IMMATURE GRANULOCYTE PERCENTAGE – A PREDICTOR OF INFECTIONS IN PATIENTS IN INTENSIVE CARE UNIT SETTING

Ali Hyder, Nasir Uddin, Asad Mahmood, Rafia Mahmood, Muhammad Ijaz Iqbal

Armed Forces Institute of Pathology/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To determine diagnostic importance of immature granulocyte percentage in patients with infection in early stages in hospital settings.

Study Design: Cross sectional study.

Place and Duration of Study: Department of Haematology, Armed Forces Institute of Pathology (AFIP) Rawalpindi, from Oct 2017 to Oct 2018.

Methodology: One hundred patients were inducted who fulfilled the criteria of systemic inflammatory response syndrome (SIRS) and sepsis. Four ml blood from the patients was taken via venepuncture or indwelling catheter in an EDTA tube, White blood cell count (WBC) and immature granulocyte (IG) percentage was analyzed by using Sysmex XN3000 haematology analyzer.

Results: The diagnostic accuracy of immature granulocyte percentage in patients with sepsis as compared to white blood cell count was recorded as 67.40%, 82.35%, 94%, 70% and 87.14% for sensitivity, specificity, positive predictive value, negative predictive value and accuracy rate respectively.

Conclusion: Immature granulocyte count at 1.0% is a reliable and effective predictor of infection, validating its addition into the diagnostic protocols in the intensive care unit settings

Keywords: Hospital acquired infections, Immature granulocyte percentage, Sepsis, SIRS, WBC count.

INTRODUCTION

Hospital-acquired infections (HAIs) have proven to be a significant health hazard. Infections in the intensive care unit (ICU) setting are paired with a high morbidity and mortality. The risk of acquiring HAIs in ICU setting is 2 to 5 times higher than in general in-patient settings[1]. A study conducted in a neighbouring country detected ICU acquired HAIs in 11.98% of patients[1]. In another study, 19.7% of the hospital-acquired infections were recovered from the ICU[2]. Incidence of infections in ICU setting is associated with length of stay, intensive care unit status, and use of peripherally inserted central catheter[3]. Pneumonia is the most frequently encountered infection[4] i.e. 62.07%, followed by urinary tract infections (UTIs) 27.59% and blood-stream infections (BSIs) i.e. 10.34%[1]. Aerobic, gram-negative bacterial isolates are the most prevalent (47.4%), followed by gram-positive bacteria (43.9%) with the remaining blood-stream infections caused by fungal (7.2%) and anaerobic (1.5%) species[2]. A retrospective analysis documented that candidemia has been persistent problem in intensive care unit patients, prevalence of 6.9 per 1000 patients with high mortality rates (42.6%)[5].

Various parameters have been used in order to promptly detect infections in ICU setting. Nasal swab culture for MRSA has been used to predict acquisition of *S. aureus* infection but with a low sensitivity (0.32, 0.20-0.48) as only one-fourth of patients who are colonized acquire the infection[6]. In addition to this, median time to the first positive culture is as long as 7 days[7], along with reassessment in order to confirm a diagnosis. Antibiotic treatment following culture results is the most frequently used management strategy today[4]. Blood stream infections (BSI) have been detected microbiologically by a combination of positive blood cultures, clinical examination with fever, chills, hypotension, and positive antigen tests on blood[8]. Polymerase chain

Correspondence: Dr Ali Hyder, Department of Pathology, Armed Forces Institute of Pathology, Rawalpindi Pakistan

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reaction (PCR)-based microbial detection in the blood is also being done for a rapid diagnosis with a higher sensitivity as compared to conventional blood cultures[9]. Many clinical investigations are time-consuming, costly, repetitive and cumbersome to the patient as well as hospital staff[10].

The changing patterns of treatment strategies and use of new medical appliances is evolving the epidemiology and the outcome of ICU acquired infections. Despite the favourable results acquired by performing IG counts, it has not been incorporated into routine diagnostic criteria for patients with infection. Our study will add to the body of knowledge to improve patient outcome by modifying prevention and detection methods of diseases.

The aim of our study was to detect immature granulocyte percentage in patients with infection in the ICU setting and to evaluate whether it can be a valuable predictor of infections in patients in the ICU by comparing its diagnostic accuracy with the standard blood culture and WBC count.

METHODOLOGY

It was a cross sectional validation study, carried out in the department of Haematology after taking approval from ethics review board committee AFIP (FC-HEM17-31-READ-IRB/402), Armed Forces Institute of Pathology Rawalpindi, Pakistan, over a period of 1 year, from Oct 2017 to Oct 2018.

A sample size of 100 was calculated using WHO sample size calculator considering 5% Level of significance. Power of test 80% and confidence interval of 95%. Sampling technique used was non-probability consecutive sampling. All adult patients who were diagnosed/suspected cases of systemic inflammatory response syndrome and sepsis, admitted in intensive care unit of Combined Military Hospital Rawalpindi were included in the study. Patients were divided into two groups based on the presence or absence of positive blood culture reports. Group I included patients with infection and group II had patients without infection. The definitions of sepsis and systemic inflammatory response syndrome (SIRS) were according to the criteria of American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference 28. Systemic inflammatory response syndrome was defined as two or more of the following conditions. (1) temperature >38°C or <36°C, (2) heart rate >90 beats/min, (3) respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg, and (4) WBC count >12,000 cells/mm^3 or <4000 cells/mm^3. Sepsis was defined as these clinical features with evidence or suspicion of infection. Patients with haematological disorders and malignancies were excluded. Four ml blood from the patients was taken via venipuncture or indwelling catheter in an EDTA tube. White blood cell count (WBC) and immature granulocyte (IG) percentage was analyzed by using Sysmex XN 3000 haematology analyzer.

Data was analysed using SPSS version 25.0. Mean and SD were calculated for numerical variables and percentage and frequency were calculated for categorical variables. WBC count and IG percentage between infected and non-infected groups was compared. Considering *p*-value of ≤0.05 to be significant.

The specificity and sensitivity of immature granulocyte percentage was calculated using a 2 x 2 table. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy for the FAST scan were determined by using the following standard formulas.

Sensitivity: TP/(TP+FN) X100, Specificity: TN/(FP+TN) X100, PPV: TP/(TP+FP) X100

NPV: TN/(FN+TN) X100, Accuracy: TP+TN /TP+TN+FP+FNX100

RESULTS

A total of 100 patients were included in this study. The age of the patients ranged from 30-79 years, mean age was 54.5 ± 14.24 years. Males accounted for 55% of the study population and 45% were females out of 100 patients with clinical suspicion of sepsis and SIRS, 48 had a positive blood culture showing infection while 52 patients had a negative blood culture. Reasons for

hospital admission included respiratory (40.9%), neurological (15.4%), renal (9.4%), postoperative (8.1%), infectious (8.1%), post-resuscitation (5.4%), hepatic (2.7%) and other (10.1%) (figure). Significant association was detected between positive blood culture and IG percentage using chi square test (p=0.01).

WBC counts and the percentage of immature granulocytes were significantly higher in patients with infection. Out of 48 patients with infection, 37 (77.08%) had a percentage of immature granulocytes of 1% or more, whereas the percentage of

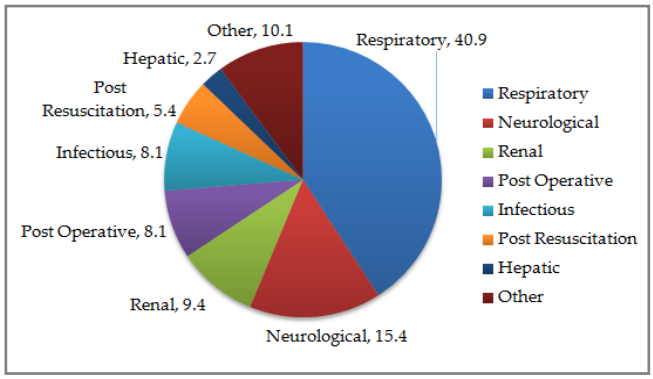

Figure: Reasons of hospital admission parameters.

immature granulocytes was 1% or more in only

Table: WBC count and IG percentage in 2 groups.

	Infected (n=48)	Non-Infected (n=52)	*p*-value
WBC count	10.7 ± 7.21 x 10^9 /µL	7.8 ± 5.0 x 10^9 /µL	0.01
IG %age	1.3 ± 2.3	0.9 ± 1.1	0.009

16 (30.76%) of 52 patients without infection. Mean WBC count in group-I and group-II patients was 10.7 ± 7.21 x 10^9 /µL and 7.8 ± 5.0 x 10^9 /µL, respectively (p=0.01), IG percentage was 1.3 ± 2.3 and 0.9 ± 1.1 respectively (p=0.03) (table).

The diagnostic accuracy of immature granulocyte percentage in patients with sepsis as compared to WBC count was recorded as 67.40%, 82.35%, 94.00%, 70.00% and 87.14% for sensitivity, specificity, positive predictive value, negative predictive value and accuracy rate respectively.

DISCUSSION

A favourable clinical outcome from hospital acquired infections is possible only if a rapid causal detection and diagnosis is made, along with administration of prompt treatment. Various haematological parameters have been evaluated in order to detect infections in hospital settings (CRP, Interleukins, D-dimers). Immature granulocyte count (IG count) is gaining increasing importance in its prompt detection of early-stage infection. Immature granulocytes are immature cells of the metamyelocytic, myelocytic and promyelocytic lineages[11]. They are normally absent in the peripheral blood, and indicate a high activity of the bone marrow[12]. In cases where neutrophilia is not detectable such as the geriatric population, neonates and patients with myelosuppression, a raised IG count (>2%) is a useful parameter to detect infection[13]. Manual IG count has been superseded by automated IG count by analysers providing improved accuracy and turn around time.

When compared with other haematological markers of infection, IG count has proved to have better specificity and positive predictive value as compared to C-reactive protein (CRP), absolute neutrophil count (ANC), and WBC count. Moreover, it increases the sensitivity to 93% and sensitivity to 86% of other markers[14] when measured together for detection of bacterial infections. IG percentage shows a higher value in the first 48 h in surgical ICU patients[15] as compared to CRP and other markers. Infection is not always detected when blood cultures are performed during suspicion of sepsis. Only 30-40% of the blood cultures are reported positive[16], making sepsis still the most common cause of death in intensive care unit settings. Owing to no gold standards available to make a prompt decision, the merits of this study hold prime importance. Previous studies suggest that IG% with a cutoff point of <2.0% yields a specificity of 90.9%[17] while another study conducted in February 2019 suggested increased cut off point to <3.0% and experienced specificity to 92.4% with a sensitivity of 27.2%[18]. Our study had a cutoff point of 1.0% for IG%,

which yielded a specificity of 82.35%. The high sensitivity observed in our study i.e. 67.40% can be attributed to lowering the cutoff point to 1.0%. While a high specificity as documented by previous studies authenticates the use of IG count for the purpose of isolating infection in sepsis in the ICU.

Our study documented that out of the 100 suspected patients, 48 had a positive blood culture while 52 had a negative blood culture. Previous studies have acknowledged that blood cultures have their drawbacks as they have a tendency to produce false-positive and false-negative results[9]. IG count proved to be a swift biomarker in our study as 77.08% of patients with infection had high IG% with a mean of 1.3 ± 2.3 (p=0.01). The results corresponded to the previous researches that reported similar results[17,18]. Geest *et al* also witnessed that those infected patients with negative blood cultures show a positive IG percentage[17]. This proves that while there is a constitutional delay in making a diagnosis through laboratory results in high-risk categories such as intensive care units, IG count can be carried out as an effective marker so that prompt treatment can be started to prevent fatalities from sepsis.

We calculated WBC count and IG count in the two groups with positive and negative blood cultures. A WBC count of 10.7 ± 7.21 x 10^9 /µL was detected in patients with a positive blood culture, while IG count was 1.3 ± 2.3. Compared to WBC count, IG count had better accuracy rate of 87.14%. A similar study reported that an increase in WBC count is not specific to infection and can be due to many other disease conditions[19]. The purpose of this distinction is to suggest combining immature granulocyte detection with leucocyte-related parameters in order to improve diagnostic accuracy of haematological parameters.

Our study calculated a statistically significant association between positive blood culture and IG% (p=0.01). Combining that with a high statistical association between the diagnosis of SIRS and IG percentage (p=0.009) calculated from our sample, it is suggested that optimizing the explorative strategies by the addition of IG count as a preliminary investigative tool along with blood culture and WBC count will produce a favorable prognosis. This idea is backed by Geest *et al*[17], Mathews *et al*[20], Maenhout *et al*[21] who advise the utility of IG count.

Our study is not without its limitations. It does not determine which kinds of infection makes IG count a better marker. Furthermore, the cutoff point for IG count was 1.0% in our study, where application of such low cutoff values may result in inclusion of false-positive results. It is recommended that IG count be evaluated in different documented infections so that its validity in various infectious conditions can be drawn. It is also recommended that receiver operating characteristic curve (ROC) analysis be done with different cutoff values to determine which IG percentage yields higher specificity and sensitivity. Our study has added to the present increasing pool of knowledge regarding the utility of immature granulocytes so that further research be carried out that validates our results.

CONCLUSION

Our study concludes that IG count of 1.0% is a reliable and effective predictor of infection, validating its addition into the diagnostic protocols in the intensive care unit settings.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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