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Hemogram Indices as a Mortality Predictor in Sepsis and Systemic Inflammatory Response Syndrome (SIRS): A Hospital-Based Clinical Study

Erum Amir[1]
Rabia Arshad[2]
Amtul Quddos Latif[3]
Rafia Siddiqui[4]
Mohammad Amir Shareef[5]
Talat Samreen[6]

Department of Pathology; Karachi Medical and Dental College; Karachi Metropolitan University, Karachi
Department of Pharmacology International Dental College, Dow University of Health Sciences, Karachi
Main Clinical and Diagnostic Laboratory, JPMC, Karachi
Department of Pathology, Karachi Medical and Dental College; Karachi Metropolitan University, Karachi
Abbasi Shaheed Hospital, Karachi
Assistant Professor; Department of Anatomy; Karachi Medical and Dental College, Karachi

Address for Correspondence
Dr Urooj Irfan
Chughtai Institute of Pathology
urooj.zae@gmail.com

Abstract

Objective: This study was designed to evaluate the prognosis and fatal outcomes by hematological parameters in patients with sepsis and Systemic Inflammatory Response Syndrome (SIRS).
Methodology: A prospective, cohort, observational hospital-based study, was conducted from October 2019 to April 2020, in the Medical and Surgical Intensive Care Units (ICUs) of JPMC, Karachi, Pakistan.With IRB committee approval, JPMC, a total of 200 patients diagnosed with SIRS and Sepsis as per SSC Guidelines, were enrolled. Demographic details, mortality stay in the ICU, clinical vitals and hemogram variables (total and differential leucocyte count, platelet count, and mean platelet volume) were observed with standard laboratory protocols on day 1 and 3. Results were analyzed by SPSS 26 with required statistical tests with p value less than 0.05 significant.
Results: Outcomes were significantly different in SIRS and septic patients for mortality (p=0.01), stay in hospital (p=0.01), and culture positivity (p=0.01). Hemogram indices in sepsis and SIRS were markedly different, with significantly elevated values of Total Leucocytes Count((TLC), Mean Platelets Volume (MPV), Neutrophils to Lymphocytes Ratio (NLCR) (P = < 0.01) in patients with sepsis exclusively.
Conclusion: Hematological parameters, MPV and NLCR can be used as prognostic markers to assess mortality in patients with sepsis. These are readily available blood markers linked to inflammation and can be useful, accessible tools for predicting patient prognosis and guiding treatment in sepsis.
Keywords: Differential leucocyte count, hospital mortality, neutrophil lymphocyte count ratio, mean platelet volume, sepsis, sequential organ failure score, systemic inflammatory response syndrome.

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Introduction

Sepsis, accumulatively fatal systemic response to infection, involves numerous adverse hemodynamic and metabolic alterations in the body. This predicament needs to be addressed promptly as each passing hour contributes to an approximate 7.6-10% rise in the fatality rate.[1]

The initial definition of "sepsis" was focused upon the "Systemic Inflammatory Response Syndrome" (SIRS) Criteria, with low specificity for "sepsis" and no details were provided regarding the host's immune response or the pathogen's virulence factors[2]. So, for more precisely defining sepsis and to enable more useful comparisons between different health care systems, the Surviving Sepsis Campaign in 2016 promulgated a revised definition of "Sepsis". Finally, it was known as a potentially life-threatening, maladaptive pathophysiological responses by host body, for which screening can be done using the "Sequential Organ Failure Assessment" (SOFA score).[3] Systemic inflammatory response syndrome has been excluded from the sepsis continuum due to its low clinical efficacy.[4]

In accordance with Sepsis-3 guidelines, a sudden escalation of 2 or more points in Sequential organ failure assessment score signifies systemic malfunction.[5] This score pivotal in mortality prediction, assesses impairment across six organ systems, either autonomously or in conjunction.[6] However not all infections culminate in multiorgan failure, posing diagnostic challenges, often leading to misdiagnosis due to non-specific clinical manifestations simulates other acute inflammatory conditions.[7] Consequently, the urgent adoption of evidence-based tools is paramount for precise and prompt sepsis identification. Traditional microbial cultures identify and isolate causative microorganisms in only 15 to 30 % of sepsis patients.[8]

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Various hematological parameters are employed to forecast outcomes and mortality rates associated with sepsis, across the globe. Among these indicators, the neutrophil and lymphocyte count ratio (NLCR) and Mean platelet volume (MPV) have displayed significant prognostic values in prior researches.[9]

Thrombocytopenia is consistently correlated with adverse outcomes in sepsis. Mean platelet volume as a hematological marker reflects the average size of the platelets, and is notably rise in admitted patients in critical care units.[10] The total leucocyte count serves as time-tested marker of bacteremia in diverse resource limited settings. NLCR has been rediscovered as cost-effective and easily calculated as ratio of absolute neutrophil to lymphocyte count.[11]

This research investigates the potential of Mean Platelet Volume (MPV) and Neutrophil-to-Lymphocyte Count Ratio (NLCR) as mortality predictors in sepsis. Both MPV and NLCR are readily available blood markers linked to inflammation and immune response. By examining their correlation with sepsis outcomes, the study aims.

Methodology

The present study was designed as a prospective cohort observational, hospital-based study. The primary aim was to evaluate and compare the clinical outcomes of patients diagnosed with Systemic Inflammatory Response Syndrome (SIRS) and sepsis using haematological markers. Using the formula, keeping the confidence interval 95%, margin of error 5% and disease prevalence as 0.99, the sample size calculated was 200.[12] IRB approval was taken from IRB committee, JPMC Karachi.

The study was conducted from October 2019 to April 2020 and study population consisted of patients admitted to the Medical and Surgical Intensive Care Units (ICUs) of JPMC, Karachi. Patients diagnosed with SIRS based on the presence of at least two of the following clinical criteria: Temperature >38°C or <36°CRespiratory rate >22 breaths per minute or PaCO2 <32 mmHg Heart rate >90 beats per minute White blood cell count >12,000/mm³ or <4,000/mm³. Patients diagnosed with sepsis according to the Sepsis-3 criteria, defined as life-threatening organ dysfunction caused by a deregulated host response to infection. Patients below 18 years of age, pregnant women, patients with chronic immunosuppressive conditions, including HIV/AIDS, or those receiving long-term steroid therapy and patients admitted with non-infectious conditions mimicking sepsis were excluded from the study.

After enrolment, each patient or their next of kin was thoroughly interviewed to gather demographic information and clinical details related to the illness. Demographic details included age, sex, medical history, and comorbidities. Vitals, Glasgow Coma Scale (GCS) score, Sequential Organ Failure Assessment (SOFA) score and laboratory Investigations (white blood cell count, platelet count, serum bilirubin, creatinine levels, and other relevant biochemical markers. All data were analysed by SPSS (Version 26.0) with required statistical tests and p-value of less than 0.05 was considered statistically significant.

Results

Out of 79 SIRS samples, 51.9% males and 48.1% females. Whereas in Group B,49.7% of patients were males and 52.1% were females (p=0.58). In Group A, the mean age group 45.24± 20.2 years with maximum patients in the age group of 18-25 years (24.1%), whereas in Group B most of the patients were in the oldest age group of more than 75 years (22.3%) with the mean age group 55.14±19.9 years (p=0.02). Most of the patients in both groups were from the medical ward (Group A=88.6%Vs Group B =85%; p value=0.48).In Group A 6.3% patients while in Group B 29.8% patients showed positive culture (p=0.01). The mortality rate was 13.9%Vs 58.3% in Group A and B respectively. The hospital stay in ICU was 12.36±7.34 days for the Group A patients whereas in Group B the stay was prolonged 15.43± 7.46 days (p=0.01). (Table I)

Mann Whitney U test with p-value < 0.05 exhibited significant differences in hematological parameters between sepsis and SIRS cases, on day 1 and day 3. Median MPV, NLCR and TLC measured in SIRS samples were 8, 8 and 14 respectively on day 1, almost similar values were observed on day 3. Samples of sepsis from Group B, showed significantly higher values of MPV, NLCR and TLC (12,19 and 23.5 respectively) on day 1 with the similar values on day 3. (Table II)

Similarly, Comparative analysis of hematological parameters between survivors and non-survivors of SIRS cases on Day 1 of ICU admission revealed the non-

significant difference in median observed for MPV (p=0.46), TLC (p=0.73) and SOFA (p=0.12), whilst for NLCR, MPV and SOFA score, highly significant results were obtained (p=<0.01) on Day-I for Survived and non-survived samples of sepsis. (Table III)

Table I: Baseline Characteristics. (n=200)

Characteristics		Group A: SIRS (n=79)		Group B: SEPSIS (n=121)		p-value
		N	%	N	%	
Gender	Male	41	51.9	58	47.9	0.58
	Female	38	48.1	63	52.1	
Age Group	18 - 25 year	19	24.1	14	11.6	0.02*
	26 - 35 years	13	16.5	8	6.6	
	36 - 45 years	13	16.5	21	17.4	
	46 - 55 years	7	8.9	14	11.6	
	56 - 65 years	11	13.9	21	17.4	
	66 - 75 years	9	11.4	16	13.2	
	>75- years	7	8.9	27	22.3	
	Mean ±SD	*45.24 ±20.2*		*55.14±19.9*		
Ward	Surgical	9	11.4	18	14.9	0.48
	Medicine	70	88.6	103	85.1	
Culture	Positive	5	6.3	36	29.8	<0.01*
	Negative	74	93.7	85	70.2	
Mortality	No	68	86.1	50	41.7	<0.01*
	Yes	11	13.9	70	58.3	
The average length of ICU	Days	*12.36±7.34*		*15.43±7.46*		

*p<0.05 was considered significant using the Pearson Chi-Square test

Table II: Comparison of haematological parameters between sepsis and SIRA sample.

Parameters	Groups				p-value
	SIRS		SEPSIS		
	Median	IQR	Median	IQR	
Day-I MPV (fl)	8	2	12	2.7	<0.01*
Day-I NLCR	8	4	17	19	<0.01*
Day-I TLC	14	5.6	23.5	14	<0.01*
Day-III MPV (fl)	8.12	1.1	12	4	<0.01*
Day-III NLCR	8	4	15	17.55	<0.01*
Day-III TLC	13	6.5	26	12.87	<0.01*

*p<0.05 was considered significant using Mann Whitney U Test

Table III: Comparison of Studied Parameters Between Survived and Non-Survived Samples of Sepsis Cases at Day 1 and 3"

Parameters	SEPSIS				p-value
	Survived (n=50)		Non-Survived (n=70)		
	Median	IQR	Median	IQR	
Day-I MPV	10.95	3.00	12.00	3.00	<0.01*
Day-I TLC	21.99	13.50	27.00	14.10	0.06
Day-I NLCR	12.00	11.45	20.00	20.00	<0.01*
Day-I SOFA	9.50	9.00	15.00	7.00	<0.01*

*p<0.05 was considered significant using Mann Whitney U Test

Table III B: Comparison of Studied Parameters Between Survived and Non-Survived Samples of SIRS Cases at Day 1 and 3.

Parameters	SIRS				p-value
	Survived (n=50)		Non-Survived (n=70)		
	Median	IQR	Median	IQR	
Day-I MPV	8.00	1.65	8.9	2.00	0.46
Day-I TLC	14.3	5.21	13.65	8.2	0.73
Day-I NLCR	7.00	3.00	12.00	7.00	<0.01
Day-I SOFA	3.00	5.00	6.00	4.00	0.12

*p<0.05 was considered significant using Mann Whitney U Test

Discussion

Diagnostic modalities of sepsis for enhancement of better survival outcomes and targeted therapeutic interventions are likely to ensure better outcome in this serious condition. Hence it is crucial and difficult to discriminate the sepsis from sterile inflammatory disorders like SIRS, for implementation of hourly sepsis treatment as per SSC recommended guidelines referred to as Early goal-directed therapy (EGTD).[13]

The definition of sepsis is established with the Third International Consensus, explaining "the life-threatening condition of organ dysfunction caused by dysregulation of the host response to infection, integrated SOFA scores to grade organ deterioration (Sequential Sepsis-related Organ Failure Assessment) of ≥ 2 points" and septic shock, as "hypotension requiring vasopressors to maintain mean arterial pressure ≥ 65 mmHg after

adequate fluid resuscitation, and serum lactate of > 2 mmol/L".[14]

Sepsis patients had a death rate (58.3%) at 28 days for all causes that was much greater than that of the SIRS group (13.9%). These results were consistent with the documented mortality of sepsis patients by Huang in a study from Southeast Asia, where sepsis-related mortality was 61%, while Asghar reported a similar mortality rate of around 51.5% in his study.[15]The high mortality in our results could be due to the reason that the sampling area was a public health care unit, and the majority of our patients were from lower socioeconomic groups.[16] They had prolonged pre-hospital sepsis-related clinical manifestations linked to chronic disorders, and most of them were unaware of the severity of their illness, therefore arrived at the hospitals late. Moreover, in community health centers only a small number of patients got instantaneous admittance in trauma and critical care units due to fewer provided facilities as compared to private hospitals, which additionally accounts for higher mortality. Population with extremes of age are most likely affected by sepsis, and 13 times more prone to develop organ failure secondary to systemic infections. Similarly, our study identified a progressive rise in sepsis incidence after the fourth decade of life that reached its peak in individuals of 75 years or more. Huang stated that increasing age appears to confer an independent risk factor for sepsis development.[16] Lewis also reported a steady rise in sepsis incidence after the third decade of life, which aligned well with our assertions. Comparable increased age incidence of sepsis in patients with an average age of around 65 reported in Asian studies. This might seem relevant to the expanding worldwide proportion of the older population, estimated to reach 16% by 2050. Comorbidities, poor response to therapy, immune-senescence and malnutrition also justify the admission of elderly patients in critical care units .[17]

The median SOFA Score at admission increased regularly in the current study and was shown to be a reliable predictor of death in sepsis patients on days 1 and 3, however, the median SOFA Scores observed were lower in SIRS criteria. Raith and colleagues conducted one of the biggest international cohorts, which revealed SOFA Score as a possible indicator of ICU mortality.[18] Kaukonen, on the other hand, claimed that SIRS criteria were a poor predictor of mortality since they missed systemic dysfunction and risk categorization in subgroups of intensive care facilities patients. The conclusions outlined here and the findings of the current study were highly correlated[19]. The median duration of ICU stay of the sepsis group of 15 days was found to be lengthier than the ICU stay of 12 days noted for non-infectious patients. Likewise, also documented in literature that the median LOS in the ICU of sepsis patients was 18 days presumed as a bad prognostic indicator.[20] Henceforth there is a high likelihood of sepsis patients contracting multidrug resistance and ventilator-associated lower respiratory tract illness attributed to mortality risk. Extended duration of patient's stay in critical care units is most likely associated with nosocomial infections specifically pneumonia, catheter-induced genitourinary tract infections, and central line-associated bloodstream infections that are found to be the major contributors to higher mortality in most cases of sepsis.[20]

This study emphasizes the effectiveness of MPV and NLCR as pivotal hemogram parameters in diagnostics and sepsis risk stratification in critical care units. MPV gains recognition as readily available cost-effective marker and has been extensively explored as independent predictive pointer of sepsis related mortality.[21] Our findings revealed a notable surge in MPV, reaching up to 12fl, after 24 and 72 hours of admission in sepsis, contrasting with much lower levels (8fl) in SIRS. Moreover, we observed positive correlation between rising levels of MPV and SOFA score in sepsis both at day 1 and day 3 post admission.[22]

This study unveiled a substantial increase in Mean platelet volume among non-survivors in initial 24 hours of ICU admission. persisting albeit appropriate antibiotics treatment.[23] Hence suggesting potential utility of MPV in tailoring antibiotic therapy in sepsis more specifically in resource constrained settings. Moreover, studies highlighted the positive correlation between rising levels of MPV and notable surge in hospital mortality among sepsis population.[24] The research also pointed towards consistently elevated MPV levels in non-survivors of sepsis in comparison to sepsis survivors, throughout their stay in ICU, possibly due to consumptive coagulopathy.[25] Additionally, it underscores the importance of ruling out the hypo-proliferative causes regarding

thrombocytopenia. Furthermore, a sharp increase in neutrophil lymphocyte count (NLCR) was observed in first 24 hours of admission in adult sepsis patients in comparison with non-septic individuals. Previous studies reinforcing a strong association of elevated NLCR levels with clinical adversities in sepsis, although the role of predictive value of NLCR is questionable in culture positive cases according to few researches. [26]

Sepsis-related all-cause mortality significantly correlated with an NLCR score of >20 in our research, within the first 24 hours and soon after. However median NLCR was found to a much lower extent in patients of SIRS with unfavorable prognosis. A strong link is ascertained between 28 days of all-cause mortality and NLCR in sepsis, likewise research explored a significant connection amid adverse outcomes of sepsis and raised levels of NLCR in comparison with traditional biomarkers.[26] Hence in ICU settings, NLCR may be utilized as an ancillary parameter for differentiating between sepsis and systemic inflammatory response syndrome (SIRS), which correctly reflects the severity of the illness. Our study showed that NLCR performed well in sepsis patients, on par with microbial culture. This is consistent with literature which suggested NLCR as a marker for early detection of community-acquired illnesses.[27] However, it is also found that conventional inflammatory biomarkers superior to NLCR in distinguishing sepsis survivors from non-survivors, which contradicted our observations.[28]

The turnaround time of the hemogram in the laboratory is short, almost 22 min after execution of the complete automation analyzers system. Efficient processing of CBC samples in our study on auto analyzers decreased the risk of data bias that otherwise occurred as a result of hospital-acquired infections. Although, the actual cause of the NLCR rise is unknown, endogenous cortisol and catecholamine are probably involved. In our environment, we proved that NLCR is the best inflammatory marker for use in both the ICU and the emergency room. Compared to other types of physiological stress, sepsis may result in a particularly expeditious rise of NLCR because it also induces lymphocyte apoptosis.[29]

Conclusion

1. Mean platelet volume and Neutrophil lymphocyte count ratio are significantly raised in the early hours of sepsis and can be utilized as predictors of clinical severity, prolonged ICU stay and mortality. These hematological parameters facilitate the clinicians to reach a definitive diagnosis and initiate targeted therapeutic measures.
2. Serial measurements of these specific hemogram indicators categorically discriminate sepsis and non-infectious SIRS as two different clinical entities with different treatment options.
3. 3.MPV and NLCR might be indexed specifically in the diagnostic algorithm as cost-effective, reliable and readily available biomarkers, particularly in low-resource settings.

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