International Journal of Research and Review
Vol.7; Issue: 3; March 2020
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Platelet to Lymphocyte Ratio as a Prognostic Marker in ICU Patients with Acute Kidney Injury

L Patil[1], Yudhishther Kuntal[2]

[1]Professor, [2]3rd Year Junior Resident,
Dept. of General Medicine, Shri BM Patil Medical College and Hospital, Vijaypura, Karnataka

Corresponding Author: Yudhishther Kuntal

ABSTRACT

Inflammation plays a key role in the initiation and progression of acute kidney injury. Evidence regarding the prognostic effect of the platelet-to-lymphocyte ratio, an easily available systemic inflammation marker, among patients with acute kidney injury is less. In this study, we investigated the value of the Platelet-to-lymphocyte ratio in predicting the outcomes of Intensive care unit patients with acute kidney injury.

Methods: The study included 91 critically ill patients with acute kidney injury of Intensive care unit and Emergency ward. Informed consent was obtained from all patients. Period of study was from November 2017 to June 2019. Platelet-to-lymphocyte ratio cut-off values were determined using Receiver Operating Characteristic analysis.

Results: A total of 91 Intensive care unit patients with acute kidney injury were enrolled. A total of 24 deaths occurred,15 worsened and 52 improved. A U-shaped relationship was observed between the Platelet-to-lymphocyte ratio and prognosis at discharge, with the lowest risk being at values ranging from 100 to 299. Out of the parameters assessed, ESR, Blood urea and platelet count was significantly higher in high Platelet-to-lymphocyte ratio (>299) group. Lymphocyte counts showed significantly lower levels in the high Platelet-to-lymphocyte ratio (>299) group.

Conclusions: The preoperative Platelet-to-lymphocyte ratio was associated in a U-shaped pattern with survival among patients with acute kidney injury. The Platelet-to-lymphocyte ratio appears to be a novel, independent prognostic marker of outcomes in critically ill patients with acute kidney injury. Its clinical impact must be validated with appropriate study design and sample size.

Keywords: Platelet-to-lymphocyte ratio, acute kidney injury, prognosis, intensive care unit

INTRODUCTION

About higher than five million patients are admitted to intensive care units (ICUs) every year around worldwide. [1] 6–24% of these patients have acute kidney injury (AKI). [2] In the presence of AKI, patient mortality and morbidity increases to 60-70%, especially within one year after ICU admission. [3,4] Keeping the point of high incidence of AKI in the ICU and its poor prognosis, an increased number of observational studies over the past two decades have been oriented in identifying the clinical predictors of mortality in AKI.

Systemic inflammation is one of the part of disease progression in critical illness and is most commonly associated with sepsis, leading to an increased risk of mortality and morbidity. [5] Inflammation plays a key role in the initiation and progression of AKI, [6] morphological &functional changes in vascular endothelial cells and/or in the tubular epithelium are observed in patients with AKI. Lymphocytes, including leukocytes, infiltrate the injured kidneys & the entire body via the circulation system and induce the generation of inflammatory mediators such as cytokines & chemokines, which will damage the kidney and other organ system. [7]

The anti-thrombotic effects of platelets can evolve into atherogenesis via the secretion of pro-inflammatory cytokines, [8] whereas the attaching of platelets to endothelial cells can trigger leukocyte trans-migration & adhesion. [9]

The platelet-to-lymphocyte ratio (PLR) has been introduced as a bio-marker of inflammation in cardiovascular disease (CVD) & tumours, which are considered as inflammation related diseases. A positive correlation between increased PLR &poor prognosis for these diseases has been reported. [10,11]

Chen-Fei Zheng et al., [12] studied the pre-operative PLR association with survival among patients with AKI. The PLR appears to be a novel, independent prognostic biomarker of outcomes in critically ill patients with AKI. Based on these facts, it is reasonable to speculate that the PLR might affect the prognosis of AKI.

The present study was undertaken to know the prognostic value of platelet-to-lymphocyte ratio among critically ill patients with AKI.

METHODOLOGY

The study included critically ill patients with AKI of ICU and emergency ward of tertiary care centre. The patients were informed about study in all respects and informed consent was obtained. Period of study was from November 2017 to June 2019. Detailed history and thorough physical examination as indicated for a particular case was done. Relevant blood and urine investigations were sent. Other investigations as needed for a patient condition were performed. Each patient in the study group was followed till discharge or death.

Sample collection

Oral and written consent was taken from the subjects prior to the collection of specimens. Sample was collected in a clean dry test tube and transported to the biochemistry laboratory at B.M. Patil medical college, Vijaypura.

Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square (χ^2) test was used for association between two categorical variables. The difference of the means of analysis variables between two independent groups was tested by unpaired t test. ROC analysis for Sensitivity- specificity was done to check relative efficiency. If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0. and Microsoft office 2007.

RESULTS

A hospital based prospective, double blinded, randomized, comparative study was conducted from November 2017 to June 2019. A total of 91 cases of critically ill patients with acute kidney injury were included in the study. Mean age of the patients was 58.4±17.9 years (Table 1). Majority of the patients (37.4%) were between 61 to 75 years of age followed by 46 to 60 years (25.3%). Out of the 91 patients enrolled, 75.8% of the patients were male whereas 24.2% patients were female. Males were predominant in our study. Out of the patients enrolled, 48.4% were known cases of hypertension and 38.5% were known cases of type 2 diabetes mellitus (Table 1).

Fifty seven percent of the critically ill patients with acute kidney injury had improved in condition at the time of discharge, 26.4% died and 16.5 patients had worsened (Table 2).

After calculating PLR, patients were divided into the following groups:

PLR <105

PLR =105-299

PLR >299

Majority (50.5) of the patients belonged to PLR group of 105 to 299. Irrespective of age, all PLR groups showed that majority of the patients belonged to the age group of 61-75 years. There was no significant difference between the age of all three groups (Table 3).

Out of the parameters assessed, ESR, Blood urea and platelet count was significantly higher in high PLR(>299) group. Lymphocyte counts showed significantly lower levels in the high PLR(>299) group. Other parameters such as total counts, random blood sugar, sodium and potassium levels were not significantly associated with any PLR groups. Comorbidities like type 2 diabetes and hypertension were not significantly related to any of the PLR groups (Table 4).

Table 1: Patient characteristics

	Range	Mean	SD
AGE (YRS)	16-92	58.4	17.9
AGE(YRS)	N	%	
16-30	10	11.0	
31-45	11	12.1	
46-60	23	25.3	
61-75	34	37.4	
>75	13	14.3	
TOTAL	91	100.0	
SEX	N	%	
MALE	69	75.8	
FEMALE	22	24.2	
TOTAL	91	100.0	
COMORBIDITIES	N	%	
DIABETES	35	38.5	
HYPERTENSION	44	48.4	

Table 2: Distribution of cases according to outcome of the patient at discharge

OUTCOME OF THE PATIENT AT DISCHARGE	N	%
DEATH	24	26.4
IMPROVED	52	57.1
NOT IMPROVED	15	16.5
TOTAL	91	100.0

Table 3: Distribution of cases according to PLR and age

RISK GROUPS	N	%
PLR(<105)	23	25.3
PLR(105-299)	46	50.5
PLR(>299)	22	24.2
TOTAL	91	100

AGE(YRS)	PLR(<105)		PLR(105-299)		PLR(>299)		p value
	N	%	N	%	N	%	
16-30	2	8.7%	5	10.9%	3	13.6%	0.328
31-45	3	13.0%	7	15.2%	1	4.5%	
46-60	7	30.4%	11	23.9%	5	22.7%	
61-75	11	47.8%	13	28.3%	10	45.5%	
>75	0	0.0%	10	21.7%	3	13.6%	
TOTAL	23	100.0%	46	100.0%	22	100.0%	

Table 4: Other parameters and comorbidities according to PLR

OTHER PARAMETERS	PLR(<105)		PLR(105-299)		PLR(>299)		p value
	Mean	SD	Mean	SD	Mean	SD	
ESR	23.9	24.7	39.1	31.1	58.4	42.7	0.021*
RBS	129.8	73.5	160.9	110.6	198.4	163.3	0.207
BLOOD UREA	64.2	58.5	71.1	49.9	112.3	63.4	0.041*
SR.CREATININE	3.5	2.6	3.5	2.8	3.3	2.3	0.955
SR.SODIUM	134.7	4.4	134.6	6.0	135.2	7.5	0.935
SR.POTASSIUM	7.4	13.0	4.7	0.9	4.7	1.1	0.235
TLC('000)	16.4	10.1	14.3	7.0	17.9	8.1	0.219
PLATELET COUNT	1.3	1.1	2.1	0.9	2.7	1.5	0.001*
LYMPHOCYTE COUNT	2.5	2.0	1.3	0.7	0.6	0.4	<0.001*

COMORBIDITIES	PLR(<105)		PLR(105-299)		PLR(>299)		p value
	N	%	N	%	N	%	
DIABETES	8	34.8%	17	37.0%	10	45.5%	0.731
HYPERTENSION	10	43.5%	25	54.3%	9	40.9%	0.504

Table 5: ROC analysis of PLR in predicting poor prognosis and cutoffs

PLR	Area Under the Curve	Std. Error	p value	95% Confidence Interval	
				Lower Bound	Upper Bound
LOWER PLR	0.564	0.087	0.465	0.393	0.735
UPPER PLR	0.631	0.082	0.135	0.47	0.792

Parameters	CUT OFF	Sensitivity	Specificity
LOWER PLR	105	60.0%	52.0%
UPPER PLR	299	63.2%	63.0%

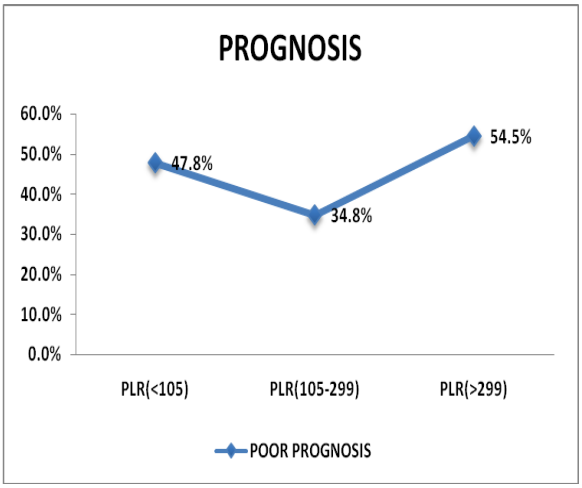

FIGURE 1: PROGNOSIS ACCORDING TO PLR

Both low and high PLR groups exhibited higher percentage of patients with poor prognosis as compared to PLR group of 105-299. However this was not statistically significant. Most patients who improved in condition belonged to PLR group of 105-299(Figure 1).

The table below shows the cutoff value for PLR in predicting poor prognosis of patients. It was found that the risk of poor prognosis was significantly higher with PLR <105 and >299 (with sensitivity of 60% and specificity of 52% for lower cut off and sensitivity of 63.2% and specificity of 63% for upper cut off)(Table 5).

DISCUSSION

A hospital based prospective, single blinded study with 91 cases of critically ill patients with acute kidney injury was conducted.

Mean age of the patients was 58.4±17.9 years which was similar to a study by Zheng *et al.* [12] with a mean age of 65.4 years. After calculating PLR, patients were divided into three groups based on PLR cutoff:

PLR <105

PLR =105-299

PLR >299

Majority of the patients were between 61 to 75 years of age. There was no significant difference between the mean age of all three groups. Irrespective of age, all PLR groups showed that majority of the patients belonged to the age group of 61-75 years. There was no significant difference between the age of all three groups. There is insufficient data about the importance of interplay between age and PLR. In a recent study conducted on Indian population, Sairam *et al.* [13] elderly people were found to have lower platelet values. Majority (50.5) of the patients in our study belonged to PLR group of 105 to 299.

Out of the parameters assessed, ESR, blood urea and platelet count was significantly higher in high PLR (>299) group. Lymphocyte counts showed significantly lower levels in the high PLR (>299) group. Both acute and chronic renal diseases correlate with local and systemic inflammation. Blood cells, endothelial cells, platelets, lymphocytes, macrophages, mast cells, and fibroblasts mediate this inflammation.

Balta *et al.* [14] reported that PLR is proportionally a better predictor of inflammation in ESRD. This association asserts that undue elevation of PLRs could foresee the same poor prognosis as other inflammation biomarkers in subjects with acute kidney injury.

Both low and high PLR groups exhibited, although insignificant, but higher percentage of patients with poor prognosis as compared to PLR group of 105-299. Most patients who improved in condition belonged to PLR group of 105-299. U-shaped relationship between the PLR and mortality, and both low and high PLRs were associated with increased mortality due to all causes as corroborated by a study conducted by Zheng *et al.* [12]

Proctor *et al.* [15] investigated the correlation between the PLR and overall survival which contrary to our study showed a positive correlation between the PLR and mortality when using a similar PLR cutoff.

Yaprak *et al.* [16] in a recent study correlated PLR and mortality with a small cohort of patients with end-stage renal disease (ESRD) and established that the PLR could autonomously predict several causes of mortality in this population. A

core cause for this difference is the deficient number of patients with reduced PLRs.

The PLR has been scrutinized as a novel inflammatory marker for predicting major complications associated with CVD. [17] In a study by Velibey *et al.* [18] they reported that elevated PLRs are self-sufficiently liked to a greater possibility of contrast-induced AKI in patients who have previously undergone primary percutaneous coronary intervention. A recent study exhibited that a raised PLR is correlated with coronary artery disease, C-reactive protein and fibrinogen values. [19]

Out of the patients enrolled, 48.4% were known cases of hypertension and 38.5% were known cases of type 2 diabetes mellitus. Comorbidities like type 2 diabetes and hypertension were not significantly related to any of the PLR groups. Other parameters such as total counts, random blood sugar, sodium and potassium levels were not significantly associated with any PLR groups. Variables affecting the outcome of AKI are multifactorial including blood pressure, [20] renal function, [21] urine output [20] and other clinical parameters (i.e., S Cr, BUN, and pH [22] as well as comorbidities (e.g., cardiac disease) [22]A study by Zheng *et al.* [12] also showed no significant interactions for sex, PO2, GCS, SBP, potassium, S Cr, urine output or BUN which was similar to findings in our study.

Fifty seven percent of the critically ill patients with acute kidney injury had improved in condition at the time of discharge, 26.4% died and 16.5 patients had worsened. Patients who worsened or died were included among patients with poor prognosis. In a study comparing the mortality rates of critical patients with those of patients suffering from acute renal failure (ARF), Mehta *et al.* [23] observed that the risk of mortality is greater than threefold higher with low platelet count patients as compared to controls with normal platelet values.

In an observational study, Chertow *et al.* [24] scrutinized the correlation of mortality with thrombocytopenia at the time of consultation which was associated with mortality in ARF patients. Similar potential risk factor with low platelet count was seen in another study. [25]

Thrombocytopenia is not uncommon among critically ill patients and is often connected to poor prognosis. The reduced platelet manufacture or unwarranted platelet destruction due to underlying disease and therapeutic interventions plays a key role in establishment of thrombocytopenia. [26] Combined, these discoveries show that reduction in platelet counts could result in a low PLR in AKI patients and could pave the way for high mortality, thus, asserting our observation of a U-shaped association between the PLR and mortality.

It was found that the risk of poor prognosis was significantly higher with PLR <105 and >299 (with sensitivity of 60% and specificity of 52% for lower cut off and sensitivity of 63.2% and specificity of 63% for upper cut off).

Limitations of this study are as follows:

- CKD status among patients with AKI could not be assessed and the role of CKD in the association between the PLR and mortality could not be established.
- PLR was calculated in the study subjects only on admission.
- A cross sectional recording of PLR does not completely demonstrate ongoing inflammation, a better assessment of which would be by synergistically measuring several inflammatory mediators.
- Sepsis and shock, both of which may escalate patient morbidity and predict higher mortality among patients with AKI was not considered. [27]

CONCLUSION

The preliminary data from our study advocates the importance of PLR as a risk adjustment tool with prognostic implications for AKI. However, to substantiate PLR as a prognostic marker, its clinical impact must be validated with appropriate study design and sample size. The cutoff value must be

established in one large cohort of patients and tested in another large cohort, and the number of patients in each group needs to be considered in statistical analyses for statistically significant validation of PLR as prognostic marker, not only in AKI, but in an array of critical diseases.

REFERENCES

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303–10.
2. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S et al. Acute Renal Failure in Critically Ill Patients. A Multinational,Multicenter Study. JAMA. 2010;294:813–8.
3. Hofhuis JG, van Stel HF, Schrijvers AJ, Rommes JH SP. The effect of acute kidney injury on long-term health-related quality of life: A prospective follow-up study. Crit Care. 2013;17:R17.
4. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004.
5. Adrie C, Pinsky MR. The inflammatory balance in human sepsis. Intensive Care Med. 2000;26:364–75.
6. Rabb H, Griffin MD, McKay DB, Swaminathan S, Pickkers P, Rosner MH, et al. Inflammation in AKI: Current Understanding, Key Questions, and Knowledge Gaps. J Am Soc Nephrol. 2016; 27:371–9.
7. Akcay A, Nguyen Q, Edelstein CL. Mediators of inflammation in acute kidney injury. Mediators Inflamm. 2009;2009: 137072.
8. Kaplan ZS, Jackson SP. The role of platelets in atherothrombosis. Hematol Am Soc Hematol Educ Progr. 2011;2011:51–61.
9. Borissoff JI, Spronk HMH, ten Cate H. The hemostatic system as a modulator of atherosclerosis. N Engl J Med. 2011; 364:1746–60.
10. Sunbul M, Gerin F, Durmus E, Kivrak T, Sari I, Tigen K, et al. Neutrophil to lymphocyte and platelet to lymphocyte ratio in patients with dipper versus non-dipper hypertension. Clin Exp Hypertens. 2014; 36:217–21.
11. Li X, Chen Z-H, Xing Y-F, Wang T-T, Wu D-H, Wen J-Y, et al. Platelet-to-lymphocyte ratio acts as a prognostic factor for patients with advanced hepatocellular carcinoma. Tumour Biol. 2015;36:2263–9.
12. Zheng C-F, Liu W-Y, Zeng F-F, Zheng M-H, Shi H-Y, Zhou Y, et al. Prognostic value of platelet-to-lymphocyte ratios among critically ill patients with acute kidney injury. Crit Care. 2017;21:238.
13. Sairam S, Domalapalli S, Muthu S, Swaminathan J, Ramesh VA, Sekhar L, Pandeya P, Balasubramaniam U. Hematological and biochemical parameters in apparently healthy Indian population: defining reference intervals. Indian J Clin Biochem. 014;29:290–7.
14. Balta S, Demirkol S, Kucuk U. The platelet lymphocyte ratio may be useful inflammatory indicator in clinical practice. Vol. 17, Hemodialysis international. International Symposium on Home Hemodialysis. Canada; 2013:668–9.
15. Proctor MJ, Morrison DS, Talwar D, Balmer SM, Fletcher CD, O'Reilly DS,Foulis AK, Horgan PG, McMillan DC. A comparison of inflammation-based prognostic scores in patients with cancer: a Glasgow Inflammation Outcome Study. Eur J Cancer. 2011;47:2633–41.
16. Yaprak M, Turan MN, Dayanan R, Akin S, Degirmen E, Yildirim M, Turgut F.Platelet-to-lymphocyte ratio predicts mortality better than neutrophil-tolymphocyteratio in hemodialysis patients. Int Urol Nephrol. 2016; 48:1343–8.
17. Azab B, Shah N, Akerman M, McGinn JTJ. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. J Thromb Thrombolysis. 2012;34:326–34.
18. Velibey Y, Oz A, Tanik O, Guvenc TS, Kalenderoglu K, Gumusdag A, et al. Platelet-to-Lymphocyte Ratio Predicts Contrast-Induced Acute Kidney Injury in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. Angiology. 2017;68:419–27.

19. Gary T, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, Eller P, Rief P, Hackl G, Pilger E, et al. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PLoSOne. 2013;8:e67688.
20. Oh HJ, Shin DH, Lee MJ, Ko KI, Kim CH, Koo HM, Doh FM, Kwon YE, Kim YL,Nam KH, et al. Urine output is associated with prognosis in patients with acute kidney injury requiring continuous renal replacement therapy. J Crit Care. 2013;28:379–88.
21. Sawhney S, Mitchell M, Marks A, Fluck N, Black C. Long-term prognosis after acute kidney injury (AKI): what is the role of baseline kidney function and recovery? A systematic review. BMJ Open. 2015; 5:e6497.
22. Cruz DN, Bagshaw SM, Maisel A, Lewington A, Thadhani R, Chakravarthi R, Murray PT, Mehta RL, Chawla LS. Use of biomarkers to assess prognosis and guide management of patients with acute kidney injury. Contrib Nephrol.2013;182:45–64.
23. Mehta RL, Pascual MT, Gruta CG, Zhuang S, Chertow GM. Refining predictive models in critically ill patients with acute renal failure. J Am Soc Nephrol.2002;13:1350–7.
24. Chertow GM, Soroko SH, Paganini EP, Cho KC, Himmelfarb J, Ikizler TA,Mehta RL. Mortality after acute renal failure: models for prognostic stratification and risk adjustment. Kidney Int. 2006;70:1120–6.
25. Paganini EP, Halstenberg WK, Goormastic M. Risk modeling in acute renal failure requiring dialysis: the introduction of a new model. Clin Nephrol.1996;46(3):206–11.
26. Parker RI. Etiology and significance of thrombocytopenia in critically ill patients. Crit Care Clin. 2012;28:399–411.
27. Zarjou A, Agarwal A. Sepsis and acute kidney injury. J Am Soc Nephrol.2011; 22:999–1006.

How to cite this article: Patil L, Kuntal Y. Platelet to lymphocyte ratio as a prognostic marker in ICU patients with acute kidney injury. International Journal of Research and Review. 2020; 7(3): 1-7.

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