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Can the percentage of immature granulocytes predict mortality of octogenarian patients in intensive care?

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ABSTRACT

Aims: This study aimed to investigate the effectiveness of immature granulocyte count and the percentage of immature granulocytes in predicting mortality in patients aged 80 years and older (octogenarians) in intensive care units.

Methods: This retrospective study included 333 patients aged 80 years and older who were followed up in the intensive care unit. Demographic data, laboratory values, clinical outcomes, and mortality status were recorded. The data were evaluated in two groups: survivors and deaths. Differences between the groups were statistically analyzed and compared.

Results: While the Glasgow Coma Scale (GCS) was lower in the mortality group, the acute physiology and chronic health evaluation II (APACHE II) and sequential organ function assessment (SOFA) scores were higher than in the survivors ($p<0.001$ for all). C reactive protein (CRP), neutrophil-to-lymphocyte ratio, and lactate values were significant markers for mortality prediction. No significant difference was found for immature granulocyte count and percentage when the groups were compared. APACHE II and SOFA scores had the highest discriminatory power in predicting mortality, with the area under the curve =0.74.

Conclusion: In octogenarian patients followed up in the intensive care unit, we found that the number and percentage of immature granulocytes was not an effective biomarker for predicting mortality despite its cheap and easy use. In the future, more comprehensive studies may show the importance of immature granulocytes.

Keywords: Octogenarian, immature granulocyte, mortality, intensive care

INTRODUCTION

In the medical literature, old age is analyzed under different categories. Although individuals between 80 and 89 are defined as octogenarians, this age group has been admitted to intensive care units more frequently due to modern medical innovations, improved surgical and anesthesia practices, and increased life expectancy.[1] However, intensive care follow-up of octogenarian patients has unique challenges due to age-related physiologic changes and the multiplicity of comorbid diseases.[2] While the risk of infection increases due to the immune system weakness that develops due to aging, the healing process is more complex, and aggressive treatment is required.[3]

Long-term survival rates in octogenarians are generally low, and intensive care mortality rates are significantly higher than in younger age groups.[4] Multiple comorbid conditions, low functional capacity before intensive care, the need for advanced supportive therapies such as mechanical ventilation and hemodialysis, and high indicators in mortality-related scoring systems are associated with mortality.[5]

There is still no definitive laboratory parameter or scoring system to indicate the severity of the disease and predict the prognosis in intensive care unit patients. However, some biomarkers are being investigated and used to predict morbidity and mortality in octogenarian patients.[6-9]

Immature granulocytes (IGs) are immature cells that pass into the peripheral blood due to stimulation of the bone marrow for various reasons and indicate bone marrow activation. They are elevated mainly due to severe infections, inflammation, sepsis, malignancies, hypoxic conditions, or bone marrow involvement.[10] Increased IG levels in patients followed up in intensive care can indicate the catabolism process in the body and disease severity and can be used as a biomarker that can predict mortality.[11] This may guide in determining patients' follow-up and treatment strategies in the intensive care unit.

In this retrospective study, we aimed to investigate the role of IG number and percentage in predicting the mortality of octogenarian patients in the intensive care unit.

METHODS

Ethics

The study was conducted retrospectively after ethics committee approval was obtained from Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee

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(Date: 08.05.2024, Decision No: AEŞH-BADEK2024-413). All procedures were carried out according to the ethical rules and principles of the Declaration of Helsinki.

Study Population and Protocol

The data of this retrospective study were obtained from patients aged ≥80 who were followed up in the intensive care units of Ankara Etlik City Hospital between May 01, 2023, and May 01, 2024. Patients who stayed in the intensive care unit for less than 48 hours, patients younger than 80, and patients with missing medical data records were excluded.

Data Collection

Age, gender, comorbidities, diagnosis and diagnosis groups, laboratory values, intensive care unit stay duration, total length of hospitalization, disease outcome (live-ex), and GCS were obtained from the hospital information management system and patient observation forms. The need for invasive mechanical ventilation in the intensive care unit, vasopressor requirement, development of acute kidney injury, and whether renal replacement therapy was administered were recorded. Arterial blood gas, hemogram, and biochemical parameters were evaluated based on samples taken on admission to the intensive care unit. IG count and percentage were recorded at the time of admission, on the day of discharge from the intensive care unit, and 24 and 48 hours before discharge. Neutrophil count, lymphocyte count, neutrophil/lymphocyte ratio, platelet count, white blood cell count, hemoglobin, creatinine, procalcitonin, CRP, and lactate values were obtained from the hospital information management system. APACHE II and SOFA scores calculated within the first 24 hours of admission were recorded. Patients were categorized into two groups: those who lived (survivors) and those who died (mortality group). The primary outcome of the study was intensive care unit mortality.

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. Continuous variables were presented as mean±standard deviation (SD) and were analyzed with the Mann-Whitney U test. Categorical variables were expressed as frequency (n) and percentage (%) and analyzed using the Chi-square test. Receiver operating characteristic (ROC) curves were employed to determine the optimal cut-off values for continuous variables that showed significant differences in paired comparisons. Metrics such as the area under the curve (AUC), sensitivity, specificity, negative likelihood ratio, and positive likelihood ratio were calculated. A two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA), and Python version 3.11.6, with the libraries "statsmodels,""scikit-learn,""matplotlib," and "seaborn."

RESULTS

A total of 333 octogenarian patients were included in the study. The median age of the patients included in the study was 84 (interquartile range (IQR): 80-98) years; 40.24% were male. Respiratory diseases accounted for 34.83%, sepsis 21.32%, and neurologic diseases 11.41% of the patients. 149 (44.74%) of the patients died (**Table 1**).

Table 1. The demographic and clinical characteristics of the patients

	n (%)
Gender	
Male	134 (40.24)
Female	199 (59.76)
Diagnosis groups	
Respiratory	116 (34.83)
Sepsis	71 (21.32)
Neurological	38 (11.41)
Postoperative	29 (8.71)
Cardiovascular	26 (7.81)
Renal-metabolic	19 (5.71)
Gastrointestinal	16 (4.8)
Trauma	12 (3.6)
Oncologic	4 (1.2)
Hematologic	2 (0.6)
Patient outcome	
Surviving	184 (55.26)
Exitus	149 (44.74)
Invasive mechanical ventilation requirement	160 (48.05)
Requirement for vasopressors in ICU	200 (60.06)
Acute kidney injury	170 (51.05)
Requirement for dialysis and/ or CRRT	83 (24.92)

ICU: Intensive care unit, CRRT: Continuous renal replacement therapy

The median values for APACHE II, SOFA, and GCS were 22 (IQR: 4-47), 6 (IQR: 1-14), and 13 (IQR: 3-15), respectively. The median values for intensive care unit length of stay and total hospitalization were 8 (IQR: 3-114) days and 18 (IQR: 3-258) days, respectively.

Of 184 patients in the surviving group, 63 (34.23%) were male, and the median age was 84 (IQR: 80-97) years. The median length of intensive care unit stay and total hospitalization were 6 (IQR: 3-96) days and 17 (IQR: 4-258) days, respectively. Of the 149 patients in the mortality group, 71 (47.65%) were male, and the median age was 85 years (IQR: 80-98). The median length of intensive care unit stay and total hospitalization were 12 (IQR: 3-114) days and 18 (IQR: 3-114) days, respectively.

While the GCS was lower in the mortality group, APACHE II and SOFA scores were higher in the mortality group compared to the survivors ($p<0.001$ for all). In laboratory results, neutrophil-to-lymphocyte ratio, lactate, and CRP values were higher in the mortality group ($p<0.001$, $p<0.001$, $p=0.014$, respectively). When the groups were compared for IG%, although the IG% values measured at discharge and 24 hours before discharge were higher in the mortality group, there was no statistically significant difference between the two groups. In addition, there was no significant difference in the IG% values measured at admission and 48 hours before discharge (**Table 2**).

When the ROC curve analyses were analyzed, the AUC value was 0.560, the cut-off value was 0.6, the sensitivity value was 0.68, and the specificity value was 0.5 in the prediction of IG % mortality 48 hours before discharge. The highest AUC values in the analyses were APACHE II and SOFA scores. The AUC value for both values was 0.740. Cut-off values were 21 and 7, respectively (**Table 3, Figure**).

Table 2. Clinical and laboratory findings of the whole study group and subgroups

	Total (n=333) study group	Survival group (n=184)	Mortality grup (n=149)	p-value
Age, years	84 (80-98)	84 (80-97)	85 (80-98)	0.13
Gender (male)	134 (40.24%)	63 (34.23%)	71 (47.65%)	0.26
Length of intensive care unit stay (days)	8 (3-114)	6 (3-96)	12 (3-114)	**<0.001**
Length of hospital stay (days)	18 (3-258)	17 (4-258)	18 (3-114)	0.63
Glasgow Coma Scale score	13 (3-15)	14 (5-15)	12 (3-15)	**<0.001**
APACHE II score	22 (4-47)	18 (4-40)	25 (5-47)	**<0.001**
SOFA score	6 (1-14)	5 (1-14)	8 (1-13)	**<0.001**
Creatinine mg/dl	1.32 (0.39-7.95)	1.265 (0.4-7.95)	1.36 (0.39-5.63)	0.143
CRP mg/L	83.8 (0.42-438.34)	65.35 (0.42-367.12)	105.62 (0.74-438.34)	**0.014**
Procalcitonin ng/ml	0.38 (0.02-100)	0.265 (0.02-100)	0.66 (0.02-100)	3.994
WBC $\times10^3$/uL	12.28 (2.06-38.53)	11.515 (2.06-31.49)	13.01 (3.6-38.53)	0.149
Hemoglobin ×g/dl	10.5 (4-17.4)	10.7 (4-17.4)	10.4 (4.3-15.9)	0.72
Thrombocytes $\times10^3$/uL	222 (11-660)	228 (16-660)	217 (11-651)	0.09
Neutrophil- lymphocyte ratio	11.75 (0.85-157.47)	10.735 (0.85-128.5)	14.06 (1.23-157.47)	**<0.001**
Lactate mmol/L	2.04 (0.67-14.76)	1.9 (0.78-14.76)	2.33 (0.67-8.75)	**<0.001**
IG admission $\times10^3$/uL	0.08 (0.01-1.99)	0.07 (0.01-1.04)	0.08 (0.01-1.99)	0.08
IG% admission	0.7 (0.1-86.2)	0.7 (0.1-13.2)	0.7 (0.1-86.2)	0.2
IG 48 hours before $\times10^3$/uL	0.07 (0.01-1.96)	0.06 (0.01-1.24)	0.07 (0.01-1.96)	0.6
IG% 48 hours before	0.7 (0.1-10.7)	0.7 (0.1-6.2)	0.7 (0.1-10.7)	0.15
IG 24 hours before $\times10^3$/uL	0.06 (0.01-1.9)	0.06 (0.01-1.26)	0.07 (0.01-1.9)	0.88
IG% 24 hours before	0.7 (0.1-11.6)	0.7 (0.1-8.4)	0.8 (0.1-11.6)	0.29
IG at discharge $\times10^3$/uL	0.08 (0.01-6.25)	0.06 (0.01-1.27)	0.1 (0.01-6.25)	0.52
IG% at discharge	0.8 (0.1-25.5)	0.7 (0.1-6)	0.9 (0.2-25.5)	0.5

Bold values are significant, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Function Assessment, WBC: White blood cell, CRP: C-reactive protein, IG: Immature granulocyte

Table 3. Results of ROC curve analyses

	AUC	p-value	Cut-off value	Sensitivity	Specifity	PLR	NLR
Glasgow coma scale score	0.73	<0.001	12	0.56	0.81	0.64	0.76
APACHE II score	0.74	<0.001	21	0.68	0.67	0.55	0.78
SOFA score	0.74	<0.001	7	0.62	0.76	0.68	0.71
IG admission $\times10^3$/uL	0.4	0.08	0.04	0.54	0.9	0.31	0.54
IG% admission	0.52	0.2	0.45	0.46	0.6	0.48	0.58
IG 48 hours before $\times10^3$/uL	0.54	0.6	0.04	0.69	0.33	0.46	0.57
IG% 48 hours before	0.56	0.15	0.6	0.68	0.5	0.45	0.72
IG 24 hours before $\times10^3$/uL	0.48	0.88	0.04	0.65	0.33	0.44	0.54
IG% 24 hours before	0.54	0.29	0.43	0.88	0.24	0.41	0.77
IG at discharge $\times10^3$/uL	0.48	0.52	0.06	0.84	0.33	0.43	0.78
IG% at discharge	0.48	0.5	0.44	0.84	0.29	0.41	0.75

ROC: Receiver operating characteristic, AUC: Area under curve, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Function Assessment, IG: Immature granulocyte

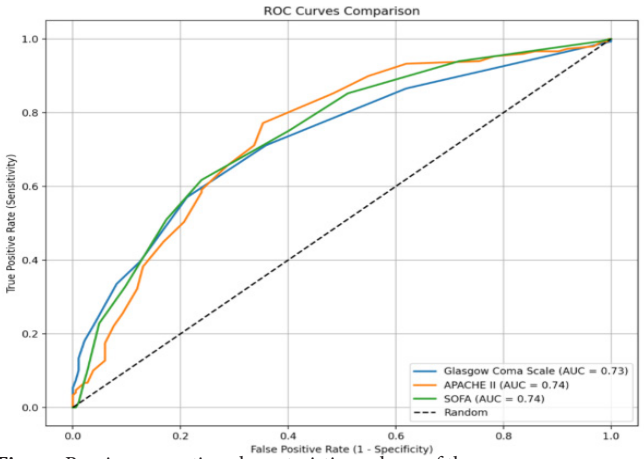

Figure. Receiver operating characteristic analyses of the scores

DISCUSSION

The elderly population is constantly increasing worldwide due to the development of modern medical techniques, increased quality of life, and improved medical diagnosis and treatment possibilities.[12] The aging of the population has also increased the incidence of acute and chronic diseases, malignancies, organ failures, and infections in these patients.[13] Therefore, many treatments that were previously not recommended or not applicable to the elderly group have started to be applied, and the intensive care needs of patients have increased during the follow-up and treatment process.[14,15]

Patients aged 80 years and older, defined as octogenarians, are a group that should be followed carefully because of their cognitive and physical capacities and comorbid diseases.[16]

Follow-up and treatment of these patients in the intensive care unit is both more difficult and associated with worse outcomes compared to the younger patient group.[17,18] In a multicenter study of patients with septic and septic shock, Bruno et al.[19] found higher mortality rates in patients over 80 years of age compared to the group aged 65-79 years. In intensive care units, predicting which patients are at risk for critical illness or mortality remains uncertain. Although there is currently no optimal biomarker to determine this, studies are ongoing worldwide.

IG is a biomarker that shows bone marrow activation and increases in conditions such as infection, inflammation, hypoxia, and sepsis. One of the reasons why it has attracted attention in recent years is that it can be easily detected during routine complete blood count and does not create an additional cost.[10] Today, many scoring systems such as APACHE II, Nutrition risk in the critically ill (NUTRIC) score, and SOFA score, and many parameters such as CRP, procalcitonin, neutrophil-lymphocyte ratio, and lactate continue to be used to evaluate the prognosis of diseases.[6-9] In the literature, many publications are investigating IG in terms of predicting the severity and prognosis of diseases such as pneumonia, appendicitis, pancreatitis, epilepsy, especially infection and sepsis.[20-24]

In a retrospective study of 438 cases in which appendectomy was performed, Unal found that the number of IGs and the percentage of IGs were significant in diagnosing acute appendicitis and had a more substantial value than classical parameters in predicting complicated appendicitis. The AUC value for predicting complicated appendicitis was 0.979, considerably higher than values such as neutrophil-lymphocyte ratio and white blood cell count.[21] Karakulak et al.[22] analyzed pancreatitis cases in a retrospective study, which included 218 cases. This study found that complicated pancreatitis and in-hospital mortality were associated with an increase in IG%. While the cut-off value of 1.1 and the AUC value of 0.698 were associated with disease severity, they reported that when the cut-off value exceeded 1.8, the AUC value was 0.708, and in-hospital mortality increased.

Akay Çizmecioğlu et al.,[23] in a study of 80 geriatric pneumonia cases, showed that although IG was effective in showing disease severity, it was low effective in showing mortality. For mortality, they determined p=0.561 and AUC value of 0.628 in all patients; when they excluded oncologic patients from the analysis, they expressed p=0.570 and AUC value of 0.732. The small number of patients in the study and the fact that the patient group included oncologic cases may be a factor in the emergence of these data. It has been stated that oncologic data affect the study's results, and the fact that the patient groups were different and no specific patient group in our study may have been decisive in our results. In the study by Bildirici et al.[24] evaluating the distinction between epilepsy and psychogenic non-epileptic seizures, the number of IGs was not found to be effective in differentiating the two conditions. Similarly, the study by Yaşar et al.[25] found that IG had no prognostic value in detecting idiopathic sudden sensorineural hearing loss. Sengul et al.[26] also found that IG count and IG% did not help determine Helicobacter pylori density and severity of inflammation.

Su et al.[27] evaluated the ability of IG to distinguish between simple and complicated diverticula of the right colon as strong in their study of 289 patients. They found a high AUC value of 0.93 and argued that surgeons could positively guide diverticulum treatment management medically and surgically.

When we compared our study with other studies, we may have obtained different results due to patient characteristics, comorbidities, presence or absence of a septic picture, malignancies, and hospital and intensive care unit admission duration. Although the IG values at discharge and 24 hours before discharge were high, we could not detect a statistically significant difference. However, it was valuable that we recorded the IG values at admission to the intensive care unit, discharge, 24 and 48 hours before discharge. In other studies, only a single IG data was evaluated. This made daily follow-up of IG values and correlation with other infection and inflammation parameters important. In systematic reviews and meta-analyses, it has been reported that IG is a strong predictor of mortality, especially in infection and sepsis.[28] IG is a valuable parameter in the early diagnosis of sepsis, exclusion of sepsis, monitoring response to treatment, and prediction of multiple organ failure. Its short half-life, ability to be obtained by routine blood count, reproducibility, and lack of additional cost make it easy to use.[10,11] There is no definite cut-off value and evaluation time for IG. Its elevation can be detected at admission to the emergency department, admission to the intensive care unit, preoperative period, postoperative period, discharge time, and any time during periodic monitoring. This can be answered by where the patient is in the picture of infection, inflammation, or sepsis. The stage of the disease and the presence or absence of complications in the postoperative period may affect the IG. In the literature, there are almost no studies on the efficacy of IG and its prognosis prediction in octogenarian patients followed up in the intensive care unit. In addition, although the number of patients in our study was high and sufficient compared to other studies, the mixed population, the presence of diagnoses in different groups, and the presence of malignant conditions may have created a heterogeneous environment regarding IG. It is possible to obtain significant results in an isolated patient group. IG, inexpensive, easy to look at, and reproducible, can be used safely in intensive care for octogenarian patients like other parameters.

Limitations

Since this was a retrospective and single-center study, the efficacy of IG should be confirmed by other studies. Secondary infection, sepsis, septic shock, and malignancy were not taken into consideration in the follow-up of IG. In addition, patients with different diagnostic groups followed up in the intensive care unit were analyzed together. IG was examined at the time of admission, at the time of discharge, and at 24 and 48 hours before discharge, while other markers were evaluated only at the time of admission.

CONCLUSION

In octogenarian patients followed up in the intensive care unit, IG, which is safe in terms of cost and ease of use, was not found to be an effective biomarker in predicting mortality. We think that regular follow-up instead of a single measurement and looking at the upward-downward trend will have an important place in patient follow-up and treatment. We believe that comprehensive studies in more specific and homogeneous patient groups will be enlightening and guiding.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 08.05.2024, Decision No: AEŞH-BADEK2024-413).

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

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