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Correlation of immature/total granulocyte ratio with return of spontaneous circulation and early mortality in nontraumatic out-of-hospital cardiac arrest

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Abstract: **Objective:** Aim of this study was to examine immature granulocyte/total granulocyte (IG/TG) ratio for prediction of return of spontaneous circulation (ROSC) and early mortality in post cardiac arrest survivors.
Methods: The study was carried out prospectively between January 2021 and January 2022. Non-traumatic out-of-hospital cardiac arrest (OHCA), over the age of 18 and non-pregnant were included. Patients' whose IG levels were not studied, with hematological disease and who receiving immunosuppressive therapy were excluded. A palpable pulsation of the main arteries for at least 15 minutes was considered ROSC. Data were compared between the <4 hour and ≥4 hour survival groups and patients with and without ROSC.
Results: Total of 254 OHCA patients were included in the study. ROSC was achieved in 84 (33.1%) of these patients and 170 (66.9%) patients were died. There were 28 patients (33.3%) with survival of <4 hours and 56 patients (66.7%) with survival of ≥4 hours in patients with ROSC. The IG count and IG/TG ratio did not differ significantly between the ROSC groups and between the groups separated by survival time (P>0.05).
Conclusion: We found no significant differences between subgroups defined according to survival duration. Similarly, no differences found between OHCA patients with and without sustained ROSC.

Keywords: Immature Granulocyte; Out-of-Hospital Cardiac Arrest; Return of Spontaneous Circulation

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1. Introduction

Out-of-hospital cardiac arrest (OHCA) is a very important health problem with high mortality and morbidity rates around the world. It is known that only 8%-10% of OHCA patients might be discharged, and among these discharged patients 65% have neurological problems and 35% have irreversible cognitive disorders (1). For these reasons, from both ethical and socioeconomic perspectives, it is important to predict the return of spontaneous circulation (ROSC) and short-term mortality rates for these patients (2). There are some clinical, laboratory, and electrophysiologic risk factors defined to predict mortality and neurological outcome among OHCA patients, but there are still no accurate predictors to use in the early period, especially for mortality (3).

One of the predictors studied for this patient population is the immature granulocyte/total granulocyte (IG/TG) ratio calculated from the complete blood count (CBC). It has been shown that systemic inflammatory response syndrome (SIRS), which is seen in cases of sepsis, may also develop after successfully resuscitation following cardiac arrest (4,5). The same studies also demonstrated that high IG/TG ratios in patients with SIRS were related to increased mortality (4,5). Similarly, some studies have described the relationship between high IG/TG ratios and increased mortality in OHCA patients with sustained ROSC (6-8). However, those studies were done in intensive care units (ICU) and included the patients with sustained ROSC for longer than 24 hours; primary aim of those studies were prediction of long term (30 days) mortality and neurologic outcome during discharge. To the best of our knowledge there were no studies about the role of IG/TG ratio to predict short term mortality in OHCA patients admitted to emergency departments (ED).

The primary aim of our study was to examine predictive role of the IG/TG ratios of short-term (<4 hours) mortality in OHCA patients with sustained ROSC, at the ED. The IG/TG ratio of OHCA patients with and without sustained ROSC was also examined.

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2. Methods

2.1. Study design and study population

This prospective study was conducted at a training and research hospital with the approval of the local ethics committee (Keçiören Training and Research Hospital Ethics Committee file number: 2012-KAEK-15/2310).

Patients older than 18 years of age admitted to the ED between January 1, 2021, and January 31, 2022, due to nontraumatic OHCA were included in the study with obtained informed consent granted by relatives. Patients with unknown granulocyte values, patients with known hematologic disorders, patients taking immunosuppressive medications, and pregnant patients were excluded (Figure 1: flow chart).

Resuscitation of the patients was begun immediately after their arrival to the ED and was performed according to standard guidelines.

ROSC was defined as feeling a pulse from the main arteries for at least 15 minutes. Researchers obtained information from bystanders (prehospital medical staff, relatives, etc.) about past medical history, medications, prehospital management, time of cardiac arrest, duration of attempted resuscitation, time interval between arrest and reaching prehospital medical care, time interval between arrest and ED arrival, initial rhythm, drugs and doses used during resuscitation, and electrocardiography (ECG) findings. Light reflex and vital signs were checked in patients with sustained ROSC by ED staff on duty and the researchers. Follow up of the survivors were done by ED physicians during the period in ED, and by ICU physicians after the patients admitted to ICU. Researcher were in contact with physicians and relatives of the surviving patients until 30th day. Mortality due to any reason was recorded. All relevant data were recorded on study forms.

2.2. Study groups

Patients were divided into two groups as those with sustained ROSC and those without sustained ROSC. The survival of patients with sustained ROSC was subsequently evaluated and this patient group was divided into two subgroups with survival of <4 hours and survival of ≥4 hours.

2.3. Laboratory methods

Blood samples were taken immediately after accessing an intravenous line and were transferred to the laboratory in blood tubes containing ethylenediaminetetraacetic acid (EDTA) for all patients. Blood samples were analyzed with a Mindray BC-6800 device (Mindray Medical International, China) using the DIFF scattergram method. Together with all other CBC parameters, the IG/TG ratio was calculated.

2.4. Sample size

The sample size of the study was calculated for short-term mortality among patients with sustained ROSC, one of the primary outcomes of the research. Our goal was to achieve sufficient statistical power to detect a 0.9 unit difference with 1 unit standard deviation (SD) between the groups with and without sustained ROSC. Using G-Power for Mac OS X (version 3.1.9.2; Universität Düsseldorf, Germany) and assuming two-sided type I error of 0.05, we anticipated a sample size of 26 patients for each group (<4 hours of survival, ≥4 hours of survival) to achieve 90% power. Therefore, we aimed to include 52 patients with sustained ROSC. Previous studies from our clinic and the literature demonstrated ROSC rates of 20%-40% after OHCA (9-11). Therefore, to reach 52 patients with ROSC, we decided to include a total of 250 patients in the study.

Table 1 Demographic, arrest, and resuscitation characteristics of the patients

Characteristics	Median (IQR 25%-75%) or n (%)
Age, year	71 (60-80)
Female gender	96 (37.8)
Time intervals, min	
Between arrest and hospital arrival	15 (10-15)
Between arrest and initiation of CPR	7 (5-10)
Duration of CPR	15 (10-20)
Witnessing of cardiac arrest	189 (74.4)
Prehospital CPR	239 (94.1)
Initial rhythm	
Asystole	210 (82.7)
PEA	13 (5.1)
VF	31 (12.2)
Having shockable rhythm throughout CPR	40 (15.7)
Possible arrest reasons	
Cardiac	162 (63.8)
Respiratory	65 (25.6)
Metabolic	16 (6.3)
Circulatory	6 (2.4)
Neurological	4 (1.6)
Intoxication	1 (0.4)
Survival	
ROSC sustained	84 (33.1)
<4 hours	28 (33.3)
4-24 hours	8 (9.5)
>24 hours to 30 days	34 (40.5)
>30 days	14 (16.7)
Exitus	170 (66.9)
Primary study variables	
Immature granulocyte count (10^3/μL)	0.13 (0.04-0.28)
IG/TG ratio	0.9 (0.22-2.07)

ROSC: Return of spontaneous circulation;
CPR: Cardiopulmonary resuscitation;
PEA: Pulseless electrical activity;
VF: Ventricular fibrillation; min: Minute;
IG/TG ratio: Immature granulocyte /total granulocyte ratio.

2.5. Statistical analysis

All data were analyzed with IBM SPSS Statistics 20.0 (IBM Corp., USA). There were no missing data. The distribution

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Table 2 Demographic, arrest, and resuscitation characteristics of patients with and without sustained ROSC

Characteristics	Median (IQR 25%-75%) or n (%)		
	Patients with ROSC, N=84	Patients without ROSC, N=170	P-value
Age, year	69 (58-80)	72 (63-81)	0.235
Female gender	29 (34.5)	67 (39.4)	0.450
Time intervals, min			
Between arrest and hospital arrival	10 (10-15)	15 (15-20)	<0.001
Between arrest and initiation of CPR	5 (5-10)	10 (5-10)	<0.001
Duration of CPR	15 (10-20)	30 (30-40)	<0.001
Witnessing of cardiac arrest	73 (86.9)	116 (68.2)	0.001
Prehospital CPR	81 (96.4)	158 (92.9)	0.208
Initial rhythm			
Asystole	58 (69)	152 (89.4)	<0.001
PEA	4 (4.8)	9 (5.3)	
VF	22 (26.2)	9 (5.3)	
Having shockable rhythm throughout CPR	25 (29.8)	15 (8.8)	<0.001
Primary study variables			
Immature granulocyte (10^3/μL)	0.13 (0.04-0.29)	0.1 (0.04-0.26)	0.497
IG/TG ratio	0.9 (0.2-2.1)	0.9 (0.3-2.05)	0.742

*Bonferroni correction was performed, and significance was observed at P<0.016
ROSC: Return of spontaneous circulation; CPR: Cardiopulmonary resuscitation; PEA: Pulseless electrical activity; VF: Ventricular fibrillation; min: Minute; IG/TG ratio: Immature granulocyte/total granulocyte ratio.

Table 3 Demographic, arrest, and resuscitation characteristics of patients with sustained ROSC and survival of <4 hours and ≥4 hours

Characteristics	Median (IQR 25%-75%) or n (%)		
	Patients with <4 hours of sur-vival, N=28	Patients with ≥4 hours of sur-vival, N=56	P-value
Age, year	75 (59-82)	66 (57-80)	0.377
Female gender	8 (28.6)	21 (37.5)	0.417
Witnessing of cardiac arrest	25 (89.3)	48 (85.7)	0.466
Prehospital CPR	28 (100)	53 (94.6)	0.210
Initial rhythm			
Asystole	15 (53.6)	43 (76.8)	0.095
PEA	2 (7.1)	2 (3.6)	
VF	11 (33.9)	11 (19.6)	
Having shockable rhythm throughout CPR	12 (42.9)	13 (23.2)	0.063
Vital parameters			
0^{th} minute			
Temperature, °C	36 (36-36.1)	36 (36-36.3)	0.421
Systolic blood pressure, mmHg	81 (66-91)	72 (60-85)	0.482
Diastolic blood pressure, mmHg	39 (31-60)	45 (32-60)	0.686
Pulse rate, beats/minute	92 (60-128)	80 (58-101)	0.102
Presence of light reflex	3 (10.7)	14 (25)	0.124
15^{th} minute			
Temperature, °C	36.1 (36-36.7)	36.3 (36-36.6)	0.530
Systolic blood pressure, mmHg	98 (91-102)	104 (96-119)	0.655
Diastolic blood pressure, mmHg	55 (45-67)	60 (56-66)	0.947
Pulse rate, beats/minute	87 (65-97)	96 (88-105)	0.628
Presence of light reflex	2 (7.1)	16 (28.6)	0.024
Primary study variables			
Immature granulocytes (10^3/μL)	0.19 (0.06-0.28)	0.09 (0.04-0.33)	0.439
IG/TG ratio	1.6 (0.6-2.3)	0.5 (0.2-1.85)	0.097

ROSC: Return of spontaneous circulation; CPR: Cardiopulmonary resuscitation; PEA: Pulseless electrical activity; VF: Ventricular fibrillation; min: Minute; IG/TG ratio: Immature granulocyte/total granulocyte ratio.

of the variables was checked with the Kolmogorov-Smirnov test. According to normality, continuous variables were described as mean±SD or median and interquartile range (IQR 25%-75%). Categorical variables were described as numbers and percentages. Chi-squared tests and Fisher exact tests were used for categorical variables, and t-tests and Mann-Whitney U tests were used for continuous variables. Values of P<0.05 were considered statistically significant.

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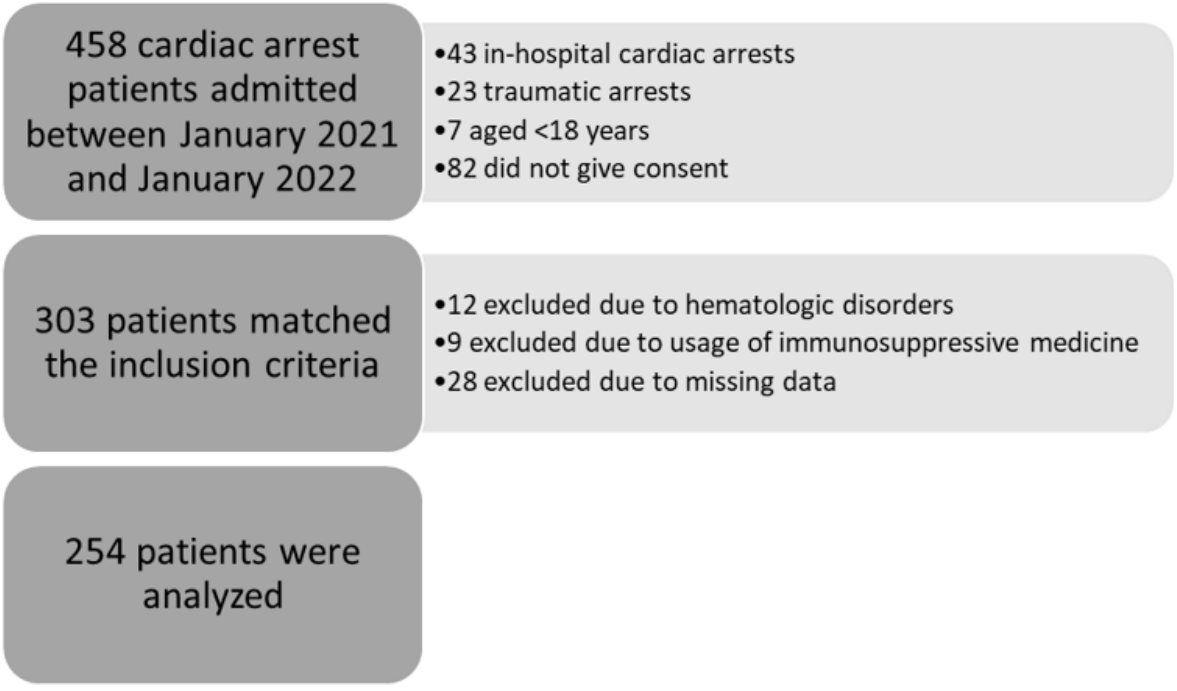

Figure 1 flow chart

3. Results

This study included 254 cardiac arrest patients, 96 (37.8%) of whom were female. The median age was 71 (IQR 25%-75%: 60-80) years. Eighty-four (33.1%) of these patients had sustained ROSC, and 170 (66.9%) patients died. Demographic variables and arrest and resuscitation characteristics of the patients were given in table 1. The median IG value was 0.13× 10^3/μL (IQR 25%-75%: 0.04-0.28) and the median IG/TG ratio was 0.9 (IQR 25%-75%: 0.22-2.07) among the entire study population.

Patients were divided into two groups as those with sustained ROSC and those without sustained ROSC (i.e., exitus). There was no difference between the groups in term of age and gender distributions, but there were significant differences between the groups in terms of arrest being witnessed, presence of a shockable rhythm throughout the cardiopulmonary resuscitation (CPR), time interval to hospital arrival and initiation of CPR, and duration of CPR (P<0.001 for all). The initial arrest rhythm was also significantly different between the groups, and Bonferroni correction showed that this was because of the higher rate of ventricular fibrillation (VF) rhythm seen in the group with sustained ROSC. The IG count and IG/TG ratio, which were the primary variables of concern in this study, were similar between the groups (P>0.05) (Table 2).

Patient with sustained ROSC were divided into two groups as those with survival of <4 hours and those with survival of ≥4 hours. There was no significant difference between these groups in terms of age, gender, prehospital CPR rate, initial rhythm, presence of a shockable rhythm throughout the CPR, and vital parameters. The only significant difference observed was for light reflex at 15 minutes, which was higher among patients with ROSC and survival of ≥4 hours (P=0.024). IG count and IG/TG ratio were analyzed between these subgroups and statistically significant differences were not found (Table 3).

4. Discussion

This study, in which IG counts and IG/TG ratios were compared between cases of nontraumatic OHCA with and without sustained ROSC, has two important findings. First, the IG counts and IG/TG ratios calculated from CBC did not differ between the OHCA patients with and without sustained ROSC. Second, IG counts and IG/TG ratios did not show significant differences between patients with sustained ROSC and survival of <4 hours or ≥4 hours. Therefore, we may conclude that IG count and IG/TG ratio are not effective predictors of survival for patients with OHCA.

OHCA still has very low survival rates, and with the aim of increasing the benefit of resuscitative interventions, recent studies have focused on predictors of prognosis in this patient group. Many factors such as age, comorbid diseases, drugs administered during CPR, other resuscitative interventions, and post-arrest management have been investigated in this context. Studies showed that the most important predictor of ROSC in cases of OHCA is the arrest being witnessed (12,13). Fernando et al. demonstrated that the witnessing of the arrest, arrest occurring during daytime, and presence of a shockable initial rhythm were predictors of increased survival in OHCA (14). Similarly, to these literature findings, the

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presence of shockable initial rhythm or shockable rhythm throughout CPR and the witnessing of the arrest were significantly more common among OHCA patients with ROSC group in our study.

Related to mortality, other factors that have been previously studied are IG counts and IG/TG ratios. During cardiac arrest, oxygen delivery to tissues is impaired and that triggers endothelium activation and systemic inflammatory response. Subsequently, global ischemia/reperfusion injury occurs with ROSC, which mimics sepsis (15). Due to ischemia/reperfusion damage in the intestines, the intestinal barrier is disrupted, leading to bacterial translocation; thus, multiorgan dysfunction syndrome and sepsis may occur. From this perspective, markers of inflammatory response such as interleukin 6 (IL-6), leukocytes, and neutrophils have been studied as mortality predictors in OHCA patients with sustained ROSC (16).

IGs are predictors of increased myeloid cell production and are related to infection and systemic inflammation (17). Sauneuf et al. demonstrated that high IG/TG ratios were correlated with increased post-resuscitative shock rates in patients with sustained ROSC, and for this patient group, the area under the curve of the IG/TG ratio for mortality was found to be 0.82 (95% CI: 0.75,0.89) (6).

Saunuef et al. determined IG counts by flow cytometric analysis, while in the present study, we used CBC data. Similar to the IG/TG ratio, Yune et al. evaluated the delta neutrophil index (DNI), which reflects the fraction of IGs in circulation, in patients with OHCA.

They concluded that DNI was an independent risk factor for 30-day mortality and poor neurological outcomes (7). Our results did not show any differences between patients with and without OHCA. The reason for these differences between our findings and those presented in the literature may be the technique that we used to obtain the IG counts. Instead of flow cytometry analysis, which has higher accuracy, we used data from automatic measurements taken in the process of CBCs. It has also been shown that ischemia/reperfusion injury does not develop immediately after sustained ROSC and the level of biomarkers of inflammation in the blood after 3 hours of ROSC might be a better predictor of mortality (18). In our study, blood samples were taken immediately after arrival to the ED and were not repeated for patients after 3 hours of ROSC. This might be another reason for not finding a significant difference between the groups in the present study.

5. Limitations

In our study, IG counts and IG/TG ratios were calculated with data obtained from a device used to perform automatic measurements of CBC parameters, although flow cytometry is considered to be the gold standard. This might have affected our results. Additionally, IG counts and IG/TG ratios may change over time in the presence of sustained ROSC. Examining blood samples obtained only at the time of admission is another limitation of this study. Different results might be obtained with repeated measurements.

Our patients were not grouped in terms of nontraumatic cardiac arrest etiology. Since the underlying causes may significantly affect the laboratory findings of the patients, it may be valuable to perform similar studies in specific patient groups. Since the primary aim of our study was to examine predictive role of the IG/TG ratios of short-term (<4 hours) mortality in OHCA patients with sustained ROSC, at the ED we had calculated the sample size according to that. We also didn't follow up the patients after ICU admission (except for mortality). So, because of small sample size calculated and missing data we couldn't do any regression or survival analyses.

6. Conclusion

In this study, in which predictive role of IG counts and IG/TG ratios for short-term mortality in nontraumatic OHCA patients with sustained ROSC, we found no significant differences between subgroups defined according to survival duration. Similarly, no differences were found between OHCA patients with and without sustained ROSC.

7. Declarations

7.1. Acknowledgement

None.

7.2. Authors' contribution

Conceiveing and design the experiments: YÇ; Performing the experiments: EK; Analyzing and interpreting the data: ŞKÇ, FNK; Contributing reagents, materials, analysis tools or data: EK, GÇI, FNK, ŞKÇ, EE, YÇ; Writing the paper: EK, GÇI.

7.3. Conflict of interest

None.

7.4. Funding

None.

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