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## Utility of Inflammatory Markers to Predict Adverse Outcome in Acute Pancreatitis: A Retrospective Study in a Single Academic Center


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# Utility of inflammatory markers to predict adverse outcome in acute pancreatitis: A retrospective study in a single academic center

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## Abstract

**Background/Aim:** Acute pancreatitis (AP) is a commonly encountered emergency where early identification of complicated cases is important. Inflammatory markers like lymphocyte to monocyte ratio (LMR) and neutrophil to lymphocyte ratio (NLR) are simple and readily available markers. In this study, we evaluated the utility of these markers in the early identification of patients with complicated AP.

**Patients and Methods:** All patients with a diagnosis of AP admitted to the University Medical Center in Las Vegas/Nevada between August 2015 and September 2018 were identified using ICD-10 codes. Medical records were reviewed retrospectively. Epidemiological measures and their associated confidence intervals were calculated using MedCalc (v. 18).

**Results:** The LMR showed a significant difference between groups, with the non-complicated cases consistently higher than the complicated cases but without significant temporal differences. The NLR showed a significant difference with a significant temporal relation. Using the bound of the 95% confidence interval separating the two groups, LMR <2 was found to be associated with a complicated case and NLR >10.5 was suggestive of a complicated case. High specificity (85–92%) with low sensitivity (23–69%) was noted; hence, these cut points were very good at discerning non-complicated cases.

**Conclusion:** Our data show persistently low LMR that is associated with severe AP and a value of <2.0 can be used clinically to predict severe AP on admission. It also shows that elevated NLR is associated with complicated AP and prolonged hospital stay with a value >10.5 that can be used to predict severe complicated AP and to monitor response to treatment over time.

**Keywords:** Acute complicated pancreatitis, lymphocytes to monocyte ratio, neutrophil to lymphocyte ratio

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## INTRODUCTION

Acute pancreatitis (AP) is a common inflammatory condition characterised by local and systemic inflammation

with symptoms ranging from asymptomatic or mild disease to severe systemic inflammatory response complicated by persistent organ failure and possibly death.<sup>[1-3]</sup>

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Therefore, it is crucial to identify patients with increased risk of developing severe disease and start evidence-based intensive care to prevent the development of severe complications and reduce morbidity and mortality.

Several scoring systems have been developed to stratify the severity of AP, but they have their own limitations, namely, Ranson's and Glasgow score require data that are not routinely available at presentation and need long time to complete. The acute physiology and chronic health examination (APACHE-II) that was developed to be used in critical care setting requires multiple parameters that are also not available at the time of presentations. Sequential organ failure assessment (SOFA) has been developed but is still suitable only in the intensive care setting and not for routine use in all patients presenting with AP. Therefore, a simplified serum biomarker that is readily available on admission with good sensitivity is required for the early identification and treatment of severe AP to lower morbidity and mortality.<sup>[4-6]</sup>

Neutrophil to lymphocyte ratio (NLR) and lymphocytes to monocyte ratio (LMR) have shown values in predicting the disease prognosis of multiple malignancies and systemic inflammatory diseases.<sup>[7-10]</sup> These parameters are readily available upon admission through a simple complete blood count. Few studies have looked into using these values to predict the disease severity in case of acute pancreatitis. Our study aims to investigate the validity of using these markers in predicting the disease severity and outcome in patients with acute pancreatitis, in addition to treatment response over the first 48 hours. It also aims to determine the optimal cut-off value that would allow the early recognition of patients with the tendency to develop severe AP of multiple etiologies.

## PATIENTS AND METHODS

This is a retrospective chart review of patients admitted to the academic medical center with a diagnosis of AP between August 2015 and September 2018. Approval from IRB and Ethics committee was obtained on November 5<sup>th</sup>, 2018. The patients were identified using ICD-10 codes. The patients were labeled as either complicated or non-complicated groups based on the hospital course and clinical outcome. Different parameters and variables were calculated and compared between the two groups (complicated vs. non-complicated) including LMR and NLR on admission and at 24 and 48 hours. Using revised Atlanta classification, the patients with moderate and severe AP were included in the complicated group and mild AP in the non-complicated group. Clinical course and

outcome were also considered including ICU admission and mortality rate.

Descriptive statistics for all variables were calculated to determine the mean, SD, and range of values. In addition, the measures of skewness and kurtosis were evaluated to discern potential deviations from normal assumptions. Independent-sample t-tests were used to compare the demographic variables of age and total length-of-stay (LOS). Of particular interest was the potential of significant differences owing to time and complication status. To address this question, RM-ANOVA was utilised. The RM-ANOVA was developed for a within-between design, with Greenhouse–Geisser estimates reported. To assess potential non-normality, both observed data and a rank-based transformation of the data were employed; the statistical results were identical in both cases and, hence, the parametric results are provided. As a final analysis, we investigated the potential cut-points of significant biomarkers for clinical use. Cut points were established using the bound of the 95% confidence limit separating the complicated cases from non-complicated cases. Using these results, the predicted complicated cases were compared to clinically known complicated cases in an epidemiological analysis to determine the sensitivity, specificity, PPV and NPV, along with their Clopper–Pearson or logit confidence intervals. Descriptive statistics and models were calculated using the SPSS software (IBM; v. 25). Epidemiological measures and their associated confidence intervals were calculated using MedCalc (v. 18).

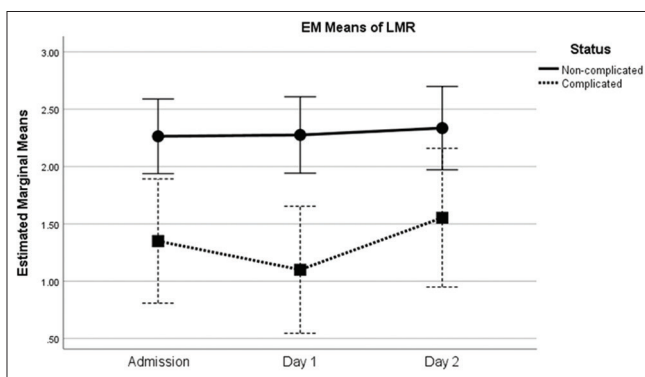
## RESULTS

The summary statistics for demographic and clinical variables for each time period are provided in Table 1. The mean age of patients was not different between the complicated and non-complicated cases ( $t = 0.26, P = 0.799$ ) but the total LOS did differ, with complicated cases representing over twice the total LOS as non-complicated cases ( $t = 8.18, P < 0.001$ ).

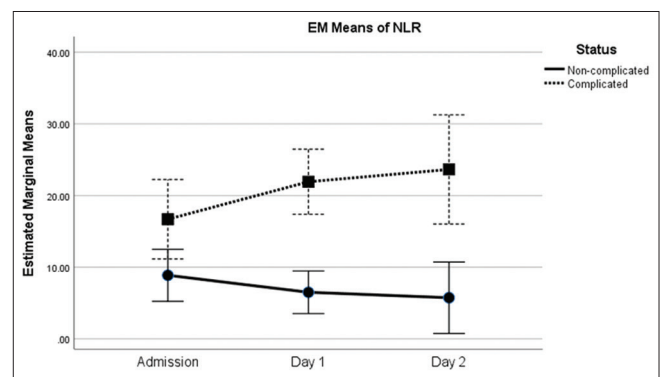
The LMR showed a significant difference between the groups, with the non-complicated cases consistently higher than the complicated cases ( $F = 11.34, P = 0.001$ ) and there were no significant temporal differences ( $F = 1.48, P = 0.232$ ) [Figure 1]. The NLR showed a significant difference between the groups, with the non-complicated cases consistently lower than the complicated cases ( $F = 23.11, P < 0.001$ ). In addition, there was a significant complication status-by-time interaction ( $F = 3.88, P = 0.040$ ), with significant differences notable at both post-admission

**Table 1: Descriptive statistics for demographic and clinical measures**

Variable	Non-complicated Cases					Complicated Cases				
	n	Min	Max	Mean	SD	n	Min	Max	Mean	SD
Age	198	14.0	87.0	46.5	15.35	41	19.0	74.0	47.1	13.44
ICU LOS	1	2.0	2.0	2.0		25	1.0	22.0	8.3	7.00
Total LOS	193	1.0	13.0	4.1	2.32	39	2.0	51.0	10.6	9.85
Lipase Admission	197	76.0	16341.0	1152.5	1324.15	41	70.0	5000.0	1204.6	943.78
Lipase Day 1	122	13.0	2079.0	527.3	559.97	22	63.0	2079.0	653.1	526.19
Lipase Day 2	102	5.0	1017.0	177.0	183.75	22	10.0	1908.0	424.5	439.04
WBC Admission	198	2.4	28.0	10.8	4.50	41	4.5	28.3	13.8	6.03
WBC Day 1	187	2.2	25.0	9.5	4.08	41	3.4	27.9	12.4	5.72
WBC Day 2	164	1.9	21.7	8.8	3.74	40	3.4	30.8	11.6	5.79
Hematocrit Admission	198	22.2	56.2	42.7	5.77	41	19.9	57.6	43.4	8.64
Hematocrit Day 1	187	9.5	54.1	38.2	5.78	41	23.2	56.3	39.4	8.83
Hematocrit Day 2	165	12.6	48.7	36.2	5.51	40	21.3	48.9	36.3	6.58
Platelets Admission	198	70.0	888.0	230.7	95.61	41	80.0	776.0	247.3	138.86
Platelets Day 1	187	56.0	1600.0	200.9	134.95	41	55.0	542.0	182.9	100.85
Platelets Day 2	165	36.9	1888.0	196.5	164.37	40	37.0	540.0	166.7	97.29
RDW Admission	195	11.4	23.4	14.5	1.75	41	12.4	25.6	15.2	2.55
RDW Day 1	186	11.9	23.9	14.5	1.70	41	12.4	40.3	15.7	4.34
RDW Day 2	165	12.0	24.2	14.5	1.78	40	12.7	166.9	19.4	24.28
Neutrophil Admission	184	44.5	97.0	77.0	11.92	40	53.0	92.0	80.6	8.86
Neutrophil Day 1	131	18.0	92.1	74.6	12.98	34	53.5	95.0	79.7	12.37
Neutrophil Day 2	99	38.0	97.0	71.8	12.75	31	49.7	95.0	79.6	11.62
Lymphocytes Admission	184	1.8	46.8	14.6	9.38	40	2.2	37.7	11.2	7.88
Lymphocytes Day 1	131	1.9	69.5	16.2	10.87	34	1.9	30.0	9.6	8.28
Lymphocytes Day 2	99	0.8	43.1	17.8	10.28	29	1.0	37.8	11.0	9.01
Neutrophil Admission	178	1.3	24.5	8.6	4.33	39	2.4	25.6	11.4	5.55
Neutrophil Day 1	131	18.0	92.1	74.6	12.98	34	53.5	95.0	79.7	12.37
Neutrophil Day 2	99	38.0	97.0	71.8	12.75	31	49.7	95.0	79.6	11.62
ABS Lymphocyte Admission	178	0.2	13.7	1.5	1.41	39	0.2	6.5	1.4	1.21
ABS Lymphocyte Day 1	130	0.2	26.7	1.5	2.32	32	0.2	26.1	1.7	4.48
ABS Lymphocyte Day 2	96	0.3	3.7	1.4	0.64	28	0.2	3.3	1.1	0.68
ABS Monocyte Admission	178	0.1	9.9	0.8	0.98	39	0.3	2.9	1.0	0.49
ABS Monocyte Day 1	130	0.1	15.2	0.8	1.31	32	0.4	6.9	1.1	1.14
ABS Monocyte Day 2	96	0.2	7.0	0.8	0.71	29	0.1	2.9	0.9	0.57
LMR Admission	178	0.2	14.9	2.4	1.84	39	0.2	5.4	1.6	1.14
LMR Day 1	130	0.3	12.0	2.3	1.69	32	0.3	4.5	1.2	0.96
LMR Day 2	65	0.4	8.0	2.4	1.32	22	0.2	9.0	1.5	1.89
NLR Admission	178	0.4	54.0	9.1	9.11	39	1.4	45.0	13.1	11.81
NLR Day 1	130	0.9	47.0	7.9	7.31	31	1.8	51.0	16.5	12.47
NLR Day 2	38	0.9	32.0	5.4	5.61	15	2.5	98.0	23.6	25.67



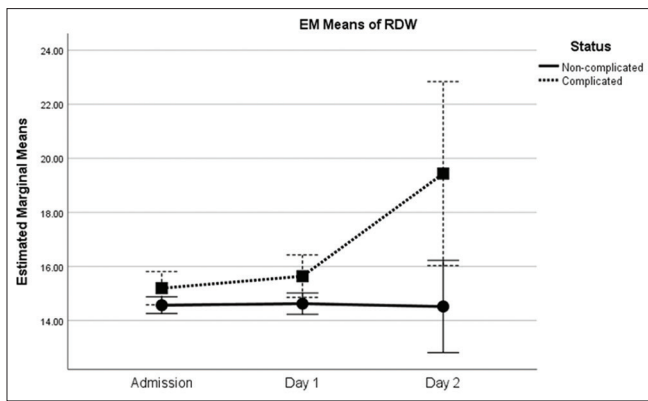
**Figure 1:** Estimated marginal means through time for LMR; 95% CI are shown



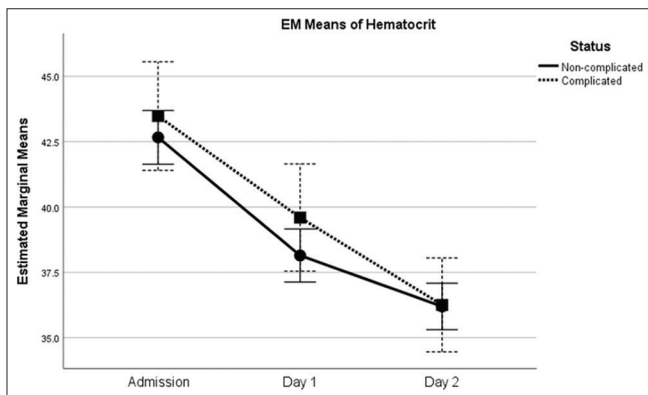
**Figure 2:** Estimated marginal means through time for NLR; 95% CI are shown

days [ $P < 0.05$ ; Figure 2]. The RDW showed both a significant change through time ( $F = 4.52, P = 0.034$ ) and a significant status-by-time interaction ( $F = 4.86, P = 0.028$ ), resulting in significant overlap between the complicated and non-complicated cases [Figure 3]. The

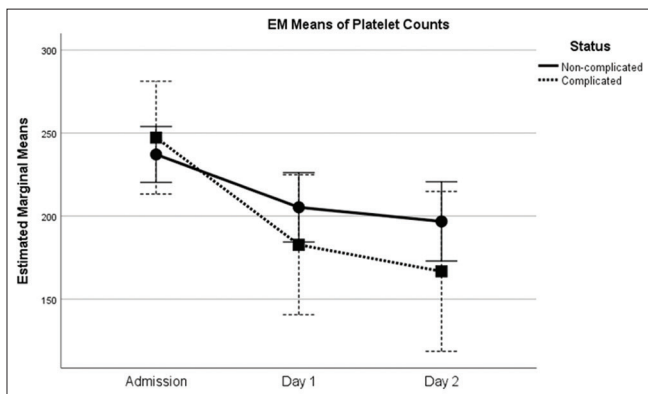
hematocrit measures showed a significant change through time ( $F = 157.95, P < 0.001$ ), but there was no significant difference between status [ $F = 0.57, P = 0.451$ ; Figure 4]. Similarly, for platelet counts, there was a significant change through time ( $F = 13.48, P < 0.001$ ), but there was no



**Figure 3:** Estimated marginal means through time for RDW; 95% CI are shown



**Figure 4:** Estimated marginal means through time for haematocrit; 95% CI are shown



**Figure 5:** Estimated marginal means through time for platelet counts; 95% CI are shown

difference between the complication status [ $F = 0.56$ ,  $P = 0.456$ ; Figure 5].

The cut-points for potential clinical use were investigated using the bound of the 95% confidence interval separating admission complicated and non-complicated cases for the two ratios that were found to be significant, namely LMR (cut-point  $<2$  indicating a complicated case) and NLR (cut-point  $>10.5$  indicating a complicated case). The overall

sensitivity was low, ranging from 23 to 69%; however, the specificity was quite high, ranging from 85 to 92%. Hence, these cut points were very good at discerning the non-complicated cases [Table 2].

## DISCUSSION

AP usually runs a mild clinical course without complications, requiring only short-term hospitalisation. However, about 20% of the patients develop a complicated clinical course. These patients may suffer long-term intensive care admission and hospitalisation, and the need for invasive interventions with significant mortality rates may occur arising mainly from organ failure or infected pancreatic necrosis.<sup>[11,12]</sup>

Haematological inflammatory markers have been widely studied as prognostic markers in multiple inflammatory and malignant conditions.<sup>[8,13-16]</sup>

In this study, we evaluated the role of different haematological markers in predicting the severity of AP, ICU admission, development of organ failure and mortality rate in our medical centre in Southern Nevada. Our goal was to validate the value of using simple, readily available parameters on admission to identify high-risk patients with the potential to develop severe disease which will generate a higher degree of clinical suspicion for possible complications and allows more aggressive care leading to lower mortality rate and medical expenses. Compared to conventional prediction scores, these markers are simple, easily accessible and immediately available on admission and can be used in facilities where other tests are not available. The conventional scores such as APACHE II, BISAP and Ranson's criteria require multiple tests and imaging studies.

White cell count (WCC) is a common serum haematological test that is routinely done in most medical and surgical emergencies. It is already incorporated in many of the current AP scoring systems; however, it is nonspecific and cannot help in predicting poor outcome upon admission.<sup>[17]</sup>

Multiple studies have shown significance in the WCC differentials as an indicator to poor prognosis in multiple benign inflammatory and malignant conditions. Neutrophils, lymphocytes and monocytes are the important components of WCC. Neutrophils induce inflammation and tissue destruction in AP via the activation of a cascade of inflammatory cytokines (IL-6, IL-8, and TNF- $\alpha$ ), proteolytic enzymes and oxygen-free radicals.<sup>[18]</sup> An increase in the neutrophil number corresponds with the development of SIRS and progression to persistent organ failure.<sup>[17]</sup>

**Table 2: Epidemiological analysis of potential cut-off values and 95% confidence limits for complicated cases (LMR <2; NLR >10.5)**

	Sensitivity	Specificity	PPV	NPV	LR+	LR-
LMR Admission	22.6 (15.6, 31.0)	88.2 (79.8, 99.0)	71.8 (57.2, 82.9)	46.1 (43.1, 49.1)	1.9 (0.8, 31.0)	0.9 (0.7, 1.0)
LMR Day 1	22.3 (18.8, 37.2)	92.1 (82.4, 97.4)	84.4 (68.7, 93.0)	44.6 (41.2, 48.1)	2.8 (1.1, 14.3)	0.8 (0.6, 1.0)
LMR Day 2	37.3 (24.1, 51.9)	91.7 (77.5, 98.3)	86.4 (66.9, 95.2)	50.8 (45.0, 56.6)	4.5 (1.1, 30.5)	0.7 (0.5, 1.0)
NLR Admission	26.6 (16.3, 39.1)	85.6 (79.0, 90.8)	43.6 (30.6, 57.5)	73.6 (70.4, 76.6)	1.8 (0.8, 4.3)	0.9 (0.7, 1.0)
NLR Day 1	35.3 (22.4, 49.9)	88.2 (80.6, 93.6)	58.1 (42.4, 72.3)	74.6 (70.4, 78.5)	3.0 (1.2, 7.8)	0.7 (0.5, 1.0)
NLR Day 2	69.2 (38.6, 90.9)	85.0 (70.2, 94.3)	60 (39.7, 77.3)	89.5 (78.8, 95.1)	4.6 (1.3, 15.9)	0.4 (0.1, 0.9)

Studies have shown that persistent lymphopenia indicates poor prognosis and is an independent marker for progressive inflammation, bacteremia and sepsis in emergency department and critical care unit.<sup>[19,20]</sup>

In this study, we investigated the role of multiple haematological inflammatory markers including NLR, LMR, RDW, platelets count and haematocrit in predicting disease prognosis and outcome, mainly persistent organ failure and mortality and we compared these parameters against each other.

Based on our results, NLR was found to be persistently higher in the complicated group compared to non-complicated group which make it a useful tool in differentiating the two groups early on admission. Furthermore, the NLR showed significant correlation with disease severity over time, making it an excellent tool to follow up on patients' prognosis with normalisation of values in patients with favourable prognosis and persistent elevation in those with worse prognosis and persistent organ failure. Per our results, the calculated cut-point value for NLR was >10.5 which indicates a higher risk for complicated case.

LMR was also investigated and found to be significant in predicting complicated cases on admission as it shows persistent lower values in complicated cases compared to non-complicated cases; however, it did not show significant temporal difference between the two groups. This makes it an excellent tool to differentiate the two groups upon admission but not good for evaluating the prognosis overtime. Our calculated cut-point value for LMR was <2 which indicates a complicated case.

Red blood cell distribution width (RDW), reported as a part of the complete blood count test, is a quantitative measure of variability in the size of circulating erythrocytes.<sup>[21]</sup> A prior study done by Senol *et al.* reported that the RDW on admission could be a predictor for mortality in patients with AP.<sup>[22]</sup> Another study showed that RDW was not associated with disease severity in AP but can predict persistent organ failure which is associated with increased mortality.<sup>[23]</sup>

Our results showed statistically significant changes in RDW with time, but it did show overlap between complicated

and non-complicated cases which make its clinical use of limited value.

Haematocrit and platelet count were investigated as independent prognostic factors to predict disease severity and both showed significant change with time but no significant difference between complicated and non-complicated cases.

These results show the high value of using simple, easily accessible parameters available immediately on admission to identify patients with higher risk of developing severe AP, prolonged hospital stay and higher risk for persistent organ failure and mortality which will help in directing acute critical care earlier to prevent complications and poor outcomes.

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Nil.

#### Conflicts of interest

There are no conflicts of interest.

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