



LEUKOCYTOSIS IN THE EMERGENCY ROOM -A BRIEF OVERVIEW !

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ABSTRACT

Introduction : Leukocytosis in the absence of infection is a fragmentarily studied topic . Despite that it is widely considered as a marker of infection and inflammation, the differential diagnosis of raised WBC count per se is an overlooked issue . (2,)Leukocytosis (elevation of WBC count $> 11 \times 10^9/L$) is a common entity seen in patients presenting to emergency department . Its well described to be associated with many infectious conditions like pneumonia, soft tissue infections, urosepsis. It can also occur in wide variety of other conditions like myocardial infarction, acute pulmonary embolism, physiological stress, trauma, medications, poisoning, surgical stress, haematological malignancy.(1,6) Very few studies have described the association of leukocytosis with mortality and quiet a small number of them have been enumerated as the specific cause of this condition in the absence of overt infection. (6,7)The present study is undertaken to investigate the relationship between leukocytosis and all cause mortality and elucidate the different conditions associated with raised leukocyte counts and to find the association between leukocytosis and mortality in a variety of conditions in the absence of overt infection. **Methods :** The present study is a prospective observational study. All the patients presenting to emergency department fulfilling the inclusion criteria , with q SOFA > 2 were included in the study . Patient details , history, total leukocyte counts and differential counts of patients were noted on day 1, day 2 and subsequently , detailed study of complete medical records of each patient , all conditions that cause fever and leukocytosis, trends of rise in WBC counts, laboratory tests, imaging studies, progress notes, diagnosis of primary care team, opinion of consultants was noted . TLC counts were noted on presentation (day 1, day 2 and day 5) ,presence or absence of sepsis and mortality was followed up , delta gap difference between leukocyte counts on day2 and day5) was calculated . Stratification and grouping of patients according to the level of rise in the WBC counts and as per the probable etiology of leukocytosis Separation of patients into survival and non survival groups ,presence or absence of sepsis and as per the other categories was done . Comparison between different groups of patients to find the strength and validity of these conditions was done by using parametric and non parametric tests for continuous variables , univariate and multivariate logistic regression models were applied to assess the various conditions associated with leukocytosis. **Results:** The study results suggest that out of the total 818 patients recruited in the study after excluding 21 patients due to inadequate data , of the total study subjects (n =771) , survival group constituted 754 (92.1) % and non survival group 17(2.2)% of patients, and the mean leukocyte count in the survival group is 18123 ± 9920 . Among the various causes of elevated leukocyte count sepsis was documented in 243 patients (31.5%). Of these 243 patients majority of them had pneumonia and urinary tract infection . Mean leukocyte counts of day 1 and day 5 did not show positive correlation with mortality (r value -0.003 and 0.018 respectively) , however as per logistic regression analysis , delta gap (difference in leukocyte counts of day 2 and day 5) predicted the probability of death in the group as a whole. **Conclusion :** This study states that although the trends of rise in the leukocyte count had a positive association with mortality in few individual subgroups like sepsis , leukocytosis as such is a marker of pathological condition or serious infection only in extreme elevations with WBC count > 25000 only. Leukocytosis in the ER room as such does not show a positive association with mortality in the study group as a whole.

KEYWORDS :**INTRODUCTION**

Leukocytosis (white blood cell count greater than $11000/mm^3$) , is a frequently encountered finding in the busy ED .There is a continuous search engine in the ED practice for markers that identify disease severity ,as early as that in the sub clinical stage .^(1,2)Leukocytosis along with C reactive protein and Erythrocyte sedimentation rate are considered as acute phase markers and prognostic indicators of organ damage .⁽²⁾It is important for physicians to be familiar with most common conditions causing raised WBC apart from sepsis and malignancy .⁽³⁾Leukocytosis can occur in a variety of conditions -non malignant causes include stressors causing acute elevation such as medications , asplenia ,smoking , obesity , and other chronic inflammatory conditions .The association between leukocytosis and mortality is not well known , and is a fragmentarily studied topic .^(3,4)Leukocytosis either independently or in association with other markers can be used as a prognostic marker for predicting mortality and morbidity of the acutely ill hospitalized patients , although further research is needed to elucidate the probable causative

mechanisms.^(2,3,4)

It was contemplated that research with an insight to evaluate the association of raised TLC count with mortality and the possible causative mechanisms, is required in the ED . It is quite possible that WCC alone or along with other clinical and laboratory parameters could be an indicator of all cause mortality and morbidity in Emergency Department admissions .

This study also aims to identify and characterize patients who present with transient leukocytosis in clinical practice, prompt and timely recognition prevents inappropriate antibiotic therapy and unnecessary investigations, benefiting both the health system and the patients themselves.

Factors Affecting The WBC Count

Important risk factors include old age , obesity, chronic stress , insulin resistance, smoking etc ; Increased leukocyte count can occur in response to external stimuli like exercise ,trauma

,infection, inflammation , drugs , ketoacidosis ,psychiatric disorders , poisoning , malignancy and other bone marrow disorders i. e myeloproliferative diseases .^(1,3,5)

MATERIALS AND METHODS

After obtaining permission from the institutional ethics committee , the study was conducted over a period of one year between December 2018 - March 2020 in the NIMS hospital emergency department

Study Design - Prospective Observational study

Methods : All patients presenting to emergency department falling in the age group of 18 years and above are included in the study , very few patients of age less than 18years are also included under the variant sub group study population.

Following entry of patient details ,the total and differential counts on day1, day 2, day 5 and prehospital (if available) were noted. Delta gap - difference between leukocyte counts on Day 1 and Day 5 was also calculated ,classification of patients into survival and non survival groups was done , and stratification into various groups as per the causes of leukocytosis and provisional admission diagnosis was done and accordingly patients' were divided into 3 strata as per the total leukocyte counts range and mean TLC counts in different sub groups as per the etiology were calculated and correlation between trends of leukocyte count variation and mortality was done. As per the categorical classification of Holland and Gallin the association of mean TLC count and mortality was measured.

Normal Variants

TLC Count :

Adult – 4000 to 11000 /mm³

Pregnant Female- 5800 to 13200/mm³

New Born Infant – 13000 to 38000/ mm³

Infant -two weeks of age – 5000 to 20,000/mm³

Identification of patients with elevated leukocyte count and classifying them as per the causes of leukocytosis was done , broadly the patients fell into the following categories , as per the general classification of Holland and Gallin^(1,3,5)

Infection: This group includes patients in whom leukocytosis was secondary to an infectious cause or sepsis .Majority of them had infections related to central nervous system , gastrointestinal system and respiratory tract infections which further led to sepsis and multiorgan involvement finally leading to death .^(1,2,6)

Physiological Stress: This categorical group included patients in which stress was assumed to be the causative mechanism for leukocytosis after excluding infectious and other non infectious causes, majority of the patients had leukocytosis which was transient and had TLC counts less than 30000. Eg ; Unstable Angina , Trauma etc .^(15,16)

Hematological Condition: This group of patients included the, patients in which hemato oncological conditions like leukemia and other malignancies were responsible for leukocytosis , majority of them had TLC counts above 30000 .^(6,7)

Inflammatory Causes: In the study group (n=771) few patients had necrosis or inflammation responsible for the elevated total leukocyte count , which included patients like myocardial infarction , rheumatological disorders , thrombosis .^(8,9)

Drug or Medication Induced Causes: Majority of the patients in whom medication or drugs were the causative factors for leukocytosis had TLC counts below 30,000 and most of them were receiving steroids , few of the patients were on inotropic

support ,very few hematological cases were receiving GCSF , which were thought to be the causative drugs responsible for leukocytosis .^(7,8,9)

Unknown: This category of patients include unclassified and post splenectomy cases in which all possible infectious and non infectious causes of leukocytosis are ruled out .^(8,9)

After detailed analysis of history, clinical and laboratory parameters ,the survival group is categorized into various groups, as per the possible causes of leukocytosis and analysis of survival group as per the variation in the leukocyte count and its correlation with mortality was done , stratification of patients into survival and non survival groups was done and analysis was done using Statistical Package for Social Sciences (SPSS) version .Comparison of the TLC counts of various conditions and different groups of subjects was done using chisquare test and analysis of variance . P values less than 0.05 were considered significant. Correlation of leukocyte count variability and mortality was done as per correlation coefficients.

RESULTS

A total of 818 patients were included in the study, 11 patients were in the sub group of age less than 18 yrs , 27 patients were excluded from the study due to inadequate data .There are a total of 224 (29)% females and 536 (69.5) % males . As per the provisional diagnosis patients were stratified into various groups (etiological classification), majority of them were surgical patients -235 (30.4)% the general medical admissions constituted 113(14.6)% cases Majority of cases had mean TLC counts below 25000 at admission.

Table 1 : Showing Distribution Of Patients As Per Provisional Diagnosis And Admission Department

Admission dept	No. of patients	No. of patients with TLC count range (Day 5) 4000-11000	No. of patients with TLC count range (Day5) 11000-25000	No. of patients with TLC count range (Day5) >25000
General Medicine	113(14.6)	28 (24.7)	76 (67.2)	9(7.9)
General surgery	235(30.4)	80 (34.04)	149 (63.4)	6 (2.5)
Gynecological	6(0.4)	-	2 (66.66)	1(33.3)
Pediatrics	11(1.4)	3(27.2)	7 (63.6)	1(9.09)
Neurology	177(22.9)	32 (18.07)	140 (79.09)	5 (2.82)
Gastroenterology	82(10.6)	15 (18.29)	60(73.17)	7 (8.5)
Respiratory	65(8.4)	10 (15.38)	52 (80)	3 (4.6)
Nephrology	40(5.1)	10 (25)	29 (72.5)	1(2.5)
Cardiology	35(4.5)	5 (14.2)	27(77.14)	3 (8.5)
Infectious diseases	27(3.5)	12 (44.4)	13(48.14)	2 (7.4)
Hemato oncology	18(2.3)	1 (5.5)	9(50)	8 (44)
Rheumatology	5(0.6)	2 (40)	2 (40)	1 (20)
Endocrine	4(0.5)	3 (75)	1 (25)	-
Pooled values (n =771)				

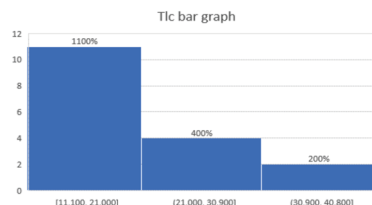


Fig 1 : Bar Diagram Showing Distribution Of Patients (Percentage) As Per Leukocyte Counts Ranging Study Group (N = 779)

Table 2 : Showing Gender Wise Distribution Of Patients

Gender		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	female	228	29.3	29.3	29.3
	male	551	70.7	70.7	100.0
Total (n = 779)			100.0	100.0	

Survival group constitutes - 754 (92.1) % and non survival group 17(2.2) % of patients. Mean age of the patients in survival group is - 49 ± 18 yrs, and non survival group - 47 ± 15 yrs. Survival group had a mean TLC count of is 16610 ± 6781 and mean TLC count of mortality group include Mean \pm SD 19058.82 ± 7283.977 , the correlation of mean leukocyte count and mortality was negative ($r = -0.003$) and delta gap (difference in the leukocyte count of day 1 and day 5) and mortality was not statistically significant ($r = 0.018$).

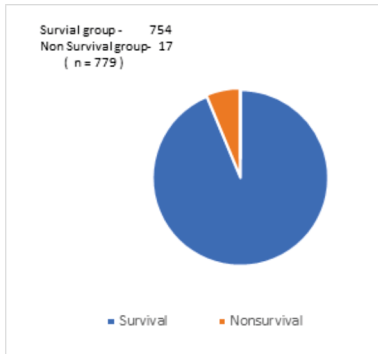


Fig 2 : Showing Distribution Of Patients As Per Mortality (N = 781)

It was found that there was no significant statistical association between mean TLC count of day 5, delta gap (difference between mean TLC count on day 1 and day 5) and mortality. There was no significant correlation with mortality in the study population when considered in total. In the total study group (n = 781) survival group constitute 754 and non survival group i.e mortality group constitute (n = 17) members. The following are the Median + IQR values of TLC counts noted in the non survival group.

Table 3 : TLC Counts Of Non Survival Group – (Median ± IQR Values)

Mortality Group (n=17)	TLC Day1	TLC Day2	TLC Day5
Median	17600.00	15700.00	14500.00
Range (IQR)	24000	44000	42600
(95 % CI) - Minimum	11100	5200	6200
Maximum	35100	49200	48800

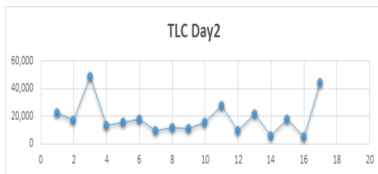


Fig 2 : Line Chart Showing The Trend Of Variation In TLC Count In Sepsis Group.

However the results differed when considered in the individual subgroups as per categorical classification of Holland and Gallin:

In the sepsis group (n=237) there was correlation between mortality and day 1 ($r = 0.476$), day 2 ($r = 0.835$) and day 5 ($r = 1$) total leukocyte counts with the respective correlations coefficients as mentioned and mean leukocyte count of the patients in this group was noted as Mean \pm SD - 18123 ± 6870 . (*Correlation is significant at the 0.01 level (2-tailed)).

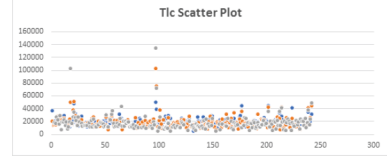


Fig 3 : Scatter Plot Showing Distribution Of TLC Counts Of Various Patients In Sepsis Group (N = 237) (Majority Fall In The Range Of (11000 - 30000)

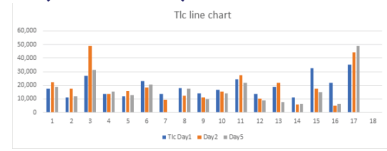


Fig 4 Graph Showing Trends Of Rise And Fall In TLC Counts On Day 1 , Day2 And Day 5 Among Non Survival Group (n = 17)

Overall, the study results states that majority of patients (167) had infections. Physiological stress was identified in 123 patients and was the next most common causal factor. Medications or drugs were implicated in 12 patients, and hematological conditions constituted 50 patients, inflammation/necrosis were found in around 51 patients.

Physiological Stress: Leucocytosis in the young people also occurs secondary to physiological stress. As per the studies neutrophil counts, total leukocyte counts were elevated after a strenuous exercise and it was observed that total leukocyte counts were elevated almost two times from the baseline values in a group of study participants – athletes after an ultra-marathon and values returned to baseline values after 24 hrs.^(15,16)

Our study results show that the following conditions were associated with raised WBC count secondary to physiological stress, diabetic ketoacidosis, heat stroke, emergency surgery under general anaesthesia and in all these conditions not associated with any other associations like sepsis there was resolution of leukocyte counts to normal range after treatment of the stressful condition.^(13,14)

Medication : Medication or drugs were found to be responsible for elevated WBC counts mostly it was observed to be in range of 15,000–19,999 cells/mm³ and among all the drugs steroids were the most common drugs responsible for elevated WBC counts, other drugs which were implicated in patients with various levels of leucocytosis include granulocyte colony-stimulating factor, lithium and elevation of WBC count associated solely with medications or drugs had an upper limit of 30,000 cells/mm³ as per our study results.⁽¹⁰⁾

Inflammatory and Necrosis : Our study results show that majority of patients in this category had pancreatitis, and other pathological conditions include SLE, umbilical hernia, patients with myocardial infarction and very few patients in this category had elevated WBC counts greater than 30,000.⁽¹⁵⁾

Haematological Conditions : As per the study results very few patients with raised WBC counts had a hematological condition association, most common conditions include lymphoma, leukemia, metastatic cancer and majority of them were associated with leukocyte counts range above 30,000.^(6,10)

Unknown : The study results also suggest that for few patients with elevated leukocyte count the cause was not determined and patients died shortly after the high WBC count was documented. Although sepsis was suspected and probably responsible, its presence was not documented.^(6,13)

More exploratory statistical analysis was done where logistic

regression analysis was performed with mortality as dependent variable , TLC count on Day 5 and delta gap as independent variable ,among them delta gap (difference in leukocyte count of day 5 –day 1) predicted the probability of the deaths when study population as a whole was considered as a group.

Table 4 : Showing The Delta Gap - Predicted The Probability Of Deaths

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I. for EXP(B)	
								Lower	Upper
Step 1 ^a	TLC - Day 5	.000	.000	.002	1	.962	1.000	1.000	1.000
	Delta gap	.000	.000	.206	1	.650	1.000	1.000	1.000
	Constant	-3.797	.32571	136.0	1	.000	.022		

a. Variable(s) entered on step 1: TLC - Day 5, Delta gap.

As per the study results , TLC count on day 5 ,delta gap and their 95% confidence intervals predicted the probability of deaths at three days of admission. Morel et al have studied⁽⁷⁾ .

Table 5 : Showing The Variables: TLC (Day 5) -standard Error Of Mean And 95 % Confidence Intervals Predicted The Probability Of Deaths

		d5-d1	mortality
(Delta Gap)	Pearson Correlation)	1	-0.019
d5-d1	Sig. (2-tailed)		0.590
TLC count	N	777	777
Mortality	Pearson Correlation	-0.019	1
	Sig. (2-tailed)	0.590	
	N	777	778

DISCUSSION

In preclinical model of traumatic brain injury, accumulation of leukocytes within first 4 to 48 hours after induced injury was demonstrated , which was possibly thought to interfere with the cerebral microcirculation, there by contributing to secondary brain damage.⁽⁸⁾

As per Sun et al initial leukocytosis was associated with early neurological deterioration within first a total of 156 blunt trauma patients ,as per their study a statistically significant elevation in WBC counts was present in patients with elevated ISS (p<0.002) , but could not At inception the study has two main objectives , one is to elucidate the causes of leukocytosis and second is to find association between trends of rise in leukocyte count and mortality among the diverse group of patients presenting to ER.^(1,5)

Very few studies have studied the relationship between leukocytic count and mortality in the Emergency department , literature review has shown variable conclusions about mortality prediction & elevated WBC count.^(5,10)

Our study included a large cohort of patients admitted to various departments after ER evaluation , demonstrate a linear relationship between the outcome and elevated WBC counts⁽⁹⁾ .

Ruggiero et al. demonstrated that mortality risk for older adults increases with elevated but normal leukocyte counts for both cerebrovascular and cancer diseases from the 'Baltimore Longitudinal Study of Aging'⁽¹¹⁾ .

Various studies have shown an independent association between elevated WBC count and increased risk for mortality among patients with vascular and cardiac events^(12,13) .

Muller et al, and Hung et al categorized patients into quartiles by leukocyte count, and showed that the patients with high leukocyte quartile were 3.3 times more likely to die of cardiac

causes than those in the lowest quartile.^(13,15)

In patients with PE ,WBC count and SIRS satisfying the peripheral WBC count criteria were significantly associated with mortality within 30 days of hospital admission (OR =1.05,95% CI =1.01-1.09)⁽¹⁰⁾ . Our study results show that measured leukocyte and neutrophil counts were transiently elevated in ER , this trend of elevation was observed in all categories of patients and was not related to individual patients' characteristics. As per the results (i.e., lack of association) it is considered that access to ER is associated with physiological anxiety , hence it can be stated that in this clinical context it might be due to psychological stress.It has been observed that physical stress may also result in leukocytosis.^(15,16)

CONCLUSIONS

- Elevated leukocyte count is not always associated with an infectious cause.
- TLC count adds value in prediction of mortality only in association with other clinical and laboratory findings ..
- Leukocytosis is a marker of serious disease (sub clinical or occult disease - in unclassified conditions) in extreme elevations (>25000) only.
- The present study do not stress leukocytosis in ER as a criteria for ED admissions.

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