

The prognostic importance of the percentage of immature granulocyte in 28-day mortality in patients with acute coronary syndrome

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ARTICLE INFO

Article history:

Submitted: 26. 8. 2024

Revised: 21. 10. 2024

Accepted: 18. 1. 2025

Available online: 4. 2. 2025

Klíčová slova:

28denní mortalita

Akutní koronární syndrom

Nezralé granulocyty

Keywords:

28-day mortality

Acute coronary syndrome

Immature granulocytes

SOUHRN

Kontext: Procento nezralých granulocytů (immature granulocytes, IG%) je časným markerem zánětu s prognostickou hodnotou u řady onemocnění.

Cíl: V této studii jsme se pokusili zjistit, zda má procento nezralých granulocytů prognostickou hodnotu z hlediska 28denní mortality pacientů s akutním koronárním syndromem (AKS).

Metoda: Jednalo se o retrospektivní studii provedenou v období mezi 1. lednem 2019 a 30. červnem 2019 na Klinice urgentní medicíny Lékařské fakulty Univerzity v tureckém Mersinu. Do studie byli zařazeni všichni pacienti ve věku nad 18 let, kteří byli dopraveni na kliniku urgentní medicíny s bolestí na hrudi a hospitalizováni s předběžnou diagnózou AKS. Pacienti byli rozděleni do dvou skupin, na ty, kteří přežili, a ty, kteří nepřežili. Byly zaznamenány hodnoty IG% a dalších laboratorních parametrů a následně byl analyzován vztah mezi hodnotami IG% a 28denní mortalitou. Kromě toho byla pro srovnání diagnostické přesnosti hodnot IG% a dalších proměnných provedena analýza ROC.

Výsledky: Do studie bylo zařazeno celkem 617 pacientů, z tohoto počtu bylo 423 (68,6 %) mužů. Průměrný věk pacientů dosahoval $63,9 \pm 12,7$ roku. Hodnota IG% byla vyšší u nepřeživších pacientů ($1,2 \pm 1,4$) než u přeživších ($0,5 \pm 0,5$) ($p = 0,007$). V predikci 28denní mortality, pokud byla mezní hodnota IG% $> 0,6$, byla zjištěna specifita ve výši 93,70 % a senzitivita 54,55 % (AUC = 0,717; $p = 0,000$). V predikci 28denní mortality na AKS představovalo IG% nezávislý rizikový faktor (poměr rizik [hazard ratio, HR] 632,962; 95% interval spolehlivosti 3,389–118 206,572; $p = 0,016$).

Závěr: U pacientů s AKS může hodnota IG% souviset s 28denní mortalitou.

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ABSTRACT

Background: The percentage of immature granulocytes (IG%) is an early marker of inflammation and has a prognostic significance in many diseases.

Objective: In this study, we tried to investigate whether the percentage of immature granulocytes has a prognostic value in 28-day mortality in patients with acute coronary syndrome (ACS).

Method: This study was carried out retrospectively between 1.1.2019 and 30.6.2019 at Mersin University Faculty of Medicine, Department of Emergency Medicine. Patients older than 18 years who applied to the emergency department with chest pain and were hospitalized with a preliminary diagnosis of ACS were included in the study. The patients were divided into two groups as survivors and non-survivors. IG% and other laboratory parameters were recorded. The relationship between IG% and 28-day mortality was analyzed. In addition, ROC analysis was performed to compare the diagnostic accuracy of IG% and other variables.

Results: A total of 617 patients, including 423 (68.6%) men, were included in the study. The mean age of the patients were 63.9 ± 12.7 . IG% was higher in non-survivor patients (1.2 ± 1.4) than in surviving patients (0.5 ± 0.5) ($p = 0.007$). In predicting 28-day mortality, when the cut-off value for IG% was > 0.6 , the specificity was found to be 93.70% and the sensitivity to be 54.55% (AUC = 0.717, $p = 0.000$). In predicting 28-day mortality for ACS, IG% was an independent risk factor (hazard ratio [HR] 632.962, 95% confidence interval 3.389–118206.572, $p = 0.016$).

Conclusion: IG% may be associated with a 28-day mortality in patients with ACS.

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DOI: 10.33678/cor.2025.009

Introduction

Despite significant advances in the diagnosis and treatment of acute coronary syndrome, it remains the leading cause of death worldwide, and about half of these deaths are due to ischemic heart disease.¹ It is believed that high levels of inflammatory factors in the blood contribute to the development of cardiovascular events and that chronic inflammation plays a key role in the pathogenesis of atherosclerosis.² Presence of macrophages, T lymphocytes, dendritic cells and mast cells in atherosclerotic lesions; detection of HLA class II antigen expression; and the secretion of various cytokines points to the role of inflammatory mechanisms in the pathogenesis of atherosclerosis.³

Predicting the prognosis in acute coronary syndromes is a very important step in treatment and follow-up. Biomarkers such as cardiac troponins, CRP, and NT-BNP are frequently used in the prognosis of ACS patients. Despite this, clinicians are still searching for many new biomarkers that can be used to predict the prognosis of patients with ACS. Examples of these are biomarkers such as cortisol, neutrophil to lymphocyte ratio (NLR), D-dimer, adinopectin, and serum albumin, and HbA_{1c}.⁴⁻⁹

Immature granulocytes are cells secreted from the bone marrow and represent immature granulocytes. Normally, blood levels of these cells are low; however, they increase in the bone marrow during infection, inflammation or ischemic events. Since inflammatory processes in ACS may result in damage to cardiac tissue, the number of immature granulocytes is an important parameter when assessing the clinical status and prognosis of the patient.¹⁰⁻¹³

In this study, we will examine the effects of the percentage of immature granulocytes on 28-day mortality in ACS patients and provide potential prognostic information for the treatment process of patients. Aiming to contribute to both clinical practice and the existing literature, this study will be an important step towards understanding the role of inflammation in the management of cardiac diseases.

Materials and methods

Patients and study design

Patients who applied to the emergency department with chest pain complaints and were diagnosed with ACS using laboratory tests and imaging methods between 1.1.2019 and 31.6.2019 were included in this study. Our study was conducted by retrospectively scanning the data of patients from hospital electronic information operating systems. The patients included in the study were divided into two groups as those who were discharged and those who died within 28 days. Ethics committee approval (No: 2021/726 Date: 03/12/2021) was received.

Patients whose laboratory data could not be reached, patients with chest pain diagnosed as other than ACS, patients receiving chemotherapy, patients with immunosuppression, pregnant, patients with hematological disease and patients under 18 years of age were excluded from the study. 21 patients were excluded from the study and the study was completed with 617 patients (Fig. 1).

Age, gender, leucocyte, platelet, immature granulocyte percentage (IG%), NLR, glucose, C-reactive protein (CRP), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, creatinine, CK, CK-MB, and troponin values of the patients were recorded. The patients were divided into two groups as those who survived and those who died in the first 28 days. All parameters were evaluated between groups. The primary endpoint of the study was 28-day mortality in ACS patients.

Laboratory examination

Blood samples for laboratory tests were collected within 2 h of admission. After blood samples were collected in the EDTA tube for the determination of leucocyte count, platelet count and IG%, measurements were performed on the automated blood cell analyzer (XN-1000, Sysmex Corp. Kobe, Japan). The normal reference values of the parameters in our study were as follows: leukocytes (4500–10000/mm³), neutrophil percentage (42.2–75.2%), and immature granulocyte percentage (0–0.6), serum CRP (0–5 mg /dL).

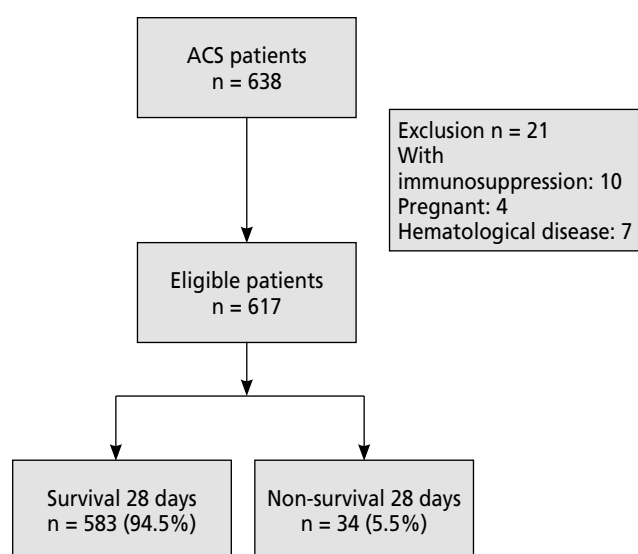


Fig. 1 – Flow chart of the study.

Table 1 – Demographic data of patients

Variables		n	Percentage
Gender	Male	423	68.6
	Female	194	31.4
IG%	Low	506	82.0
	High	111	18.0
Group	STEMI	98	15.9
	Non-STEMI	222	36.0
	USAP	297	48.1
Outcome	28-day mortality	34	5.5
	Survivor	583	91.4

Table 2 – Comparison of laboratory parameters between deceased and surviving patients

Variables	Deceased (n = 34)	Surviving (n = 583)	p
Age	73.0 ± 14.4	63.2 ± 12.3	<0.001
Leucocyte	12.92 ± 6.81	9.56 ± 3.45	0.007
Neutrophil	9.7 ± 6.8	6 ± 2.9	0.003
NLR	9.1 ± 9.8	3.1 ± 3.4	0.001
Lymphocytes	2.1 ± 1.7	2.6 ± 1.4	0.034
Platelets	238 ± 95.4	254.8 ± 79.2	0.237
IG%	1.2 ± 1.4	0.5 ± 0.5	0.007
Glucose	181.1 ± 80.9	167 ± 97	0.413
AST	83.1 ± 162	34.8 ± 53.5	0.097
ALT	42.5 ± 86	27 ± 38.2	0.309
LDH	628.5 ± 534.2	256.3 ± 108.1	0.149
CK	334.5 ± 1013.2	168.3 ± 236.1	0.385
CK-MB	49 ± 86	17.7 ± 47.6	0.047
Troponin	41.3 ± 68.9	4.6 ± 8.4	0.008
CRP	41.3 ± 68.9	11.2 ± 20.1	0.018

Statistical analysis

Statistical analyzes of this study were performed with SPSS Statistics for Windows program. Frequency distributions for categorical variables and normality controls for continuous measurements were tested with the Shapiro–Wilk test. Analysis of variance was used for group comparisons. Levene test was used for homogeneity of variances. One-way ANOVA was used for the differences between the group means in cases where the homogeneity of variances was provided, and the Welch test was used when the condition was not met. For pairwise comparisons, Bonferroni test was used when variances were

homogeneous and Games Howell test was used when heterogeneous. Pearson correlation coefficient was used to control the relationship between continuous variables. Numbers and percentages were given as descriptive statistics. $P < 0.05$ was taken as statistical significance. ROC analysis was performed for survival analysis and the area under the curve was calculated. $P < 0.05$ value was used for statistical significance.

Results

A total of 617 ACS patients, including 423 (68.6%) men and 194 (31.4%) women, were included in the study. Ninety-eight (15.9%) of the patients were STEMI, 222 (36.0%) NSTEMI and 297 (48.1%) USAP patients. The mean age of the patients were 63.9 ± 12.7 (Table 1, Fig. 1).

When the laboratory parameters of the died and surviving patients were compared; IG% (1.2 ± 1.4 , 0.5 ± 0.5 , $p = 0.007$), leukocytes (12.92 ± 6.81 , 9.56 ± 3.45 , $p < 0.007$), CRP (41.3 ± 68.9 , 11.2 ± 20.1 , $p = 0.018$), neutrophil (9.7 ± 6.8 , 6 ± 2.9 , $p = 0.003$), NLR (9.1 ± 9.8 , 3.1 ± 3.4 , $p = 0.001$), troponin (41.3 ± 68.9 , 4.6 ± 8.4 , $p = 0.008$) and creatinine (1.52 , 0.89 , $p = 0.04$) values in the deceased group was found to be higher. Lymphocyte value was significantly lower among patients who died (2.1 ± 1.7 , $p = 0.034$) (Table 2). In the ROC analysis performed to predict 28-day mortality, when the cut-off value for IG% was 0.6 and above; specificity was 93.70%, sensitivity 54.55%, PPV 15.93%, and 97.02% (AUC = 0.717, $p = 0.0001$) (Fig. 2, Table 3).

When Cox regression analysis (univariate Cox regression) was performed one by one with all parameters thought to affect death in the study, all variables except ALT value were found to be significant. After the variables thought to affect death in the study were determined as a result of univariate Cox regression analysis, multivariate Cox regression analysis was performed. As

Table 3 – Performance characteristic of laboratory parameters in predicting 28-day mortality

Variables	Cut-off	AUC (p)	Sensitivity	Selectivity	PPV	NPV
Leucocyte	>11.33	0.675 (0.0008)	55.88 (37.89–72.80)	77.53 (73.92–80.86)	12.67 (7.80–19.07)	96.79 (94.76–98.19)
Neutrophil	>8.76	0.708 (0.0001)	50.00 (32.44–67.56)	87.14 (84.14–89.75)	18.48 (11.15–27.93)	96.76 (94.87–98.10)
NLR	>3.64	0.728 (0.0001)	67.65 (49.47–82.59)	76.84 (73.20–80.21)	14.56 (9.46–21.04)	97.60 (95.75–98.80)
Lymphocytes	≤1.38	0.652 (0.0005)	50.00 (32.44–67.56)	85.93 (82.84–88.765)	17.17 (10.34–26.07)	96.72 (94.80–98.08)
IG%	>0.6	0.717 (0.0001)	54.55 (36.36–71.88)	83.70 (80.45–86.61)	15.93 (9.73–24.00)	97.02 (95.13–98.32)
CKMB	>6.2	0.681 (0.0006)	66.67 (48.17–82.02)	69.13 (65.20–72.86)	10.89 (6.95–16.03)	97.34 (95.29–98.66)
Troponin	>0.484	0.693 (0.0002)	54.55 (36.36–71.88)	76.39 (72.70–79.80)	11.69 (7.08–17.84)	96.70 (94.62–98.14)
CRP	>12.65	0.675 (0.0009)	51.52 (33.55–69.19)	78.73 (75.14–82.03)	12.32 (7.35–18.99)	96.55 (94.46–98.02)

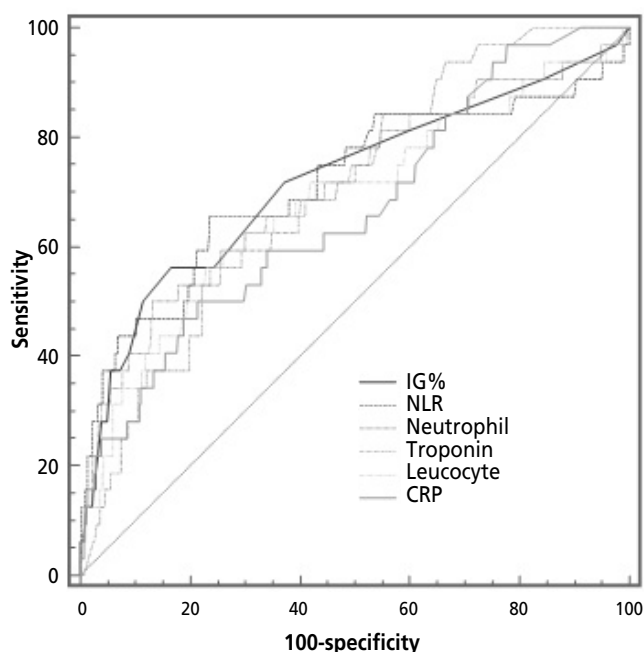


Fig. 2 – ROC curves for IG%, NLR, neutrophil, troponin, leucocytes, and CRP levels to predict 28-day mortality.

a result of the analysis, a statistically significant difference was found only in terms of IG% level (hazard ratio [HR] 632.962, 95% confidence interval 3.389–118206.572, $p = 0.016$). Accordingly, it can be said that the risk of death is 632.962 times higher as the IG% level increases ($p = 0.016$) (Table 4).

Discussion

Considering the important results of this study; The IG% was higher in patients who died (1.2 ± 1.4) than in patients who survived (0.5 ± 0.5) ($p = 0.007$). In predicting 28-day mortality, when the cut-off value for IG was $>0.6\%$, the specificity was 93.70% and the sensitivity was 54.55% (AUC = 0.71, $p = 0.000$). In predicting 28-day mortality for ACS, IG was an independent risk factor of % (hazard ratio [HR] 632.962, 95% confidence interval 3.389–118206.572, $p = 0.016$).

In a study investigating sudden cardiac arrest and sudden cardiac death following unstable angina pectoris and myocardial infarction, the incidence rates were 45.8% for NSTEMI, 35.5% for STEMI, and 18.7% for USAP. In another study conducted in China, the incidence of USAP was found to be quite high.^{14,15} In our study, STEMI occurred in 15.9% of cases, NSTEMI in 36%, and USAP in 48.1%. We believe that the high rate of USAP may be attributed to

Table 4 – Univariate and multivariate Cox regression analysis for 28-day mortality

Variables	Univariate analysis			Multivariate analysis		
	B	HR (95% CI)	p	B	HR (95% CI)	p
Age	0.058	1.060 (1.036–1.084)	<0.001	0.203	1.226 (1.03–1.457)	0.021
Leucocyte	0.114	1.121 (1.075–1.168)	<0.001	1.217	3.377 (0.033–343.458)	0.606
Neutrophil	0.135	1.144 (1.101–1.190)	<0.001	–1.253	0.86 (0.003–29.576)	0.597
NLR	0.098	1.103 (1.076–1.131)	<0.001	–0.054	0.948 (0.689–1.303)	0.740
IG%	1.615	5.028 (2.961–8.539)	<0.001	6.45	632.962 (3.389–118206.572)	0.016
Glucose	0.002	1.002 (1.000–1.004)	0.023	0.004	1.004 (0.984–1.025)	0.689
AST	0.003	1.003 (1.001–1.005)	0.001	–0.140	0.869 (0.673–1.121)	0.281
ALT	0.003	1.003 (0.999–1.007)	0.105	–0.185	0.831 (0.642–1.076)	0.160
LDH	0.002	1.002 (1.001–1.004)	<0.001	0.003	1.003 (0.996–1.010)	0.407
CK	0.001	1.001 (1.000–1.001)	0.002	–0.003	0.997 (0.970–1.025)	0.849
CKMB	0.005	1.005 (1.001–1.008)	0.007	0.013	1.013 (0.878–1.170)	0.857
CRP	0.014	1.014 (1.010–1.017)	<0.001	0.113	1.120 (0.969–1.294)	0.126

the absence of an hsTN kit in our hospital and the use of the classical troponin test.

Early evaluation and treatment in the emergency department is of great importance in patients with cardiovascular disease associated with high mortality, such as ACS.¹⁶ Various biomarkers and clinical scoring, including troponin, CRP, NT-proBNP, and NLR, have been used as prognostic indicators in studies. The IG% is a simple hemogram parameter that is less well known among clinicians. Several recent studies have suggested that IG% can be used to predict both short-term and long-term mortality associated with many diseases.¹⁷ Immature granulocytes are the common name of myelocytes, promyelocytes, and meta myelocytes, that is, granulocyte (neutrophil) precursors, which are not found in peripheral blood except in the neonatal period.^{17,19} Studies show that immature granulocytes can be used as a marker of inflammation in the early period.²⁰ Recently, more studies have been carried out on this parameter, which is not used enough by clinicians. Its efficacy has been investigated for the prediction of sepsis in patients with severe burns, the prognosis of patients with acute pancreatitis, the prediction of in-hospital mortality in patients with upper gastrointestinal bleeding, the prognosis of patients with STEMI, the early prediction of mesenteric ischemia, and as an innovative biomarker for SARS-COV-2 infection.^{11,12,21–24} As seen from these studies, it is seen that there is still a need for more research and evaluation by clinicians for the use of this biomarker in different clinical situations.

Krishnan et al. reported that IG count is an effective marker in estimating the severity of infection and in determining the need for early intervention in critically ill patients.¹² In another recent study, it was reported that the IG% was associated with mortality in upper gastrointestinal system diseases, and the IG5 helped predict mortality with a cut-off value of 0.95 with a sensitivity of 66.7% and a specificity of 75.7%.²⁵ Park et al. examined the diagnostic value of the IG count and its role in predicting the occurrence of complications in patients with acute appendicitis. In this study, it was shown that IG count is not as effective as other inflammatory markers in diagnosing and predicting the occurrence of complications.²⁶ Sinaga et al. reported that the IG count obtained at presentation to the emergency department serves as a marker that can effectively help predict 30-day mortality in patients with peritonitis, with a cut-off value of 1.05.²⁷ Huang et al. reported that IG count may be an indicator of possible pulmonary complications at the onset of acute pancreatitis.²⁸

The relationship between ACS and inflammation has been known for many years. In addition, inflammation is closely associated with prognosis and possible complications in ACS patients.²⁹ Increasing the severity of inflammation increases the likelihood of atherosclerotic plaques causing MI.³⁰ In many previous studies, it has been reported that hemogram parameters (e.g. leucocyte, neutrophil counts, etc.) and the ratios of these parameters to each other have prognostic value in patients with CAD and STEMI.^{31–34} Korkut et al. found the mean IG levels in patients with STEMI to be significantly higher in patients who died compared to those who survived (1.12 ± 0.22

vs 0.50 ± 0.28 , $p < 0.001$). They showed that IG predicted mortality with a sensitivity of 72.2% and a specificity of 77.8% at a cut-off value of 0.65 (area under the curve: 0.740, 95% CI 0.635–0.846, $p < 0.001$). They emphasized that high IG values at the time of admission to the emergency department may be an indicator of mortality in patients with STEMI.¹² Kong et al. emphasized in their study that the increased DNI value, which reflects the proportion of immature granulocytes circulating in the blood, is an independent predictor of 30-day mortality and poor clinical outcomes in patients with acute STEMI after PPCI.¹³

As seen in the above studies, studies examining the relationship between ACS and IG% are limited. In our study, IG% was found to be higher in deceased patients than in surviving patients. In the ROC analysis performed to determine the 28-day mortality, when the cut-off value for IG% was 0.6 and above; specificity was 83.70% and sensitivity was 54.55%. When we examine in terms of IG (%) level, it can be said that while patients with a cut-off value of >0.6 die, individuals below this value live. Also, the area under the curve for this parameter is 0.717. In other words, the probability of distinguishing between the survivors and the deceased was found to be quite high and statistically significant. In predicting 28-day mortality for ACS, IG% was determined as an independent risk factor. The pathophysiology of the relationship between ACS and immature granulocytes is an issue that needs to be investigated. The possible mechanism is that in cases of sterile inflammation after ACS, the mechanism of increase of immature granulocytes is probably similar to that in sepsis. Rapid expansion of circulating neutrophils is a possible mechanism to compensate for the loss of active neutrophils due to the massive consumption and destruction of mature cells in severe inflammation.

This study has several limits. First, it is designed as a single-centered, retrospective study. Secondly, IG% serial measurements could not be made. Thirdly, the hs-troponin kit was not available in our hospital laboratory, so we could not include it in the study.

Conclusion

Overall, the percentage of immature granulocytes can serve as a prognostic marker in patients with acute coronary syndrome, particularly regarding short-term mortality risk. Further studies may continue to elucidate the mechanisms and refine the clinical applications of this measurement in risk assessment and management strategies in ACS patients.

Credit authorship contribution statement

HN and CC conceived and designed the study. HN and CC conducted the acquisition of the data. SE provided methodological and statistical expertise. CC and AY analyzed and interpreted the data. CA, AY provided support with the literature search. HN, CA, and ÖÖ provided content expertise about this topic. HN, CA, and ÖÖ drafted the manuscript and all authors contributed substantially to its revision with critical revision of the manuscript for important intellectual content.

Conflict of interests

There are no conflicts of interest.

Funding

None.

Ethical statement

Ethics committee approval (No: 2021/726 Date: 03/12/2021) was received.

Informed consent

Informed consent was not obtained from the patients due to retrospective nature of the study.

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