

Immature granulocytes: Innovative biomarker for SARS-CoV-2 infection

VASILIKI EPAMEINONDAS GEORGAKOPOULOU¹, SOTIRIA MAKRODIMITRI¹,
MARIA TRIANTAFYLLOU¹, STAMATIA SAMARA¹, PANTAZIS M. VOUTSINAS¹,
AMALIA ANASTASOPOULOU², CHRYSOVALANTIS V. PAPAGEORGIOU³, DEMETRIOS A. SPANDIDOS⁴,
AIKATERINI GKOUFA², PETROS PAPALEXIS^{5,6}, EUTHALIA XENOU⁷, GEORGIOS CHELIDONIS⁸,
PAGONA SKLAPANI⁹, NIKOLAOS TRAKAS¹⁰ and NIKOLAOS V. SIPSAS^{1,11}

¹Department of Infectious Diseases-COVID-19 Unit, Laiko General Hospital; ²First Department of Internal Medicine, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens; ³Pulmonology Department, Laiko General Hospital, 11527 Athens; ⁴Laboratory of Clinical Virology, Medical School, University of Crete, 71003 Heraklion; ⁵Unit of Endocrinology, First Department of Propedeutic and Internal Medicine, Laiko General Hospital, National and Kapodistrian University of Athens, 11527 Athens; ⁶Department of Biomedical Sciences, University of West Attica, 12243 Athens; ⁷Laboratory of Hematology, Laiko General Hospital, 11527 Athens; ⁸National Actuarial Authority, 10559 Athens; ⁹Department of Cytology, Mitera Hospital, 15123 Athens; ¹⁰Department of Biochemistry, Sismanogleio Hospital, 15126 Athens; ¹¹Department of Pathophysiology, School of Medicine, National and Kapodistrian University of Athens, 11527 Athens, Greece

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Abstract. Immature granulocytes (IGs) include metamyelocytes, myelocytes and promyelocytes, and are the precursors of neutrophils. Increased IG counts found in peripheral blood indicate an enhanced bone marrow activity. In addition, IGs have been evaluated in numerous clinical conditions, such as severe acute pancreatitis, systemic inflammatory response syndrome and infectious complications following open-heart surgery under cardiopulmonary bypass. Neutrophils are considered to play a crucial role in the host defense during bacterial and fungal infections, and are involved in the antiviral immune response. Numerous studies have reported the role of neutrophils in coronavirus disease 2019 (COVID-19) infection, concluding that the percentage of neutrophils may be a predictor of the severity of COVID-19 infection. There has been limited research regarding the role of neutrophil precursors in viral infections, including severe acute respiratory syndrome coronavirus 2 infection. The present thus aimed to evaluate the role of the IG count in patients hospitalized due to COVID-19 infection. The patients were predominantly infected with the alpha variant and were all unvaccinated. The

IG count was measured and was found to be associated with disease severity, with patient outcomes, with the duration of hospitalization and with the development of complications. The IG count was significantly associated with the severity of COVID-19 infection, with greater IG count values being detected in severe and critical cases. In addition, greater IG count values were associated with a longer duration of hospitalization. Furthermore, the IG count was found to be an independent prognostic biomarker of intubation and mortality in patients with COVID-19, according to multivariate logistic regression analysis, including age, the male sex and the presence of comorbidities as confounders.

Introduction

Immature granulocytes (IGs) include metamyelocytes, myelocytes and promyelocytes, and are the precursors of neutrophils. The percentage of IGs can be measured using automated hematology analyzers, and elevated IG count values found in peripheral blood indicate an enhanced bone marrow activity (1).

IGs have been evaluated in numerous clinical conditions. In a previous study, the IG count was reported as an independent prognostic biomarker in patients with severe acute pancreatitis (1), while in another study, the IG count was found to be independently associated with the development of acute respiratory distress syndrome in patients with acute pancreatitis (2). Furthermore, according to certain studies, the IG count is a useful marker for discriminating between infected and non-infected patients early during systemic inflammatory response syndrome (3); a low IG count can exclude sepsis with high specificity, and the IG count is more positively associated with infections and positive blood cultures than the white

Correspondence to: Dr Petros Papalexis, Unit of Endocrinology, First Department of Propedeutic and Internal Medicine, Laiko General Hospital, National and Kapodistrian University of Athens, 17 Agiou Thoma Street, 11527 Athens, Greece
E-mail: petranpapalex@gmail.com

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blood cell count (4,5). Moreover, a post-operative increase in the IG count has been shown to be associated with post-operative organ failure and may be used to identify patients who are at risk of developing infectious complications following open-heart surgery under cardiopulmonary bypass (6).

Neutrophils are leukocytes derived from bone marrow, and are considered to play a major role in the host defense during bacterial and fungal infections. Neutrophils are also involved in the antiviral immune response, and are the first and predominant cell population that reaches affected tissues after viral infection (7). The beneficial and harmful effects of neutrophils in viral infections, as well as the antiviral mechanisms of neutrophils have been previously reported (7,8). The role of neutrophils has been mostly studied in the context of influenza A virus infection, a human respiratory virus that causes severe disease with high rates of mortality, particularly among the elderly (9). The importance of neutrophil function has also been studied in infections from other viruses, such as herpes simplex virus types 1 and 2, cytomegalovirus, vesicular stomatitis virus (9), West Nile virus (10) and respiratory syncytial virus (11).

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) (12), which was first identified in December, 2019 in Wuhan, China, and has since spread globally, resulting in an ongoing pandemic (13). Several researchers have reported the role of neutrophils in COVID-19 infection, demonstrating that the percentage of neutrophils along with other markers may be predictors of the severity of COVID-19 infection (14,15) and that an increased neutrophil count and neutrophil-to-lymphocyte ratio are predominant in critical cases or non-survivors (16).

However, to date, there has been limited research concerning the role of neutrophil precursors in viral infections, including SARS-CoV-2 infection, at least to the best of our knowledge. The present study thus aimed to evaluate the role of the IG count in patients with COVID-19 infection.

Materials and methods

Study design. The design of the present study was prospective. Data were collected at the 'Laiko General Hospital' between October, 2020 and June, 2021. The present study was approved by the Institutional Board of Laiko General Hospital (protocol no. 716) and was in line with the declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Written informed was obtained from all patients.

Study participants and data collection. In the present study, adult patients who visited or were hospitalized at the COVID-19 Unit of Laiko General Hospital due to SARS-CoV-2 infection, were enrolled. The patients were predominantly infected with the alpha variant and were all unvaccinated. All patients were treated according to the National Institutes of Health (NIH) protocols (17). Patients suffering from a disease or receiving medication that affects bone marrow neutrophil production were excluded from the study. More specifically, the exclusion criteria were the following: Hematological disorders, active cancer with or without chemotherapy or radiation treatment,

autoimmune disorders and the administration of immunosuppressive agents. SARS-CoV-2 infection was confirmed by the positive detection of SARS-CoV-2 nucleic acid in examined nasopharyngeal samples with the use of reverse transcription-polymerase chain reaction (RT-PCR). Whole blood from the participants upon admission was collected and used for the measurement of the IG count using an automated Sysmex XE 2100 hematology analyzer (TOA Medical Electronics). The patients were classified into the following severity of illness categories: Mild/moderate, severe and critical based on the clinical spectrum of SARS-CoV-2 infection (17).

The following data were collected from all patients: i) Demographics: Age and sex; ii) the presence of comorbidities; iii) outcomes (recovery, intubation, mortality); iv) the duration of hospitalization; v) the development of disease-related complications (pulmonary embolism, myocardial infarction, hemorrhage, mesenteric ischemia, pneumothorax, hematological complications). The IG count was associated with disease severity, outcomes, the duration of hospitalization and the development of complications.

Statistical analysis. Categorical variables are summarized as the number (percentage) and continuous variables as the mean \pm standard deviation. The normal distribution of variables was assessed using the Kolmogorov-Smirnov test. Normally distributed variables were compared using an independent samples Student's t-test on factors with two groups and one-way analysis of variance (ANOVA) with Bonferroni post hoc pairwise comparisons on factors with three groups. Multivariate logistic regression analysis was performed to identify independent variables. Odds ratios (ORs) with 95% confidence intervals (CIs) are presented. Values of $P < 0.05$ were considered to indicate statistically significant differences. Statistical analysis was performed using IBM SPSS-Statistics version 26.0 (IBM Corp.).

Results

A total of 1,005 patients, 581 (57.8%) males and 424 (42.2%) females with COVID-19 were enrolled in the study. The mean age of the patients was 62.07 ± 16.83 years. A total of 798 (79.4%) patients had comorbidities. In addition, 134 (13.1%) patients had mild/moderate disease, 627 (62.4%) patients had severe disease and 243 (24.2%) patients had critical disease. Furthermore, 712 (70.8%) patients had a duration of hospitalization >10 days, 27 (2.7%) patients developed complications, 92 (9.2%) patients were intubated and 142 (14.1%) patients did not survive (Table I).

The mean IG count was $0.03 \pm 0.02 \times 10^9/l$ in patients with mild/moderate disease, $0.05 \pm 0.10 \times 10^9/l$ in patients with severe disease and $0.09 \pm 0.15 \times 10^9/l$ in patients with critical disease. There was a statistically significant difference in the mean values of the IG counts between the three groups of disease severity, with the greatest mean value of IG observed in patients with critical disease ($P = 0.0001$) (Fig. 1 and Table II).

The mean IG count was $0.05 \pm 0.09 \times 10^9/l$ in patients with a duration of hospitalization <10 days and $0.07 \pm 0.12 \times 10^9/l$ in patients with a duration of hospitalization >10 days. There was a statistically significant difference in the mean values of IG

Table I. Characteristics of the study population.

Characteristic	No. of patients (%), n=1,005
Sex	
Male	581 (57.8)
Female	424 (42.2)
Age (years ± SD)	62.07±16.83
Disease severity	
Mild/moderate	134 (13.1%)
Severe	627 (62.4%)
Critical	243 (24.2%)
Outcomes	
Hospitalization >10 days	712 (70.8%)
Complications	27 (2.7%)
Recovery	863 (85.9%)
Intubation	92 (9.2%)
Mortality	142 (14.1%)

SD, standard deviation.

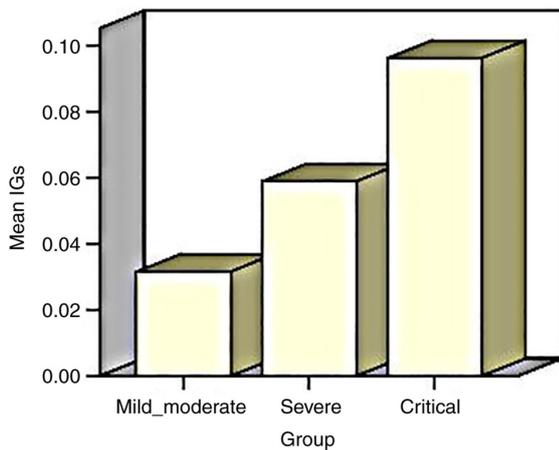


Figure 1. Mean values of IG counts in mild/moderate, severe and critical disease. The greatest mean IG count value was observed in patients with critical disease, when comparing patients with mild/moderate, severe and critical disease (P=0.0001). IG, immature granulocyte.

counts between the patients with a duration of hospitalization >10 and <10 days (P=0.029; Table II).

The mean IG count was $0.07 \pm 0.06 \times 10^9/l$ in patients who developed complications and $0.06 \pm 0.11 \times 10^9/l$ in patients who did not develop complications. Although the mean value of IG count was higher in patients who developed complication, no statistically significant difference was observed (P=0.66; Table II).

The mean IG count was $0.11 \pm 0.15 \times 10^9/l$ in patients who were intubated and $0.06 \pm 0.10 \times 10^9/l$ in patients that were not. There was a statistically significant difference in the mean IG count between patients who were intubated and patients who were not intubated (P=0.002; Table II).

The mean IG count was $0.11 \pm 0.15 \times 10^9/l$ in patients who did not survive and $0.05 \pm 0.10 \times 10^9/l$ in patients who recovered.

There was a statistically significant difference in the mean IG count between patients who did not survive and patients who recovered (P=0.001; Table II).

Following multivariate logistic regression analysis, including as confounders age, male sex and the presence of comorbidities, an independent association was found between the IG count and intubation (OR, 13.98; 95% CI, 3.7-52.83; P=0.003) (Table III). An independent association was also detected between the IG count and mortality (OR, 42.17; 95% CI, 10.23-173.85; P=0.001) (Table IV).

Discussion

Severe stressors, including sepsis, trauma and viral infections, can trigger emergency granulopoiesis, a hematological response mechanism that rapidly enhances *de novo* neutrophil production to cope with increased demands (18). This process leads to the presence of both immature and mature neutrophils in the peripheral circulation, which can have immunosuppressive or pro-inflammatory effects (19). Despite a lack of understanding of the role of mature and immature neutrophils in the immune response, as well as their distinct characteristics, clinical interest in these cells is increasing due to their increasingly apparent association with disease severity and treatment response in a variety of pathologies, including sepsis and severe influenza (20). It has been reported that the process of emergency granulopoiesis and the availability of numerous freshly generated granulocytes may increase their destructive capacity (21).

According to the results of the present study, the IG count was associated with disease severity, with greater IG count values being detected in severe and critical cases. In addition, greater IG count values were found to be associated with a longer duration of hospitalization. Furthermore, the IG count was an independent prognostic biomarker of intubation and mortality in patients with COVID-19.

Several studies have demonstrated the efficacy of standard blood tests performed upon patient admission to the hospital for the diagnosis and prediction of the severity of COVID-19 infection (15,22-24). The IG% is a metric that is poorly understood and underutilized by clinicians. In a routine blood count, this parameter may be measured inexpensively and swiftly (22). The early release of immature neutrophils from bone marrow into peripheral blood has been linked to inflammation, particularly in numerous infectious diseases (24). As a result, the IG% may be a reliable biomarker, which may be extremely useful in the context of the prediction of the severity of COVID-19 infection and patient outcomes. Moreover, the half-life of IGs is 3 h and a short half-life marker easily reflects the inflammation status compared to other parameters with a longer half-life (25).

The IG count has been reported as an indicator of the severity of COVID-19 infection in some studies. Kuri-Cervantes *et al* (26) demonstrated that patients with severe COVID-19 infection were distinguished from those with mild or moderate infection by the extensive induction and activation of various immune lineages, including the modulation of innate lymphocytes and granulocytes, manifested as changes in the frequency and phenotype of circulating IGs. Carissimo *et al* (24) performed the comprehensive flow

Table II. Mean IG counts in the study groups.

Study group	IG count (mean±SD x10 ⁹ /l)	P-value
Mild/moderate	0.03±0.02	0.0001
Severe	0.05±0.10	
Critical	0.09±0.15	
Hospitalization <10 days	0.05±0.09	0.029
Hospitalization >10 days	0.07±0.12	
Complications	0.07±0.06	0.66
No complications	0.06±0.11	
Intubation	0.11±0.15	0.002
No intubation	0.06±0.10	
Mortality	0.11±0.15	0.001
Recovery	0.05±0.10	

IG, immature granulocyte.

Table III. Multivariate logistic regression analysis of factors independently associated with intubation.

Parameter	Odds ratio	95% Confidence interval	P-value
Age	1.854	1.160-2.964	0.010
Male sex	1.021	1.006-1.036	0.006
IGs	13.986	3.703-52.823	0.003
Comorbidities	3.795	1.458-9.879	0.006

IGs, immature granulocytes.

Table IV. Multivariate logistic regression analysis of factors independently associated with mortality.

Parameter	Odds ratio	95% Confidence interval	P-value
Age	1.084	1.066-1.102	0.001
Male sex	2.237	1.463-3.421	0.001
IGs	42.173	10.230-173.856	0.001
Comorbidities	7.409	1.732-31.695	0.007

IGs, immature granulocytes.

cytometric analysis of whole blood samples from patients with SARS-CoV-2, which revealed a significant increase in the number of IGs. This increase was found to be prominently associated with disease severity (24). Schulte-Schrepping *et al* (27), in their study, mentioned that severe COVID-19 infection was marked by the presence of neutrophil precursors, as evidence of emergency myelopoiesis, indicating that COVID-19 induces marked alterations in the neutrophil compartment.

According to the study by Combadière *et al* (28), increased proportions of circulating IGs expressing either CD123 or

lectin-like oxidized low-density lipoprotein receptor-1 in critical COVID-19 cases were associated with disease severity and thromboembolic complications. In addition, in their study on 368 patients with SARS-CoV-2 infection, Myari *et al* (22) discovered that the IG count may be a useful indicator of critical disease.

The delta neutrophil index (DNI) represents a marker obtained by calculating the fraction of circulating IGs. Birben *et al* (29), in their study on 388 patients with COVID-19 requiring intensive care, concluded that the DNI could be used as an effective prognostic biomarker for mortality in these patients. Moreover, according to the study by Karagol *et al* (30), there was a statistically significant association between the DNI levels and the severity of multisystem inflammatory syndrome in children with COVID-19.

Notably, Daix *et al* (31) reported that the IG count could aid in the identification of pulmonary bacterial infections in patients in the intensive care unit hospitalized for acute respiratory distress syndrome caused by COVID-19. To the best of our knowledge, the present study is the first to mention a statistically significant association between the IG count and the duration of hospitalization, and between the IG count and intubation and mortality in patients hospitalized in general hospital wards due to COVID-19.

However, there are some limitations to the present study. Although the strong points of the study are the large number of participants and reliable follow-up, this was a single-center study. In addition, patients vulnerable to SARS-CoV-2 infection, such as those suffering from hematological disorders, active cancer and autoimmune disorders were excluded. Thus, further comprehensive multicenter, prospective studies are required for more detailed results.

In conclusion, the present study demonstrates that the IG count is associated with the severity of COVID-19 infection, with greater IG count values observed in severe and critical cases. In addition, greater IG count values were found to be associated with a longer duration of hospitalization. Furthermore, the IG count was found to be an independent prognostic indicator of intubation and mortality in patients with COVID-19.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

AG, DAS and PP conceptualized the study. VEG, SM, MT, SS, PMV, CVP, AA and NVS were involved in the design of the study and prepared the draft of the manuscript. VEG and NVS provided critical revisions. PS, GC, NT and EX obtained

the data, and prepared the tables and figures. VEG and NVS confirm the authenticity of all the data. All authors contributed to manuscript revision and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Research Ethics Committee of Laiko General Hospital (protocol no. 716). The study was in line with the declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Written informed consent was obtained from all patients. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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