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Mean Platelet Volume versus Total Leukocyte Count and C-reactive Protein as an Indicator for Mortality in Sepsis

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ABSTRACT

Background: sepsis is a major cause of morbidity and mortality, and the incidence is rising, probably due to the growing elderly population, antibiotic resistance, immunosuppressive medication and, invasive surgery. Pneumonia is the most common infection leading to sepsis, followed by urinary tract infections and abdominal infections. These infections are usually localized and controlled by the immune system, but they can sometimes spread and cause sepsis. Mean platelet volume (MPV) is a measurement that describes the average size of platelets in blood. MPV is ordered routinely as part of the complete blood count panel by an automated flow cytometry machine. In septic shock, most of the coagulation factors are depleted and platelet count is decreased, a close relationship between sepsis severity and thrombocytopenia has already been documented. **Aim of the Work:** this work aimed to find a relation between the mean platelet volume and mortality in patients with sepsis in correlation with C-reactive protein and total leukocyte count. **Methods:** 80 adult critically ill patients of both sexes with sepsis and sever sepsis who admitted to the units of Critical Care Medicine Ain Shams University Hospitals. The mean platelet volume (MPV) evaluated and correlated to both total leukocyte count (TLC) and C-reactive protein (CRP) on a daily basis starting from the day of admission and over 14 days. In addition, patients observed regarding outcomes including mortality and discharge from ICU. **Results:** MPV was able to detect sepsis prognosis with high statistical significance from admission, CRP also was a good predictor and on the contrary TLC had poor prognostic value on admission and after 24 hours, but for the whole hospital stay a significant association was found. **Conclusion:** elevated MPV on admission is an important marker for sepsis diagnosis and prognosis. Progressively elevated MPV during hospital stay correlates well with mortality. Decreased platelet count after admission is significantly associated with mortality in septic patients. MPV and platelet count can be used as prognostic markers for sepsis and indicators of mortality on daily basis.

Keywords: sepsis, sepsis markers, mean platelet volume (MPV) .

INTRODUCTION

Infectious diseases are a global health problem, causing many deaths per year. Respiratory infections as well as diarrhea, malaria, measles and HIV/AIDS are major causes of morbidity and mortality worldwide [(1)]. Many of the signs and symptoms that are associated with infectious diseases are a direct manifestation of the host immune response. For many years, physicians have recognized the hallmarks of a localized bacterial infection: dolor, rubor, calor and tumor. These signs result from different leukocytes and their metabolites in the immune system, which attempt to kill the invading pathogen. For the host, the challenge with infections is to recognize the foreign invaders and to direct the appropriate immune response effectively without inflicting self-damage. The body uses different mechanisms to avoid such inappropriate responses, but occasionally this mechanism fails causing severe tissue damage and death [(2)].

Sepsis was first mentioned in Homer's poems around 2,700 years ago. The word "sepsis" comes from the word σῆψις, (sipsi), which in original Greek means decomposition of organic matter. During the late 19th and the 20th centuries, sepsis was described as a systemic infection supposedly caused by the invasion of the blood stream by pathogenic microorganisms. However, patients still died of sepsis even when the microorganisms had been eradicated with antibiotics [(3)].

Sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year and killing as many as one in four and often more [(4)].

Similar to polytrauma, acute myocardial infarction, or stroke, early identification and appropriate management in the initial hours after sepsis develops improved outcomes [(5)].

Mean platelet volume (MPV) describes the average size of platelets in a blood sample and routinely measured by automated hematology analyzers using either electrical impedance or optical fluorescence method [(6)]. A rise in MPV during sepsis caused by increased platelet destruction and increased production of larger

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and younger platelets [7].There is a strong relation between MPV and prognosis described by medical researchers, so an increase in platelet size in a patient with bacterial infection could suggest that the infection has become invasive [8].

PATIENTS AND METHODS

This study carried out on 80 adult critically ill patients of both sexes with sepsis and sever sepsis who admitted to the units of Critical Care Medicine Ain Shams University Hospitals.

Inclusion Criteria

- Age more than 18 years.
- Patients presented with sepsis defined as a suspected source of infection plus ≥2 of the following:
  - Fever of >38º or hypothermia <36º
  - Heart rate of >90 beats/min
  - Respiratory rate of >20 breaths per minute or $PaCO_2$ <32 mmHg
  - White blood cells >12 x 10^9/cmm or <4 x 10^9/cmm, or >10% immature forms.
- Patients presented with severe sepsis defined as sepsis associated with secondary organ dysfunction.

Exclusion Criteria

- Age less than 18 years.
- Pregnant females.
- Patients with acute cerebro-vascular event.
- Patients with acute coronary syndrome.
- Patients on chemotherapy.
- Patients with malignant hematological disease.
- Patients with immunosuppression.
- Patients with active hemorrhage.
- Patients who had used anti-PLT drugs such as clopidogrel prior to admission.

All patients included in this study were subjected on admission to the followings:

A. History:

- Personal data: name, age and gender.
- Present history of medical condition.
- Past medical history including:
  - Heart disease.
  - Liver disease
  - Renal disease
  - Hypertension.
  - Diabetes mellitus.
  - Hematological disorder.
  - Oncological disorder.

B. Clinical examination:

Complete physical examination was done with emphasis on:

- Vital signs :(heart rate, mean pressure, respiratory rate, temperature).
- Mental status according to Glasgow Coma Score (GCS)
- Chest examination.
- Cardiac examination.
- Abdominal examination.

C. Laboratory investigations

Done on admission and daily during the period of the study and included:

- Serum Na, K.
- Urea, creatinine.
- Random blood sugar.
- C-reactive protein.
- Complete blood picture (Hemoglobin, White blood count (TLC), Platelet count, and mean platelet volume (MPV)).

D. Radiological examination that helps to detect source of sepsis included:

- Chest X-ray.
- Ultrasound of the abdomen.
- CT abdomen with contrast.
- Echo.

E. Sepsis workup

- Blood cultures from one central and two peripheral lines.
- Sputum culture or mini bronchio-alveolar lavage.
- Urine culture.
- Culture from a known source like abscess or tissue
- Cerebrospinal fluids analysis (in suspected cases of meningitis)

Period of the study

The mean platelet volume (MPV) was evaluated and correlated to both total leukocyte count (TLC) and C-reactive protein (CRP) on a daily basis starting from the day of admission and over 14 days. In addition, patients observed regarding outcomes included mortality and discharge from ICU.

The study was approved by the Ethics Board of Ain Shams University.

Results

Our study was carried on 80 adult patients of both sexes admitted to ICU with sepsis, patients (45%) survived and patients (55%) were non-survivors.

Demographic Data: 61% were male and **39**% were females. Age ranged from 46 to 91 years with a mean 68 ± 9.34 years. Sex did not affect mortality, no statistical significance found. Age found to affect mortality, the mean age of non-survivors was higher than of survivors (73.5 ± 6.68 years and 61 ± 7.19 years respectively).

Table 1: relation between demographic data and mortality

		Survivors (N = 36)		Non-survivors (N = 44)		Test of sign	P
		No.	%	No.	%		
Sex	Male female	21 15	58 42	28 16	63 37	$\chi^2 = 498$	0.480
Age	Min – Max Mean ± SD	46 – 77 61 ± 7.19		57 – 91 73.5 ± 6.68		t = 4.183*	< 0.001*

χ^2 chi square test t: Student t-test *: P< 0.05: Significant, P < 0.01: Highly significant

Past Medical History: associated co-morbidities significantly affected the mortality.

Table 2: relation between co-morbidities history and mortality

	Survivors (N=36)		Non-survivors (N=44)		t	P
	No.	%	No.	%		
HTN	25	69.5	37	84	9.781*	0.002*
DM	15	41.5	23	52	0.642	0.486
Cardiac disease	8	22.2	16	36.4	2.431	0.103
Kidney disease	-	-	15	34	18.213*	<0.001*
Liver disease	-	-	10	23	11.574*	<0.001*
COPD	4	11	10	23	3.061	0.077

χ^2 chi square test t: Student t-test *: P< 0.05: Significant, P < 0.01: Highly significant

Vital signs: vital signs of patients significantly affected the mortality.

Table 3: relation between vital signs and mortality:

		Survivors (N=36)	Non-survivors (N=44)	t	P
Mean blood pressure	Min – Max Mean ± SD	66 – 90 73.37 ± 4.93	25 – 45 32 ± 5.08	10.313*	<0.001*
Temperature	Min – Max Mean ± SD	37.10 – 38.50 37.82 ± 0.27	37.0 – 40 38.87± 0.71	9.914*	<0.001*
Respiratory rate	Min – Max Mean ± SD	18 – 26 21 ± 1.78	22 – 34 26 ± 2.73	8.123*	<0.001*
Heart rate	Min – Max Mean ± SD	85 – 105 92 ± 9.4	105 – 141 115 ± 11.31	16.986*	<0.001*

t: Student t-test *: P< 0.05: Significant, P < 0.01: Highly significant

Complete Blood Picture: difference was found between survivors and non-survivors concerning hemoglobin concentration, hematocrit value and platelet count.

Table 4: relation between complete blood picture and mortality

	Complete blood picture	Survivors (N=36)	Non survivors (N=44)	t	p
Hb % (g/dL)	Min – Max Mean ± SD Median	9 – 15 11.2 ± 1.23 11	8.5 – 11.2 9.6 ± 0.66 9.5	t = 7.122*	<0.001*
HCT (%)	Min – Max Mean ± SD Median	28 – 42 35.5 ± 3.55 35	26 – 40 30.4 ± 2.96 30	t = 7.752*	<0.001*
Platelet Count ($\times 10^3$/µl)	Min – Max Mean ± SD Median	80 – 261 187 ± 38.5 198	42 – 184 122 ± 36.4 163	t = 9.026*	<0.001*

t: student t-test *: P< 0.05: significant, P < 0.01: highly significant

Source of sepsis*:* the most common was chest infection in 32 of patients, but statistical significance was not found between source of sepsis and mortality

Table 5: relation between source of sepsis and mortality

Source of sepsis	Survivors (N=36)		Non-survivors (N=44)		t	P
	No.	%	No.	%		
Chest infection	14	39	18	41	0.049	0.801
Urinary tract infection	13	36	9	20.5	5.122	0.021
Blood stream infection	4	11	9	20.5	2.186	0.106
Skin and soft tissue infection	4	11	4	9	1.021	0.316
Abdominal infection	1	3	4	9	3.427	0.077

MPV: significantly affected the outcome, as statistical significance was found between mortality and elevated MPV on admission, after 24 hours and elevated MPV average during the whole hospital stay. Non-survivors had a higher MPV comparing to survivors.

Table 6: relation between MPV and mortality

	MPV (fl)	Survivors N=36	Non survivors N=44	t	P
On admission	Min- Max Mean ± SD Median	8.1 – 10.4 9.51 ± 0.557 9.5	8.3 – 11.3 10.05 ± 0.88 9.9	3.133*	0.003*
After 24 hours	Min- Max Mean Median	8.5 – 11.3 9.78 ± 0.67 9.65	8.3 – 12.1 10.56 ± 0.89 10.62	4.316*	<0.001*
Average	Min- Max Mean Median	7.92 – 10.8 9.22 ± 0.455 9.3	8.8 – 12.34 10.74 ± 0.81 10.78	10.021*	<0.001*

t: student t-test *:
P< 0.05: significant, P < 0.01: highly significant

CRP level: affected the outcome, statistical significance was found between mortality and elevated CRP on admission, after 24 hours and elevated CRP average.

Table 7: relation between CRP level and mortality

CRP (mg/dl)	Survivors N=36	Non survivors N=44	t	P
On admission Min – Max Mean ± SD Median	 45 – 124 78.6 ± 18.80 75	 48 – 138 95 ± 24.60 105.5	3.296*	<0.001*
After 24 hours Min – Max Mean ± SD Median	 35 – 133 82.7 ± 21.79 79	 65 – 153 105.5 ± 23.19 114	4.493*	<0.001*
Average Min – Max Mean ± SD Median	 35.8 – 89.7 62.94 ± 14.4 61.59	 72 – 143.8 111 ± 19.66 116	12.210*	<0.001*

t: student t-test *:
P< 0.05: significant, P < 0.01: highly significant

TLC*:* no statistical significant difference was found between mortality and TLC on admission and after 24 hours, but during the whole hospital stay significantly affected the outcome.

Table 8: relation between TLC and mortality

	TLC ($\times 10^3/\mu l$)	Survivors N=36	Non survivors N=44	t	P
On admission	**Min – Max** **Mean ± SD** **Median**	4.5 – 21 13.9 ± 3.72 14	3.6 – 22 14.35 ± 3.77 14.5	0.557	0.579
After 24 hours	**Min – Max** **Mean ± SD** **Median**	4.1 – 22 14.6 ± 4.36 15.1	2.3 – 28 16.2 ± 4.67 16	1.563	0.122
Average	**Min – Max** **Mean ± SD** **Median**	4 – 21.3 12.35 ± 2.74 13.6	1.9 – 32 17.5 ± 4.91 19	5.615*	<0.001*

t: Student t-test *:
P< 0.05: significant, P < 0.01: highly significant

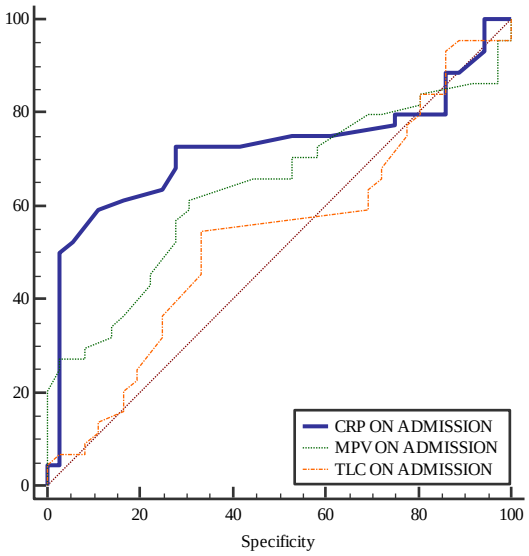

Figure 1: ROC curve showing relation between CRP, MPV, TLC and mortality on admission

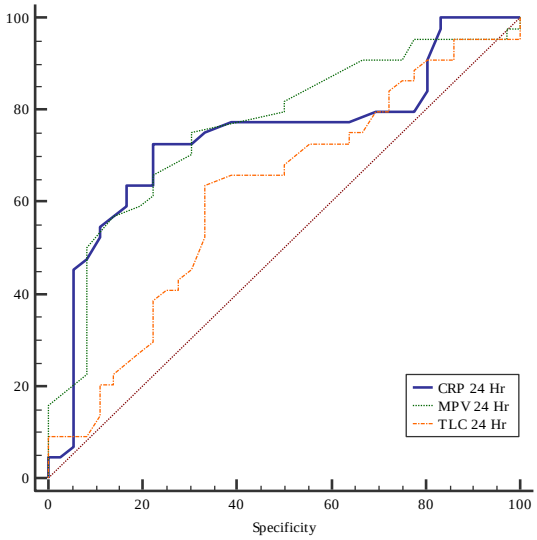

Figure 2: ROC curve showing Relation between CRP, MPV, TLC after 24 hours and mortality

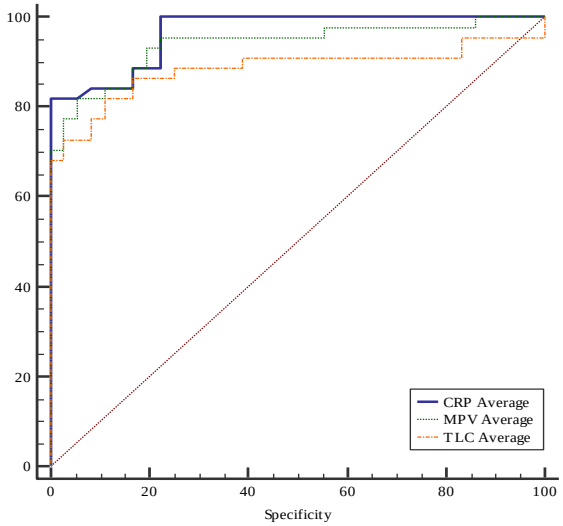

Figure 3: ROC curve showing relation between the average of CRP, MPV, TLC and mortality

DISCUSSION

Currently, sepsis is a major concern; within the last decade, several trials and protocols have focused on this condition, aiming to establish better measures for its management and prevention of potential complications. Therapeutic measures with considerable positive impacts have been largely emphasized; however, assessing the prognosis of sepsis remains difficult [(9)].

Several physiological and blood chemistry parameters are used in daily practice in intensive care units for both diagnosis and prognosis in septic patients (e.g. CRP and TLC).

Mean platelet volume (MPV), which is generally overlooked by clinicians and its parameter changes have been already observed and some studies suggested that MPV increases during sepsis as in acute appendicitis, pancreatitis, infective endocarditis, and malaria, this test is routinely provided by a full blood count analyzer, not requiring any complex or expensive technologies [(10)].

In this study, a comparison between mean platelet volume (MPV), total leukocyte count (TLC) and C-reactive protein (CRP) levels were done to assess the possible role of mean platelet volume in prediction of mortality and prognosis of patients with sepsis.

Regarding the outcome, the mortality rate in this study was 55%, men were more to develop sepsis as 61% of patients were males and 39% were females, the mean age in our study was 68 ± 9.34 years. Gender did not affect mortality as no significant difference was found between males and females 57% and 51.61% respectively. In contrary to sex, age was found to affect mortality significantly, as the mean age in the non-survivors group was higher than in the survivors group 73.5 ± 6.68 years and 61 ± 7.19 years respectively with p value < 0.001.

A significant association was found between associated co-morbidities and mortality, especially hepatic and renal disease as all patients presented with hepatic or chronic kidney disease were non-survivors.We found a significant relation between vital signs and mortality. Non-survivors compared to survivors tend to have lower mean blood pressures, higher body temperatures, higher respiratory rates, and higher heart rates.The mean of platelet count for patients on admission was 171.12 ± 103.73 $\times 10^3/\mu l$. For the whole hospital stay; mean of platelet count was significantly lower in non survivors compared to survivors 122 ± 36.4 $\times 10^3/\mu l$ and 187 ± 38.5 $\times 10^3/\mu l$ respectively with p value (< 0.001).Chest infection was the most common primary source of infection with 40% of patients, but no significant difference between the source of sepsis and mortality.In this study, MPV on admission ranged between 8.1-11.30 fl/l with a mean of 9.71 ± 0.77 fl/l which was consistent with **Guclu *et al.*** [(11)] study**,** who reported that MPV levels higher than 8 fl/l had a good role for sepsis diagnosis.

The cut off value for MPV was 9.6 fl which was found to be significant and of a magnitude considered to be clinically useful, with sensitivity 61.5%, specificity 69.4%, **p** value (0.003) and accuracy 65.7% in predicting mortality. The cut off value for MPV was 9.7 fl which was found to be significant and of a magnitude considered to be clinically useful, with sensitivity 75%, specificity 69.4% (p value <0.001) and accuracy 72.3% in predicting mortality. The cut off value for MPV during

whole hospital stay was 10.2 fl which was found to be significant and of a magnitude considered to be clinically useful, with sensitivity 77.3%, specificity 83.3%(p value <0.001) and accuracy was 80% in predicting mortality.

Concerning the relation between the CRP level on admission and mortality, the cut off value for CRP level was 101 mg/l which was found to be significant and of a magnitude considered to be clinically useful, with sensitivity 63.6%, specificity 75%(p<0.001) and accuracy was 68.75% in predicting mortality. Concerning the relation between the CRP level after 24 hours and mortality, the cut off value for CRP level was 94 mg/l which was found to be significant and of a magnitude considered to be clinically useful, with sensitivity 72.7%, specificity was 77.8% (p <0.001) and accuracy was 75% in predicting mortality. The cut off value for CRP level during whole hospital stay was 90 mg/l which was found to be significant and of a magnitude considered to be clinically useful and sensitivity was 81.8%, specificity was 80.5% and 81.25 % (p <0.001) and accuracy was 81.25% in predicting mortality.

Concerning the relation between TLC on admission and mortality, the cut off value for TLC was 14 $\times 10^3$/µl which was not significant with sensitivity 54.5%, specificity was 66.7% (p 0.579) and accuracy was 60% in predicting mortality.

Concerning the relation between TLC after 24 hours and mortality, the cut off value for TLC was 15.4 $\times 10^3$/µl which was not significant with sensitivity 63.64%, specificity was 66.7%) (p 0.077) and accuracy was 65% in predicting mortality. Concerning the relation between the average of TLC during the whole hospital stay and mortality, the cut off value for TLC was 16.3 $\times 10^3$/µl which was found to be significant and of a magnitude considered to be clinically useful, with sensitivity 70.45%, specificity was 66.66%(p <0.001 and accuracy was 68.75% in predicting mortality.

CONCLUSION

We concluded that elevated mean platelet volume on admission is an important marker in sepsis with increased mortality in patients with elevated mean platelet volume on admission and from this study we can recommend:

- Routine measurement of the MPV in sepsis patients as its increase can predict mortality.
- Conduct further studies on larger samples of patients.

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