Lika A, Mone I, Korita I, Barbullushi A. Diagnostic value of immature-to-total neutrophils (I/T) in sepsis (Original research). JGPOH 2024, posted: 05/07/2024
DOI: 10.61034/JGPOH-2024-15

Viewpoint

Diagnostic Value of Immature-to-Total Neutrophils (I/T) Ratio in Sepsis

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Recommended citation:
Lika A, Mone I, Korita I, Barbullushi A. Diagnostic value of immature-to-total neutrophils (I/T) in sepsis. JGPOH 2024. DOI:10.61034/JGPOH-2024-15, Website: https://jgpoh.com/

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Abstract

Aim: To evaluate the diagnostic usefulness of immature-to-total neutrophils ratio in sepsis diagnosis, differentiating from the Systemic Inflammatory Response Syndrome (SIRS), and also to compare it with other established predictive markers of sepsis.
Methods: This study included 188 patients (67, or ≈36% females) admitted at the University Hospital Centre in Tirana, Albania. Participants were divided into three groups: sepsis, SIRS and local infection (without SIRS). For all patients there were measured WBC, total neutrophils, neutrophils to lymphocytes ratio, immature-to-total neutrophils ratio, C-reactive protein (CRP) and procalcitonin (PCT). CRP and PCT were used as comparative, well-established predictive markers of sepsis.
Results: Mean value of WBC in study groups were 19±7.5 cells/mm^3 in sepsis, 16.6±6.6 cells/mm^3 in SIRS group, and 18±6 mm^3 in group with local infections. Absolute neutrophils had the following mean values: in sepsis 15.8±7.1 cells/mm^3, in SIRS group 14±4.4 cells/mm^3 and 17±6.2 cells/mm^3 in local infections. Immature-to-total neutrophils ratio was higher in sepsis group 0.2±0.11, compared to 0.1±0.089 in SIRS group and 0.12±0.077 in the local infection group. Neutrophil-to-lymphocyte ratio (NLR) had a higher mean value of 16.8±20.4 in sepsis, 11.3±15.1 in SIRS and lower in local infection group (8.7±5.7). Similarly, mean PCT level was very high in sepsis 10.0±18.7ng/ ml, 0.3±0.2 in SIRS and 0.4±0.4 in participants with local infections. Furthermore, mean CRP level was considerably higher among patients with sepsis (149±100mg/l) than in those with SIRS (42.3±45.3 mg/l) and participants with local infections (34.6±75.1mg/l). Analysis of variance (ANOVA) demonstrated a statistically significant difference in the mean levels by disease categories of study participants (sepsis, SIRS, local infections) for I/T neutrophils ratio ($P<0.001$), but for not for absolute neutrophils ($P=0.175$), WBC ($P=0.097$) or NLR ($P=0.163$). For PCT and CRP, there was evidence of a statistically significant difference between groups ($P<0.001$). Multiple comparisons according to Tukey HSD test demonstrated significant pairwise differences between the following disease categories: a higher mean level for PCT, CRP, I/T neutrophils ratio in patients with sepsis compared to SIRS ($P<0.001$) and those with local infections ($P=0.04$, $P=0.37$, $P=0.07$).
Conclusion: I/T neutrophils ratio seems a highly accurate marker in sepsis diagnosis and differentiating from SIRS. This marker can be obtained at no-added cost, and monitoring serial levels can predict sepsis early, allowing to initiate treatment early, optimize antibiotic use, and reduce overall mortality.

Keywords: I/T neutrophils ratio, NLR, Sepsis; SIRS, total neutrophils, WBC.

Conflict of interests: The authors report no conflicts of interest.

Financial disclosure: Not applicable.

Introduction

Sepsis is a cascade of events originating from innate and adaptive immune responses: it is characterized by the activation of various cell types and release of both pro-inflammatory and anti-inflammatory molecules. In the initial phase of sepsis, a predominantly hyperinflammatory state caused by cellular interaction with the infectious agent develops, followed by a state of immune hypo responsivity [1,2]. Neutrophils are the first cell to migrate through the vascular epithelium and reach the site of infection [3]. Microbial infections lead to the generation of granulocytes in the bone marrow and subsequently a release of both immature and mature forms of neutrophils into the peripheral blood [4]. Excessive immature form of neutrophils in the peripheral is a hallmark of systemic inflammatory response syndrome and is also related to clinical deterioration in patients with sepsis [5]. The migration of neutrophils to infection site is critical for their antimicrobial function. It has been suggested that all the phases responsible for neutrophil migration have been impaired during sepsis, including mobilization and release from the bone marrow, migration and rolling, adherence, and transmigration [6].

The transmigration of neutrophils from the vascular compartment into the infection site is driven by the interaction between chemoattractants and CXCR2 on neutrophils which is downregulated during sepsis progression. Once neutrophils have found and recognized an invading pathogen, they exert their antimicrobial function through phagocytosis, and subsequently pathogen killing, which occur in the ph phagolysosome [7]. The recognition of pathogen or pathogen products by neutrophils also has an impact in the following antimicrobial activities, among which Toll-like receptor (TLRs) are suggested to play a critical role during these processes [8]. Therefore, the septic milieu alters the TLR signaling and promote the hypo responsiveness of neutrophils, which may trigger the inhibition of immune response against secondary infection. Despite the intrinsic regulation of antimicrobial function in neutrophils, environmental stimulus can also influence the antimicrobial capacity of neutrophils during sepsis. Mediators expressed by bacteria and host derived factors have shown to impair neutrophil phagocytosis through limiting complement –mediated opsonization [9]. As the most abundant immune cells in the peripheral with a relatively short half-live, neutrophils undergo constant replenishment from the bone marrow to peripheral blood [10]. The developmental path and functional properties of neutrophils in the bone marrow include granulocyte – monocyte progenitor (GMP) differentiating into neutrophils precursor population [11], which can further rise to un intermediate immature population and subsequently the mature population [12]. As a result, both immature and mature neutrophils were driven to peripheral blood, which has been confirmed in patients with sepsis, although detailed mechanism for the presence of immature neutrophils is still lacking [12,13]. As previously described, a compromised expression of CXCR2 was identified in neutrophils of septic patients. However, since immature neutrophils also displayed low or negative expression of CXCR2 [12], the downregulation of CXCR2 on neutrophils in patients with sepsis may also partly attribute to the presence of immature neutrophils. Immature neutrophils were shown to have decreased phagocytic capacity [14] and reduced antimicrobial function [15].

Early diagnosis has always been the key for successful management of sepsis. Every hour of delay in antibiotic therapy has been shown to increase the mortality of septic shock by 7.6% [16].

Biomarkers such as serum procalcitonin (PCT), C-reactive protein (CRP), IL6, IL8, and others have been found helpful to predict sepsis, but are not widely used due to limited availability and high costs. Functional and morphological evaluation of leukocytes is considered a more affordable and practical strategy for monitoring the inflammatory response in sepsis. Parameters like manual band count, left shift, and immature to total neutrophils ratio are widely used in pediatric patients to predict bacterial infection. [16]. The IG includes bands, promyelocytes, myelocytes, and metamyelocytes of the neutrophils. This fraction is believed the first reaction of the bone marrow in an infection [17]. Quantification of this fraction can be used as a predictive marker for sepsis. It is not only easily available, but also simple, inexpensive and reproducible.

The aim of our study was to evaluate the diagnostic usefulness of immature-to-total neutrophils ratio as an early marker of sepsis and also to compare it with other established predictive markers of sepsis (PCT, CRP). A biomarker which can easily, rapidly, and accurately differentiate sepsis from other inflammatory conditions.

Methods

In this study were included 188 patients, 67 (36.2%) females and 121(64.8) males, who were admitted and received treatment at the Intensive Care Unit (ICU) and Emergency Departments in the Hospital of infectious Diseases and the Pediatric Hospital of "Mother Teresa "University Hospital Centre in Tirana, Albania.

With the patients who met the inclusion criteria (two or more sing of Systemic Inflammatory Response Syndrome [SIRS]), following protocol approved by the Biochemical-Clinical Laboratory Service and respective clinical departments , a medical chart was completed, which included demographic data, clinical and anamnestic data, co-morbidities, routine examinations: complete blood counts (WBC, absolute neutrophils, immature neutrophils, I/T neutrophil ratio), urine exam, biochemical balance, basic routine of coagulation (INR, APTT, fibrinogen), microscopic and microbiological examinations. Specific parameters (PCT and CRP) were measured.

Conform to the American College and Chest Physicians and the Society of Critical Care Medicine Conference 1992, that determine clinical and laboratory finding in SIRS and different degrees of sepsis, the patients incorporated in our study, were classified in three groups:

- First group were patients with sepsis (103, or 55.1% of the total), defined as SIRS with positive culture for bacterial infections.
- Second group included patients with SIRS (71, or 37.4%of the total).
- Third group patients (14, or 7.5%of the total) included patients with confirmed bacterial infections, but without SIRS. This group was referred to as patients with "local infection".

DOI: 10.61034/JGPOH-2024-15

Statistical analysis was performed using the statistical software package SPSS, version 21.0 (SPSS Ins, Armonk, NY: IBM Corp). Mean values, standard deviations (SD), and 95% confidence intervals (95%CI) within groups and between groups were calculated using ANOVA test. Spearman's rank correlation coefficients were calculated to measure the relationships between numerical variables. For multiple comparisons, Tukey HSD test was used, assessing the relationship between mean values difference and study groups and their statistical significance was determined (values of $P \leq 0.05$ were considered statistically significant).

Results

Descriptive analysis showed that mean values of WBC in study groups were 19±7.5 cells /mm^3 in sepsis, 16.6±6.6 cells/mm^3 in the SIRS group, and 18±6 mm^3 in the group with local infections. Absolute neutrophils had the following mean values: in sepsis 15.8±7.1 cells/mm^3, in the SIRS group 14±4.4 cells/mm^3 and 17±6.2cells/mm^3 in the group with local infections. Immature-to-total neutrophils ratio was higher in the sepsis group 0.2±0.11, compared to 0.1±0.089 in the SIRS group and 0.12±0.077 in the local infection group. Neutrophil-to-lymphocyte ratio (NLR) had a higher mean value in the group with sepsis 16.8±20.4, 11.3±15.1 in SIRS and lower in local infection group 8.7±5.7. Similarly, mean PCT level was very high in sepsis 10.0±18.7ng/ ml,0.3±0.2 in SIRS and 0.4±0.4 in participants with local infections. Furthermore, mean CRP level was considerably higher among patients with sepsis 149±100mg/l than in those with SIRS 42.3±45.3 mg/l and participants with local infections 34.6±75.1mg/l (Table 1).

Table 1. The distribution of mean values among parameters in the study by category: Analysis of Variance (ANOVA)

						95% Confidence Interval for Mean			
		N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound	Minimum	Maximum
I/T NEUT	Sepsis	92	0.201	0.112	0.012	0.177	0.224	0.040	0.520
	SIRS	50	0.108	0.090	0.090	0.082	0.133	0.010	0.410
	I.Lokal	12	0.129	0.078	0.022	0.801	0.179	0.020	0.320
	Total	**154**	**0.165**	**0.112**	**0.009**	**0.147**	**0.183**	**1.000**	**0.520**
WBC	Sepsis	103	19.039	7.501	0.739	17.570	20.500	2.900	49.000
	SIRS	70	16.670	6.630	0.793	15.090	18.250	9.700	53.000
	I.Lokal	14	18.690	6.050	1.619	15.100	22.190	10.900	30.700
	Total	**187**	**18.120**	**7.145**	**0.523**	**17.100**	**19.150**	**2.900**	**53.000**
NLR	Sepsis	75	16.800	20.430	2.341	12.160	21.560	0.700	97.000
	SIRS	42	11.350	15.175	2.340	6.620	16.080	0.800	93.000
	I.Lokal	11	8.750	5.706	1.720	4.910	12.570	4.470	23.500
	Total	**128**	**14.350**	**18.150**	**1.600**	**11.180**	**17.530**	**0.700**	**97.000**
ABS NEUT	Sepsis	76	15.850	7.180	0.820	14.210	17.490	1.000	44.500
	SIRS	43	14.020	4.480	0.683	12.640	15.400	4.000	27.900
	I.Lokal	10	17.540	6.280	1.980	13.040	22.030	9.700	28.300
	Total	**129.0**	**15.370**	**6.380**	**0.560**	**14.260**	**16.480**	**1.000**	**44.500**

Analysis of variance (ANOVA test) demonstrated a statistically significant difference in the mean levels by disease categories of study participants (sepsis, SIRS, local infections) for I/T neutrophils ratio ($P<0.001$), but for absolute neutrophils P=0.175, WBC P=0.097 and NLR

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P=0.163. For PCT and CRP there was evidence of a statistically significant difference between groups (P<0.001) (Table 2).

Table 2. Variance analysis (ANOVA) of the study parameters within groups and between groups

		df	Mean Square	F	Sig.
I/T NEUT	Between Groups	2	0.296	13.860	<0,001
	Within Groups	151	1.600		
	Total	**153**	**1.970**		
WBC	Between Groups	2	238.000	2.367	0.970
	Within Groups	184	9 258.000		
	Total	**186**	**9 496.000**		
NLR	Between Groups	2	1 196.000	1.830	0.163
	Within Groups	125	40 676.000		
	Total	**127**	**41 872.000**		
ABS NEUT	Between Groups	2	142.500	1.770	0.175
	Within Groups	126	5 072.000		
	Total	**128**	**5 215.000**		

Multiple comparisons according to Tukey HSD test demonstrated significant pairwise difference between disease category included the following: a higher mean level for PCT, CRP, I/T neutrophils ratio in patients with sepsis compared to SIRS (P<0.001)and those with local infection (P=0.04, P=0.374, P=0.067). There was no statistically significant difference in the mean levels of other parameters included in the study, NLR, absolute neutrophils and WBC. WBC had e borderline difference between sepsis and SIRS (P=0.082) and with participants with local infection P=0.98). A higher value was for absolute neutrophil and NLR in sepsis compared to SIRS, and in patients with local infection, respectively: P=0.290, P=0.711, P=0.256, P=0.347 (Table 3).

Table 3. Multiple variable comparisons by groups in the study

						95% Confidence Interval	
Depend. var	**(I)kat**	**(J)kat**	**Mean Difference (I-J)**	**Std. Error**	**Sig.**	**Lower Bound**	**Upper Bound**
I/T NEUT	**Sepsis**	SIRS	0.093	0.018	<0.001	0.050	0.014
		L.Inf	0.071	0.317	0.067	(0.004)	0.146
	SIRS	Sepsis	(0.093)	0.018	<0.001	(0.136)	(0.050)
		L.Inf	(0.022)	0.033	0.790	(0.100)	0.057
	L.Inf	Sepsis	(0.071)	0.032	0.067	(0.146)	0.004
		SIRS	0.022	0.033	0.790	(0.057)	0.100
WBC	**Sepsis**	SIRS	2.367	1.099	0.082	(0.230)	4.963
		L.inf	0.357	2.021	0.984	(4.428)	5.121
	SIRS	Sepsis	(2.367)	1.099	0.082	(4.963)	0.230
		L.inf	(2.020)	2.077	0.595	(6.927)	2.887
	L.Inf	Sepsis	(0.347)	2.021	0.984	(5.121)	4.428
		SIRS	2.020	2.077	0.595	(2.887)	6.927
NLR	**Sepsis**	SIRS	5.511	3.477	0.256	(2.736)	13.756
		L.inf	8.120	5.824	0.347	(5.695)	21.935
	SIRS	Sepsis	(5.510)	3.477	0.904	(13.756)	2.736
		L.inf	2.610	5.824	0.347	(11.883)	17.102
	L.Inf	Sepsis	(8.120)	3.477	0.904	(21.935)	5.695
		SIRS	(2.610)	6.110	0.347	(17.102)	11.883
ABS NEUT	**Sepsis**	SIRS	1.829	5.824	0.290	(1.043)	4.700
		L. Inf	(1.683)	6.110	0.711	(6.746)	3.379
	SIRS	Sepsis	(1.823)	1.211	0.290	(4.700)	1.043
		L. Inf	(3.512)	2.228	0.259	(8.795)	1.771
	l.Inf	Sepsis	1.688	2.134	0.711	(3.379)	6.746
		SIRS	3.512	2.278	0.259	(1.771)	8.795

The mean difference is significant at the 0.05 level.

According to Spearman's test bivariate analysis, there was evidence of a strong correlation between PCT, CRP and immature to total neutrophil ratios for all patients included in the study (respectively r=0.506, r=534 and P<0.001) (Table 4). P-value was significant at the level of 0.01.

Table 4. Bivariate correlations between I/T Neut. ratio and PCT, PCR in patients included in the study

Variable		I/T NEUT Ratio
PCT	Correlation coefficient	0.506
	Significance	0.000
PCR	Correlation coefficient	0.534
	Significance	0.000

Discussion

Neutrophils are the first line of defense in protecting body from infection [18]. The migration of neutrophils included four distinct phases, all of which are impaired during sepsis: mobilization and release from the bone marrow, margination and rolling, adherence, and transmigration [19]. The granulocytic shift to left characterized by the presence of immature granulocytes in the peripheral blood reflects active bone marrow response to bacterial infection.

Formally, these are classified on the basis of cell morphology by microscopical examination of blood films, into promyelocytes, myelocytes, metamyelocytes, and band forms [8]. With advances of technology, automated hematology analyzers accurately identify and count immature granulocytes and are cheap and simple to use.

Leukocytes count was used as marker in sepsis diagnosis, because studies have shown that sepsis is usually presented with high leukocytes and neutrophils, and with left shift in leukocytes, that mean lower mature neutrophils and higher bands neutrophils than normal [20]. But other studies have demonstrated that immature–to-total neutrophils ratio is more sensitive marker than leukocytes, absolute neutrophils, and bands neutrophils [21,22]. Even in our study we have arrived in the same conclusion. Leukocytes, lymphocytes, total neutrophils were measured in automated hematologic analyzer, while neutrophils morphology and their quantification were done by blood smear microscopic examination. Our results demonstrated that leukocytes are not a specific parameter for sepsis even with high value, because according to the variance analysis ANOVA, mean value in sepsis was 19.03 cells/mm^3, 16.67 cells/mm^3 in SIRS, and 18.69 cells/mm^3 in patients with local infection. Multiples comparisons according Tukey HSD test have shown there is not a significant difference in the mean value of leukocytes between groups, because $P>0.05$ (0.082 between sepsis and SIRS and 0.98 between sepsis and local infection groups). The same conclusion has arrived for NLR and absolute neutrophil parameters. For NLR there is not a significant difference between sepsis and SIRS ($P=0.256$), or between sepsis and local infections ($P=0.347$).

Analyzing our results for immature to total neutrophil ratio, we have high mean value in sepsis group (0.2), compared to SIRS and local infection groups (0.1 and 1.02). Multiple comparisons (Tukey HSD test) shown a statistically significant difference in mean value differences between patients with sepsis and SIRS group ($P<0.001$), and nonsignificant between sepsis group and local infection ($P=0.67$).

According to Spearman‘s test correlation between I/T neutrophils ratio and CRP, PCT markers (as established predictive markers of sepsis) demonstrated high significance in all patients in the study ($P<0.001$). These results are similar to other studies [22-25].

Conclusion

Our study demonstrated that immature to total neutrophil ratio is a sensitive marker in differential diagnosis between sepsis and SIRS. Predicting sepsis early could have many implications in managements protocols, could decrease high mortality. I/T neutrophils ratio can be obtained at no -added costs, and monitoring the serial levels can predict sepsis early, allowing to initiate adequate treatment and optimize antibiotic use.

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