PLATELET COUNT AND MEAN PLATELET VOLUME AS PROGNOSTIC MARKERS OF UROSEPSIS

[1]Andri Kusuma Harmaya, [2]Budiono, [1]M. Ayodhia Soebadi, [1]Soetojo.

[1]Department of Urology, Faculty of Medicine/Universitas Airlangga, Soetomo General Hospital, Surabaya.
[2]Department of Community Health Sciences, Faculty of Medicine/Universitas Airlangga, Soetomo General Hospital, Surabaya.

ABSTRACT

Objective: *To know and determine platelet count (PLT) and mean platelet volume (MPV) as prognostic factor for outcome in patients with urosepsis.* ***Materials & Methods:*** *This was an analytic observational study. Thirty patients were assigned to the test for PLT and MPV at the day of admission, 36 hours and 72 hours after admission. All subjects were managed according to standard urosepsis therapy. At the 28th day of treatment, patients were evaluated and classified the outcome as survivors and non-survivors. The statistical analysis was performed using multivariate logistic regression with software SPSS 21. In all tests, p<0.05 was considered to indicate significance.* ***Results:*** *The mean of PLT in non-survivors was lower than that in survivors at the day of admission (420 ± 343.57 x103/mm^3 vs 423.04 ± 220.15 x103/mm^3, p=0.838). Decrease in PLT during the first 72 hours after hospitalization in non-survivors (Δ PLT72h) was greater than that in survivors (-143.43 ± 154.15 x103/mm^3 vs -51 ± 121.77 x103/mm^3, p=0.050). The mean of MPV in non-survivors was lower than that in survivors at the day of admission (6.30 ± 0.53 fL vs 7.25 ± 1.78 fL, p=0.333). Increase in MPV during the first 72 hours after hospitalization in non-survivors (Δ MPV72h) was greater than that in survivors (3.51 ± 0.86 x103/mm^3 vs 1.48 ± 1.54 x103/mm^3, p=0.028). In multivariate analysis, Δ MPV72h was an independent predictor of 28-day mortality [OR 9.41 (95% CI, 1.27 – 69.81)].* ***Conclusion:*** *An increase in MPV during the first 72 hours after hospitalization can be used as poor prognostic in urosepsis patients.*

Key words: *Mean platelet volume, platelet count, prognosis, urosepsis.*

ABSTRAK

Tujuan: *Untuk mengetahui dan membandingkan platelet count (PLT) dan mean platelet volume (MPV) sebagai marker prognostik pada pasien urosepsis.* ***Bahan & Cara:*** *Penelitian analitik observasional dengan sampel sebanyak 30 pasien urosepsis. Dilakukan pemeriksaan PLT dan MPV pada saat masuk rumah sakit, 36 jam, dan 72 jam setelah masuk rumah sakit. Seluruh sampel mendapatkan terapi standar untuk urosepsis. Observasi dilakukan maksimal pada hari ke-28 untuk dilakukan penilaian outcome yaitu hidup dan meninggal. Analisa statistik seluruh variabel menggunakan analisis multivariat regresi logistik dengan software SPSS 21. Nilai signifikan p<0.05.* ***Hasil:*** *Pada pasien yang meninggal didapatkan rerata PLT saat masuk rumah sakit yang lebih rendah dibandingkan pasien yang hidup (420 ± 343.57 x103/mm^3 vs 423.04 ± 220.15 x103/mm^3, p=0.838). Penurunan PLT dalam rentang 72 jam setelah masuk rumah sakit (Δ PLT) pada pasien yang meninggal lebih besar dibanding penurunan PLT pada pasien yang hidup (-143.43 ± 154.15 x103/mm^3 vs -51 ± 121.77 x103/mm^3, p=0.050). Rerata MPV pada pasien yang meninggal pada saat masuk rumah sakit lebih rendah dibandingkan pasien yang hidup (6.30 ± 0.53 fL vs 7.25 ± 1.78 fL, p=0.333). Peningkatan MPV dalam rentang 72 jam setelah masuk rumah sakit (Δ MPV) pada pasien yang meninggal lebih besar dibanding peningkatan MPV pada pasien yang hidup (3.51 ± 0.86 x103/mm^3 vs 1.48 ± 1.54 x103/mm^3, p=0.028). Dari analisis multivariat didapatkan kesimpulan bahwa Δ MPV merupakan prediktor terjadinya kematian pada pasien urosepsis [OR 9.41 (95% CI, 1.27 – 69.81)].* ***Simpulan:*** *Peningkatan MPV dalam rentang 72 jam setelah masuk rumah sakit dapat digunakan sebagai marker prognostik pada pasien urosepsis.*

Kata kunci: *Mean platelet volume, platelet count, prognosis, urosepsis.*

Correspondence: Andri Kusuma Harmaya, c/o: Department of Urology, Faculty of Medicine/Universitas Airlangga, Soetomo General Hospital. Jl. Mayjend. Prof. Dr. Moestopo 6-8, Surabaya 60286. Phone: +62 31 5501318; Fax: +62 31 5024971. Mobile phone: 085648106346. Email: andrijournal@gmail.com.

INTRODUCTION

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1,2] Sepsis are major health care problems affecting millions of people worldwide each year. The mortality rates of these conditions are 25 - 80%, depending on illness severity, and the number of occurrences and the severity of organ failure.[3] Approximately 750.000 cases of sepsis per year were seen in the United States (US), and led to 215.000 deaths. The economic burden of this disease for the US was 16.7 billion US dollars/year.[4]

Urinary tract infections (UTI) can manifest from bacteriuria with limited clinical symptoms to sepsis or severe sepsis, depending on localized and potential systemic extension.1 Urosepsis accounts for approximately 25% of all sepsis cases and may develop from a community or nosocomial acquired UTI.[5]

Clinical signs and symptoms can be used to assess the stages and prognosis of sepsis.[6] The prognosis of sepsis can also be assessed through biomarkers. Sepsis biomarkers may provide additional information in risk stratification, evaluation of therapeutic response and outcome predictors.[7] At the moment, 178 identified biomarkers are useful in evaluating sepsis, 118 of them can be used to assess the prognosis. Biomarkers that often used as prognostic marker are including C-reactive protein (CRP) and procalcitonin (PCT). CRP has a high sensitivity value but its specificity is still questioned. PCT has a better prognostic value but more expensive and the availability is limited.[8] Easily accessible, inexpensive, and widely used laboratory tests that show the severity of sepsis are important. Platelet count (PLT) and mean platelet volume (MPV) are widely and routinely used in clinical practice worldwide.[9]

Van der Lelie and Von dem Borne showed a higher MPV in patients with sepsis than in patients with localized infection and suggested that an increase of MPV in patients with bacterial infection could indicate the occurrence of septicemia.[10] Becchi et al, examined the trends of PLT and MPV during the course of sepsis in a small population and found that the average MPV gradually increased in non-survivors, whereas it decreased in survivors.[11] Furthermore, in studies of septic animal models, MPV increased after the induction of sepsis whereas platelet count changed inversely.[12]

The time course of platelet counts and its function in critically ill patients, especially in patients with sepsis, have been elucidated by several previous studies. Although the underlying mechanism is not yet completely understood, the sophisticated interaction of platelets with pathogens and endothelial cells may culminate in sepsis, a severe pathophysiologic cascade characterized by significant reductions in platelet counts and platelet dysfunction. Only a few studies have revealed the relationship between MPV and prognosis in infectious diseases, including urosepsis.[3] Therefore, it is necessary to investigate the changes in PLT and MPV between the baseline values compare to the values after 36 and 72 hours of treatment as the prognostic markers in urosepsis patients. Based on the previous studies, we analyzed the changes of PLT and MPV in urosepsis patients and compared them between survivors and non-survivors. Since the platelet has a larger size when produced by the bone marrow, and then going to be smaller, we hypothesize that PLT and MPV have a greater influence on non-survivors and positive correlation with worsening of the disease.

OBJECTIVE

The purpose of this study was to determine the effect of PLT and MPV on the prognosis of urosepsis patients.

MATERIAL & METHODS

This study was a prospective observational study that aimed to know and to determine platelet count (PLT) and mean platelet volume (MPV) as prognostic factor for outcome in patients with urosepsis. The study was approved by Soetomo General Hospital Surabaya Ethics Committee (registry number 517/Panke.KKE/VIII/2017).

From June to October 2017, all patients admitted in Soetomo General Hospital Surabaya diagnosed with urosepsis were evaluated for inclusion in the study. Exclusion criteria were as follows: age <18 years; diabetes mellitus; history of HIV; history of cardiovascular and cerebrovascular disease; received thrombocyte transfusion during observation; use of immunosuppressant medication. All patients or their legal surrogates provided written informed consent for inclusion in the study.

All patients who meet the sample criteria at the time of admission were assessed for their MPV, PLT, mean arterial pressure measurement (MAP), blood leukocytes (WBC), serum creatinine (SC),

CRP, Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score, urinalysis, urine culture and blood culture. Patients were reassessed for their PLT and MPV at 36 and 72 hours after admission. Patients continue to be followed until the last day of the patient's death or recovery (maximal 28 days after admission). They were also assessed for the outcome on the last day as survivors (alive) and non-survivors (dead).

Sepsis was defined in accordance with 2017 European Association of Urology (EAU) Guidelines on urological infections. Systematic inflammatory response syndrome (SIRS) was defined by two or more of the following conditions resulting from infection: (i) temperature greater than 38°C or less than 36°C, (ii) heart rate greater than 90 beats/min, (iii) respiratory rate greater than 20 breaths/min or arterial carbon dioxide tension less than 32 mmHg, and (iv) WBC count greater than 12.000 cells/mm^3 or less than 4.000 cells/mm^3. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical application, organ dysfunction can be represented by an increase in SOFA score of 2 points or more.

Continuous variables were expressed as means with standard deviations and categorical variables as numbers with percentages. A multivariate logistic regression model was implemented to determine PLT, MPV, and other covariates associated with prognosis of urosepsis patients. A p-value <0.05 was considered significant. Analyses were performed using IBM SPSS Statistics 21.

RESULTS

A total of 30 urosepsis patients were included in this study. The study population consisted of 16 males (53.5%) and 14 females (46.7%). The mean age of the urosepsis patient was 49.13 years old with the youngest was 22 years old and the oldest was 75 years old (table 1).

The most common source of infection was urinary tract stones with 10 cases (33.33%) that consist of 5 cases (16.67%) of kidney stone, 4 cases (13.33%) of ureteral stone and 1 case (3.33%) of bladder stone. The second most common was abscess case that consist of 7 cases (23.33%) of peri-pararenal abscess and 2 cases (6.67%) of scrotum abscess (table 2).

In this study, the outcome was assessed based on the patient's clinical condition at the end of the observation (maximum at day-28 after hospitalization) which classified into two groups: survivors and non-survivors. From the total of 30 samples, 23 patients (76.67%) were survivors and 7 patients (23.33%) were non-survivors.

In figure 1, PLT at the day of admission were lower in non-survivors (420.000.00 ± 343.574.83/mm^3 vs 423.043.48 ± 220.146.95/mm^3, p=0.838). PLT at 36 hours and 72 hours after admission decreased in survivors group (383.000.00 ± 220.858.24/mm^3 and 372.043.48 ± 211.707.02/mm^3, respectively). While in non-survivors group, MPV at 36 hours and 72 hours after admission also decreased (331.571.43 ± 241.115.37/mm^3 and 276.571.43 ±

Table 1. Demographic characteristics and laboratory findings of patients with urosepsis.

Characteristics	Sample Size		Min	Max	Mean	SD
	N	%				
Sex						
Male	16	53.3	-	-	-	-
Female	14	46.7	-	-	-	-
Age (years)	30	100	22	75	49.13	13.16
MAP (mmHg)	30	100	60	107	86.70	11.34
WBC (x 10^3/mm^3)	30	100	2.85	47.66	23.34	10.19
Serum Creatinine (mg/dL)	30	100	0.59	17.62	5.52	4.49
Total Bilirubin (mg/dL)	30	100	0.30	27.53	2.20	4.92
CRP (mg/L)	30	100	4.70	320	146.08	112.21
SOFA score	30	100	2	13	4.33	2.37

Table 2. Description of urosepsis patients based on source of infection.

Source of infection	Number of cases	Percentage (%)
Urinary tract stone	10	33.33
Kidney stone	5	
Ureteral stone	4	
Bladder stone	1	
Abscess	9	30
Peri-pararenal abscess	7	
Scrotum abscess	2	
Clot retention	8	26.67
Cervical cancer infiltrate to bladder	4	
Bladder cancer	3	
BPH	1	
Fistula	2	6.67
Nephrocutan fistula	1	
Vesicorectal fistula	1	
Orchitis	1	3.33
Total	30	100

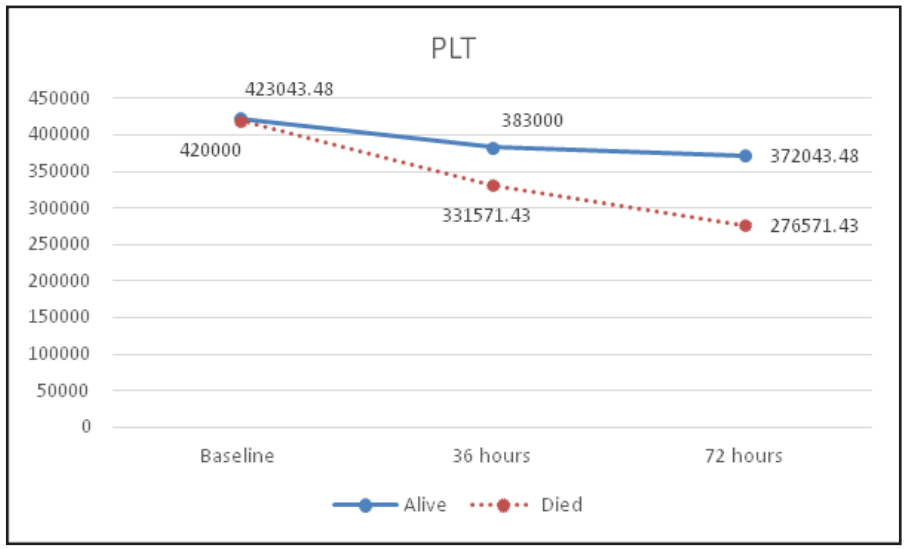

Figure 1. The Comparison chart of PLT rends within 72 hours after hospitalization between survivors and non-survivors.

214.594.08/mm^3, respectively). The difference of PLT between PLT at 72 hours after admission and PLT at the day of admission (Δ PLT72h) in non-survivors were greater than survivors (-51.000.00 ± 121.774.75/mm^3 vs -143.428.57 ± 154.149.12/mm^3, p=0.050).

In figure 2, MPV at the day of admission were lower in non-survivors (6.30 ± 0.53 fL vs 7.25 ± 1.78 fL, p=0.333). MPV at 36 hours and 72 hours after admission increased in survivors group (8.27 ± 2.26 fL and 8.73 ± 1.71 fL, respectively). While in non-survivors group, MPV at 36 hours and 72 hours after admission also increased (8.34 ± 1.84 fL and 9.81 ± 0.80 fL, respectively). The difference of MPV between MPV at 72 hours after admission and MPV at the day of admission (Δ MPV 72h) in non-

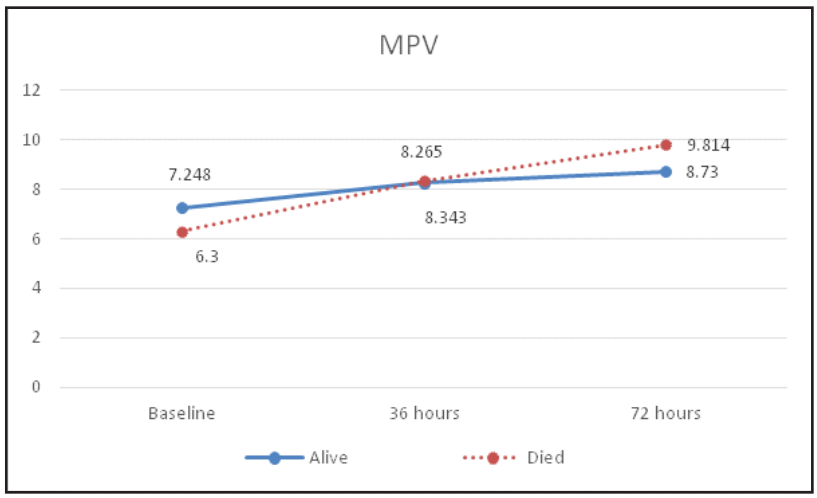

Figure 2. The comparison chart of PLT trends within 72 hours after hospitalization between survivors and non-survivors.

Table 3. Urosepsis outcome based on characteristics and laboratory findings.

Variable	Survivors (n=23)	Non-survivors (n=7)	p-value*
Male, n (%)	12 (52.17%)	4 (57.14%)	0.818
Age (years)	48.00 ± 14.74	52.86 ± 4.38	0.413
WBC (x 10^3/mm^3)	23.52 ± 8.40	22.74 ± 15.58	0.403
Serum creatinine (mg/dL)	5.37 ± 4.82	6.03 ± 3.49	0.695
CRP (mg/L)	143.30 ± 123.32	155.22 ± 70.47	0.780
MPV at admission (fL)	7.25 ± 1.78	6.30 ± 0.53	0.333
Δ MPV (fL)	1.48 ± 1.54	3.51 ± 0.86	0.028
PLT at admission (x10^3/mm^3)	423.04 ± 220.15	420 ± 343.57	0.838
Δ PLT (x10^3/mm^3)	-51 ± 121.77	-143.43 ± 154.15	0.050

*Multivariate analysis with logistic regression test.

survivors were greater than survivors (3.51 ± 0.86 fL vs 1.48 ± 1.54 fL, p=0.028).

According to logistic regression analysis after stepwise selection, only Δ MPV72h was associated with increased mortality [OR 9.41 (95% CI, 1.27 – 69.81)]. Neither MPV at the day of admission, PLT at the day of admission nor Δ PLT72h were associated with increased mortality (table 3).

DISCUSSION

From the results of this study, we obtained that male was more dominant than female (53.3% vs 46.7%, respectively). Epidemiological data in the United States also showed that male was more often than female in the case of sepsis.[4] The mean age of urosepsis patients from this study was 49.13 years, with an age range of 22-75 years. This result was similar with the results of research on urosepsis conducted by Prilistiyo et al, in Soetomo General Hospital Surabaya that male was dominant, with an average age of 47.12 years and age range 25-65 years.[13] Mean age of non-survivors were older than survivors (52.86 ± 4.38 years vs 48.00 ± 14.74 years, p=0.413). The prognosis of urosepsis may be affected by some risk factors such as age. Sepsis was a serious problem among the geriatric population as its incidence and mortality rates dramatically increase with advanced age.[14]

Serum creatinine (SC) level in survivors was lower than non-survivors (5.37 ± 4.82 mg/dL vs 6.03 ± 3.49 mg/dL, p=0.501). Acute renal failure occurs in approximately 19% of patients with moderate sepsis; this number increases to 51% when there is septic shock and blood cultures are positive. Platelet P-selectin, not endothelial P-selectin, is key in the development of ischaemic acute kidney injury. Platelets attached to endothelium recruit leukocytes to the kidneys and platelet-leukocyte aggregates get trapped in narrow peritubular capillaries, both contributing to damage and obstruction of flow. Septic patients with renal dysfunction demonstrated an increase in microparticles (MPs). The levels of platelet derived MP levels correlated with serum blood urea nitrogen (BUN) and creatinine concentrations, suggesting a role for these platelet MPs in the development of renal failure.[15]

CRP levels in non-survivors were higher than survivors (155.22 ± 70.47 mg/L vs 143.30 ± 123.32 mg/L, p=0.811). This result was in accordance with the results of research on urosepsis conducted by Wahyudi et al., that CRP levels can be used as prognostic markers in urosepsis patients. The higher the CRP level, the worse the prognosis of the urosepsis patient.[16]

The most predisposing factor resulting in urosepsis from this study was urinary tract obstruction either in the upper urinary tract or lower urinary tract. These blockages were caused by urinary tract stones (30%) in both of the kidney and ureter, malignancy (23.33%), and prostate enlargement (3.33%). While 43.33% was not caused by a blockage of the urinary tract. Serniak et al. reported that the most common predisposing factor was urinary tract blockage that caused by stones (43%), prostate enlargement (25%), malignancy (18%), and other urological disorders (14%).[17]

In this study, PLT at the day of admission were lower in non-survivors (420.000.00 ± 343.574.83/mm^3 vs 423.043.48 ± 220.146.95/mm^3, p=0.838) and according to logistic regression analysis, Δ PLT72h were not associated with increased mortality. The results of this study are similar to those by Vanderschueren et al. who have shown that in adults admitted in the ICU, patients who died had a lower PLT than survivors.[18] Moreau et al. found that on the receiver operating characteristic curve, PLT decline of 28.3% was associated with the best discrimination between survivors and non-survivors. Thirty seven percent of those who died had a decline of more than 28.3% whereas 20.9% of survivors had this platelet decline. Thrombocytopenia was associated with longer ICU stays, a higher incidence of bleeding events, greater transfusion requirements and higher mortality. It could be that the inability of the bone marrow to increase the production of platelets and release them into the circulation during sepsis maybe a risk factor for death.[19] Gucyetmez et al. also concluded that PLT were associated with sepsis and mortality.[20] Low PLT in non-survivors sepsis patients presumably arises from depletion of coagulation factors and platelet consumption during the septic process, and is a significant prognostic indicator of mortality.[21]

No significant association between Δ PLT72h and the outcome of urosepsis patients could be due to the fact that 72 hours interval may be too short to evaluate fluctuations in platelet count during observation. This was also found in the results of research conducted by Zampieri et al. which found no significant association between decreased PLT within 24 hours after hospitalization with outcome of sepsis patients.[22] Akca et al. reported that PLT decreased significantly in the first days after admission to reach a nadir on day 4 in both survivors and non-survivors. In the survivors, the platelet count returned to the admission value by the end of the first week and continued to rise to become significantly greater than the admission value by day 9. In the non-survivors, the platelet count also returned to the admission value after 1 week, but there was no subsequent increase in platelet count. In the end, patients who did not experience elevated PLT values on day 14 experienced a significant increase in mortality rate. It was concluded that serial PLT measurements correlated with the outcome of sepsis patients where PLT in the second week of treatment was more predictive than PLT during the first week of treatment.[23] Golwala et al. reported that if the count had not increased above 245 x 103/µL the chance of death is significantly higher.[24]

In this study, MPV at the day of admission were lower in non-survivors (6.30 ± 0.53 fL vs 7.25 ± 1.78 fL, p=0.333) and according to logistic regression analysis, Δ MPV72h were associated with increased mortality [OR 9.41 (95% CI, 1.27 - 69.81)]. MPV changes have been already observed in some infected patients, such as those presenting with acute appendicitis, pancreatitis, infective endocarditis, and malaria.[21] Van der Lelie and Von dem Borne reported that MPV was higher in patients with extensive infection than local infection and its value will return to normal after the infection has

been resolved.10 Zampieri et al. reported that adding MPV to other prognostic sepsis markers such as SAP-3 increases the prognosis capability.[22]

Septic rat models have shown that MPV increase in sepsis with appearance of large and heavy platelets in circulation.[12] Canine models of endotoxemia have shown that PLT decreased whereas MPV increased showing that PLT correlate negatively with MPV during early endotoxemia in dogs.[25] In human studies, Nelson and Kehl reported that in acute infection there was platelet consumption and it was associated with an increase in MPV.26 In neonates with sepsis, a low PLT and an increase in MPV has been observed by Guida et al.[27] Patrick et al. demonstrated that neonates with late onset sepsis (bacteremia after 3 days of age) had a dramatic increase in MPV.[28]

Aydemir reported that MPV increased significantly in the first 3 days of patients with Gram-positive sepsis, 4 days in patients with Gram-negative sepsis, and 5 days in patients with fungal sepsis.[29] Guida et al. also reported that sepsis was associated with thrombocytopenia and increased MPV in low birth weight babies.[27] Icli reported that MPV were higher in patients with infective endocarditis and declined significantly after therapy. Increased MPV shows the proportion of young platelet in the peripheral circulation, and it is a sign of an increase in platelet production or an increase in platelet destruction.[30]

In a study by Akarsu et al, a MPV >9.5 fl was considered above normal range, and in another study, MPV elevation was defined >10.4.[31] The MPV normal value in the Gao et al, study was 9-17 fl, that was less suitable for evaluation of sepsis patients. Most of the patients in this study had MPV within normal limits. However, although there was no abnormality in the MPV, the changes of MPV value during observation may be used as prognostic markers. As a prognostic marker, a cut-off of 10.5 fL was recommended by Gao et al, in which patients with MPV value above it was more likely to develop mortality from the sepsis. MPV prognostic value was higher when compared with WBC and hematocrit (Hct) in observation of sepsis patients. A possible explanation could be that WBC count may be affected by factors other than infection, such as stress and cortico-therapy. Hct was affected not only by the hemoglobin level, but also by blood volume.[21]

Becchi et al. evaluated the impact of PLT and MPV on prognosis of critically ill septic patients and concluded that lower MPV on admission were associated with increased mortality.[11] However, MPV tends to increase in non-survivors and decrease in survivors, with PLT having an inverse trend. These findings suggest that trends in changes in MPV and platelet counts may be more reliable markers of poor prognosis than the corresponding absolute values. The discrepancies between baseline MPV values in previous reports may be related to variations in sources of samples (sepsis versus non-sepsis, newborns versus adults).[22]

Kim et al. concluded that MPV can be used as an additional and complementary marker with several established measures of illness severity such as SOFA score, APACHE II score, CRP, albumin, and lactate. Moreover, repeating measurement of MPV may be helpful to predict the prognosis of patients with severe sepsis and/or septic shock. Patients with an increased MPV tendency should be given special attention.[3]

CONCLUSION

An increase in MPV during the first 72 hours after hospitalization can be used as poor prognostic in urosepsis patients. There was no significant association between PLT change and the outcome of urosepsis patients.

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