14 (32.6%)	.823
Variables			n	%
Referring clinic		Chest diseases clinic	71	61.7
		Emergency department	23	20.0
		ICU admission	21	18.3
Culture growth in intensive care admission		No	73	63.5
		Yes	42	36.5
Pathogen		<i>P aeruginosa</i>	29	25.2
		<i>A baumannii</i>	68	59.1
		<i>P aeruginosa</i> + <i>A baumannii</i>	1	0.9
		<i>K pneumoniae</i>	1	0.9
		<i>A baumannii</i> + <i>K pneumoniae</i>	12	10.4
		<i>A baumannii</i> + <i>P aeruginosa</i>	4	3.5
Culture sample type		Endotracheal aspirate	71	61.7
		Sputum	44	38.3

*A baumannii* = *Acinetobacter baumannii*, APACHE II = acute physiology and chronic health evaluation II, CAD = coronary artery disease, CHF = congestive heart failure, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CVD = cerebrovascular disease, DM = diabetes mellitus, HT = hypertension, ICU = intensive care unit, IQR = interquartile range, *K pneumoniae* = *Klebsiella pneumoniae*, *P aeruginosa* = *Pseudomonas aeruginosa*, SD = standard deviation.

univariate logistic regression analysis, leukocyte elevation was found to be significant as a 90-day mortality factor ( $P = .019$ ). Age, gender, comorbidities, APACHE II score, durations of hospital and ICU stay, and the number of emergency room admissions within the 90-day had no significant effect on mortality ( $P = .076$ ,  $P = .374$ ,  $P = .488$ ,  $P = .794$ ,  $P = .553$ ,  $P = .673$ , and  $P = .725$ , respectively). Similarly, no significant relationship was found between the presence and type of bacterial infection and mortality ( $P > .05$ ).

**Table 2**  
**Relationships between laboratory parameters and mortality.**

Variables	Mortality		P
	Yes (n = 43)	No (n = 72)	
HGB (g/dL) (Median/IQR)	11.4 (7.24–17.4)	12.6 (8.41–17.9)	.249
PLT ( $10^3/\mu\text{L}$ ) (Median/IQR)	236.5 (20–772)	224 (68–553)	.865
RDW (%) (Median/IQR)	18.2 (13.7–35.6)	18.2 (13.6–26.6)	.737
MPV (fL) (Median/IQR)	7.42 (5.66–11.2)	7.73 (6.15–14.8)	.239
WBC ( $10^3/\mu\text{L}$ ) (Median/IQR)	14.3 (3.21–40)	12.5 (6.35–22.5)	<b>.037</b>
ALB (g/L) (Mean $\pm$ SD)	3.08 $\pm$ 0.54	3.20 $\pm$ 0.53	.263
CRP (mg/L) (Median/IQR)	9.58 (0.12–32)	8.11 (0.87–32)	.956
PCT (ng/mL) (Median/IQR)	0.41 (0.05–100)	0.51 (0.05–35.23)	.995

Statistically significant  $P$ -values are in bold.

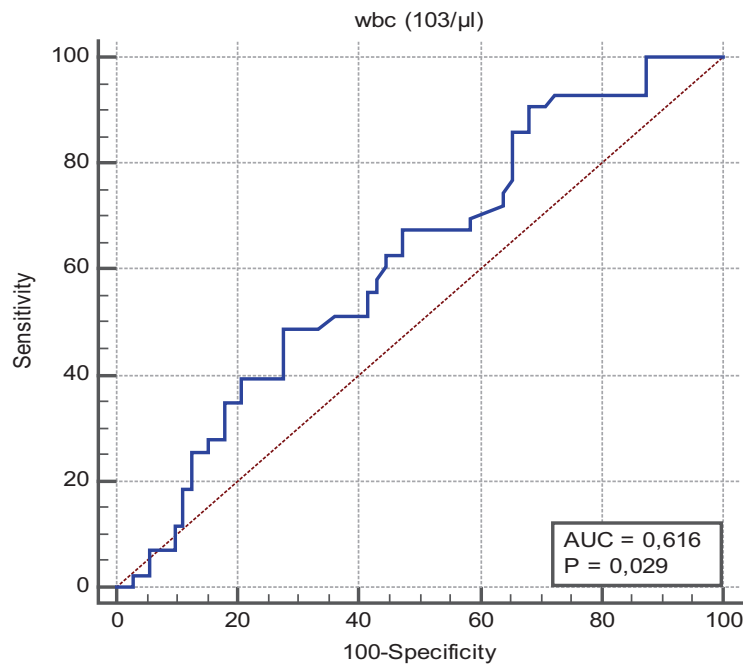
ALB = albumin, CRP = C-reactive protein, HGB = hemoglobin, IQR = interquartile range, MPV = mean platelet volume, PCT = pro-calcitonin, PLT = platelet (thrombocyte), RDW = red cell distribution width, SD = standard deviation, WBC = leukocyte count.

No significant difference was found between the surviving and no-surviving patients regarding serum hemoglobin, PLT, RDW, MPV, ALB, CRP, and PCT levels ( $P > .05$ ). Table 2 shows the relationship between laboratory parameters and 90-day mortality. WBC value was statistically significant in predicting 90-day independent mortality ( $P = .037$ ). In the receiver operator characteristics curve analysis, a WBC value  $18.2 \times 10^3/\mu\text{L}$  predicted 90-day independent mortality with a sensitivity of 90.70% and specificity of 31.94% (Fig. 2). Moreover, the serum WBC value was significantly higher in patients with a history of hospitalization within the past 90-day ( $P < .05$ ) and established a positive correlation with the number of emergency room admissions within the past 90-day ( $P < .05$ ).

Multivariate logistic regression analysis indicated that the durations of hospital and ICU stay, APACHE II score, and number of emergency room admissions within the past 90-day had no significant effect on hospital and ICU admission.

#### 4. Discussion

Aging is a normal physiological process involving changes in all bodily functions, the respiratory system, causing a decrease in elastic recoil, compliance, mucociliary transport, and cough reflex in lung functions, as well as changes in cellular and humoral immunity. For these reasons, the frequency of pneumonia is higher in individuals aged over 65 years compared with younger individuals and the mortality rate has been reported to be 10% to 30% in this population.<sup>[1,3]</sup> Cascini et al evaluated HAP patients aged over 65 years and reported the prevalence of in-hospital mortality as 32.3% and 30-day mortality



	<b>WBC</b>
<b>AUC</b>	0,616
<b>Cutoff</b>	≤18,2
<b>Sensitive (%)</b>	90,70
<b>95%-CI (%)</b>	77,9-97,4
<b>Spesitive</b>	31,94
<b>95%-CI (%)</b>	21,4-44,0
<b>PPV</b>	44,3
<b>NPV</b>	85,2
<b>+LR</b>	1,33
<b>-LR</b>	0,29
<b>p</b>	<b>0,029</b>

Figure 2. Effect of WBC (white blood cell) in predicting 90-day mortality.

as 38.2%. Maruyama et al evaluated geriatric HAP patients and reported the prevalence of in-hospital mortality as being 51.5%.<sup>[13]</sup> Because of the numerous factors affecting mortality, such as comorbidities and microbiological culture results, the rate of mortality from HAP is between 30% and 70%, regardless of age.<sup>[2]</sup>

In our study, only HAP patients aged over 65 years were evaluated; patients with VAP and HCAP were excluded. Our results have shown that the prevalence of 90-day independent mortality was 62.6%. Because studies evaluating geriatric patients with HAP have mostly investigated in-hospital and 30-day mortality, no comparison could be performed between our mortality rate and the literature because of the scarcity of studies investigating 90-day independent mortality in HAP patients aged over 65 years. Even so, the rate of short-term mortality in our study was found to be higher than that reported in the literature, which could be attributed to the higher APACHE II scores, longer durations of hospital and ICU stay, and the higher rate of bacterial infections in our patients.

In our study, hospital and ICU admission and the number of emergency room admissions within the past 90-day, which could be risk factors for geriatric HAP patients, had no significant effect in predicting long-term mortality. To the best of our

knowledge, there has been no study investigating the effect of hospital and ICU admission and the number of emergency room admissions within the past 90-day on mortality in geriatric HAP patients. Therefore, no comparison could be performed. Accordingly, our study is the first of its kind in the literature. In addition, the literature has indicated that the mean durations of hospital and ICU stay in HAP patients are higher than those of CAP and HCAP patients. In our study, durations of hospital and ICU stay were not statistically significant in predicting 90-day independent mortality. Accordingly, our findings were inconsistent with those reported in the literature in terms of short-term mortality.<sup>[2,13,14]</sup>

Aging has been associated with changes in pro-inflammatory cytokines and acute-phase reactants as a result of normal physiological processes. In turn, these changes have led to different interpretations of the reference values of laboratory parameters in geriatric individuals compared with those of young individuals. In a retrospective study, Nouvenne et al evaluated patients with CAP and HCAP aged over 65 years, reporting that high-sensitive CRP was more useful than PCT.<sup>[6]</sup> Ahkee et al evaluated geriatric patients with CAP and found an inverse relationship between WBC values and mortality.<sup>[15]</sup> Li et al evaluated geriatric patients with severe pneumonia and reported that WBC, ALB, and CRP levels were statistically significant in predicting



mortality.<sup>[4]</sup> However, recent studies have shown that RDW and MPV could be beneficial when it comes to predicting mortality in inflammation-based diseases.<sup>[16–18]</sup> Another study found that both CRP and PCT were reliable in diagnosing HAP, suggesting that PCT could be used in predicting mortality.<sup>[7]</sup> A study conducted on CAP patients found a significant relationship between RDW and MPV levels and high mortality risk.<sup>[19]</sup>

In our study, however, RDW, MPV, ALB, CRP, and PCT levels were not noted as significant predictors of 90-day mortality. Other studies have mostly evaluated CAP patients, and to the best of our knowledge, there is little documentation on the relationship between these serum markers and long-term independent mortality in HAP patients. For these reasons, no comparison could be performed. On the other hand, the absence of a significant effect of RDW, MPV, ALB, CRP, and PCT in predicting mortality could be attributed to the fact that a single measurement was performed for these parameters and that this measurement might not have been performed at a time period when these parameters were elevated (at least 6–24 hour after admission).<sup>[20]</sup>

Our results show that WBC value was statistically significant in predicting 90-day independent mortality and a positive correlation was found between serum WBC value and the number of emergency room admissions within the past 90-day. Additionally, serum WBC levels were significantly higher in patients with a history of hospitalization within the past 90-day and a WBC value  $18.2 \times 10^3/\mu\text{L}$  predicted 90-day independent mortality. Studies exploring the role of WBC value in predicting mortality in the geriatric population have mostly investigated CAP and evaluated short-term mortality. A comparison 4 findings with those of studies investigating short-term mortality in geriatric patients with CAP, HAP, and VAP indicated that our serum WBC value was consistent with the values reported in those studies. The literature indicates that WBC has been used both in the Clinical Pulmonary Infection Score, which is used in the diagnosis of VAP and in the APACHE II scoring system, which is used for predicting short-term mortality in the ICU.<sup>[13,21]</sup> In each of these scoring systems, a single measurement is performed. Similarly, in our study, the serum WBC level was assessed by a single measurement. Our findings indicated that serum WBC value established a significant relationship with emergency room and hospital admissions within the last 1 year, both of which may be risk factors particularly in the geriatric population. In the light of these data, we consider that novel risk assessment systems involving WBC should be developed for the diagnosis of HAP patients and for predicting long-term mortality in such patients. Accordingly, multi-center prospective studies are needed.

Our study was limited in several ways. First, it was a single-center retrospective study and included a relatively small number of patients. Second, serum levels blood parameters, and acute-phase reactants were assessed by a single measurement during ICU admission and no serial measurements were performed. Third, geriatric patients only included individuals aged over 65 years. Finally, long-term mortality was evaluated based on independent mortality, not based on specific causes of death. When the power of our study is calculated in terms of other variables, especially the APACHE score, it is calculated below the 80% value. Therefore, when evaluating the main results of our study, it should be considered that the risk of type-2 error is high. This result is due to the small number of our patient population.

In conclusion, geriatric HAP patients have high morbidity and mortality rates. Our study is 1 of the few evaluating the effect of inflammation-based biomarkers and acute-phase reactants on long-term independent mortality (90-day) in HAP patients aged 65 years and older. The results indicate that serum WBC levels can be used for predicting long-term mortality (90-day) and prognosis in HAP patients aged 65 years and

older. In the light of these data, a new risk assessment system including WBC can be developed to diagnose HAP patients and to predict long-term mortality in these patients. However; more studies with larger patient populations are needed on this subject.

## Author contributions

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**Formal analysis:** Derya Hoşgün, Semih Aydemir.

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**Project administration:** Derya Hoşgün, Semih Aydemir.

**Validation:** Derya Hoşgün, Semih Aydemir.

**Visualization:** Derya Hoşgün, Semih Aydemir.

**Writing – original draft:** Derya Hoşgün, Semih Aydemir.

**Writing – review & editing:** Derya Hoşgün, Semih Aydemir.

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