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Analyzing the Relationship Between Red Cell Distribution Width and Total Serum Calcium in Acute Pancreatitis Severity Predictions

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Abstract: ***Title: Analyzing the Relationship Between Red Cell Distribution Width and Total Serum Calcium in Acute Pancreatitis Severity Predictions. Background: The severity of acute pancreatitis (AP) might vary at the time of presentation, and the illness can be deadly. Patients at increased risk of serious complications must be identified in order to improve their prognosis by the rapid administration of medicinal or endoscopic therapy and admission to a dedicated intensive care unit (ICU). There is currently no valid tool for determining the severity of AP when it first manifests, despite the availability of several rating systems and methodologies. Predicting the severity of AP may be done using affordable indicators that are easily accessible upon admission, such as red cell distribution width (RDW) and blood calcium levels. Materials and methods: The 85 patients enrolled to Saraswathi Medical College in Hapur were the subjects of an observational cross - sectional research. Those suffering from AP were divided into two groups: MAP, or mild AP, and MSAP/SAP, or moderately severe AP. At admission and again at 24 hours, RDW was checked in all patients. Results: The results showed that out of 85 AP patients, 55 were diagnosed with MAP, 17 with MSAP, and 13 with SAP. Patients treated with MSAP/SAP had significantly lower mean blood calcium levels than those treated with MAP. Patients with MSAP/SAP also had substantially higher values for the following metrics compared to MAP patients: modified Marshall score (MM), bedside index for severity in acute pancreatitis (BISAP) index, RDW at 0 and 24 hours, and RDW/total serum calcium (RDW/TSC) ratio. The most accurate severity predictors were the BISAP index and MM, with RDW/TSC also showing good predictive value. The predictive power of RDW/TSC for AP severity was higher than that of RDW evaluated at admission and 24 hours. Nevertheless, no particular metric was shown to be a significant predictor of AP on its own. Conclusion: The BISAP index and red cell distribution width/TSC ratio are both good indicators of AP severity, similar to each other. They allow for early intervention by providing a simple and inexpensive way to predict the severity of AP upon arrival.***

Keywords: Acute Pancreatitis, BISAP, MAP, RDW, TSC.

1. Introduction

Acute pancreatitis (AP), a potentially lifethreatening condition, manifests with varying degrees of severity. In developed nations, approximately 60–80% of AP cases stem from either gallstone disease or alcohol abuse.1 It's imperative to promptly identify patients at elevated risk of severe or fatal AP to enhance prognosis through timely medical or endoscopic intervention and admission to a specialized intensive care unit (ICU).

Red cell distribution width (RDW) is a routine parameter of the complete blood count test that was initially used for differential diagnosis of anemia. In the presence of active inflammation due to oxidative stress and circulating inflammatory cytokines, there is reduction in red blood cell (RBC) survival and maturation. This results in the release of newer and larger RBC into the peripheral circulation and changing of membrane glycoproteins and ion channels of RBC with consequent morphological alteration which leads to an increase in RDW. Hypocalcemia is a metabolic derangement commonly associated with AP more so in patients with severe AP (SAP). However, isolated total serum calcium (TSC) has not been established as direct marker of severity for AP severity, RDW/TSC ratio has been evaluated to be an excellent predictor of AP severity and a very good predictor of AP mortality.2

A recent study by Gravito - Soares et al.3 compared RDW and TSC at varying time points to Ranson, bedside index for severity in acute pancreatitis (BISAP), and MM scores, especially when evaluated at admission and within the initial 24 hours. RDW0h, alongside the RDW0h/TSC ratio, emerged as particularly strong indicators. RDW0h exceeding 13.0 and RDW0h/TSC surpassing 1.4 proved to be excellent predictors of AP severity, while RDW0h exceeding 14.0 and RDW0h/TSC surpassing 1.7 were identified as very good predictors of AP mortality.

The revised Atlanta classification5 is not suitable to differentiate moderately severe and severe pancreatitis in the first 48 hours of admission. Ranson score6 has been used but takes 48 hours to complete and therefore cannot be used at admission. Other scoring systems such as the SOFA have been developed but have only found to be useful in the intensive care setting and not for routine use in all patients presenting with AP. Other markers, such as tumor necrosis factor alpha (TNF - α), interleukin - 6, interleukin - 8, and procalcitonin, have been said to be able to predict the severity of AP, but these are not readily available and are expensive. An ideal marker/prognostic score should be simple, easily available at admission, economic, accurate, and quantitative.3

2. Materials and Methods

This study was an observational crosssectional investigation involving 85 AP patients admitted to the medicine and surgery wards at Saraswathi medical college, Hapur. Each patient underwent comprehensive history - taking, clinical examination, and relevant diagnostic tests.

Acute pancreatitis was defined by the revised Atlanta criteria.5 Diagnosing a patient with AP, required two of the following three features:

- Abdominal pain consistent with AP, that is, acute onset, persistent, severe, epigastric pain often radiating to back.
- Serum lipase or amylase activity at least more than three times the upper limit of normal.
- Imaging showing characteristic findings of AP.

Inclusion Criteria

- All diagnosed cases of AP based on revised Atlanta classification.5 • Age >18 years.

Exclusion Criteria

- Patients on immunosuppressive therapy. • Any infectious condition. • Any malignancy. • Chronic use of erythropoietin. • Recent transfusion history. • Pregnancy.

Statistical Analysis

The categorical variables were presented as counts and percentages (%), while quantitative data were expressed as means ± standard deviation (SD) and as median with interquartile range (25th and 75th percentiles). Data entry was completed in Microsoft Excel, and the final analysis was carried out using Statistical Package for Social Sciences (SPSS) software, version 25.0. A p - value of <0.05 was considered statistically significant.

3. Results

A total of 85 cases of AP were taken up for the study. The severity of cases based on revised Atlanta classification were mild in 55 (64.71%) of patients, moderate in 17 (20.00%), and was severe in 13 out of 85 patients (15.29%). The patients were divided into two groups based on severity—mild AP (MAP) and moderately severe AP/SAP (MSAP/SAP) —and correlation was done between these two groups. No significant association was seen between age, gender, etiology, hemoglobin, and platelet count with severity of AP (Table 1).

Table 1: Characteristics of patients with AP

Parameters	*MAP (n = 55)*	*MSAP/SAP (n = 30)*	*p-value*
Age	50.33 ± 10.43	53.43 ± 19.18	0.415
Males	34 (61.82%)	21 (70%)	55 (64.71%)
Hemoglobin (gm/dL)	13.17 ± 2.47	13.48 ± 2.81	0.343
TLC (cells/mm^3)	10247.27 ± 3629.04	14858.33 ± 7392.01	0.0004
Platelets (cells/mm^3)	209836.36 ± 88835.21	213333.33 ± 127027.1	0.541
Blood urea (mg/dL)	30.47 ± 12.61	100.07 ± 40.99	<0.0001
Serum creatinine (mg/dL)	0.72 ± 0.26	2.25 ± 0.99	<0.0001
Serum bilirubin (mg/dL)	1.61 ± 1.58	2.27 ± 2.15	0.631
SGOT (IU/L)	99.09 ± 68.5	89.2 ± 60.56	0.679
SGPT (IU/L)	209.16 ± 98.45	170.37 ± 119.3	0.064
ALP (IU/L)	204.04 ± 204.46	382.37 ± 236.37	<0.0001
RDW (%) at 0 hour	12.96 ± 1.39	15.3 ± 2.55	<0.0001
RDW (%) at 24 hours	12.47 ± 1.35	14.79 ± 2.16	<0.0001
Serum calcium (mg/dL)	9.09 ± 0.62	8.18 ± 0.57	<0.0001
RDW/TSC ratio	1.38 ± 0.2	1.83 ± 0.33	<0.0001
BISAP	0.62 ± 0.73	2.93 ± 0.87	<0.0001
MM	0.02 ± 0.13	2 ± 1.05	<0.0001

There was a significant increase in the total leukocyte count (TLC), urea, and creatinine in the MSAP/SAP group compared with the MAP group. Serum calcium levels were significantly lower in the MSAP/SAP group when compared with the MAP group. RDW at 0 and 24 hours, RDW/TSC ratio, BISAP score, and MM score were also significantly higher in patients in the MSAP/SAP group than in the MAP group. Area under the receiver operating characteristic (AUROC) of RDW (%) (Table 2) at 0 hour was 0.794 ($p < 0.0001$) for a cutoff of >13 with sensitivity of 83.33%, specificity of 72.73%, positive predictive value (PPV) of 62.5%, negative predictive value (NPV) of 88.9%, and with diagnostic accuracy of 76.47%. AUROC of RDW at 24 hours was 0.821 ($p < 0.0001$) for a cutoff of >13 with a sensitivity of 76.67%, specificity of 83.64%, PPV of 71.9%, NPV of 86.8%, and a diagnostic accuracy of 81.18%. AUROC of serum calcium (mg/dL) was 0.870 ($p < 0.0001$) for a cutoff of ≤8.7 with a sensitivity of 83.33%, specificity of 80%, PPV of 69.4%, NPV of 89.8%, and diagnostic accuracy of 81.18%. AUROC for RDW/TSC was 0.884 ($p < 0.0001$) for a cutoff of >1.5 with a sensitivity of 86.67%, specificity of 83.64%, PPV of 74.3%, NPV of 92%, and diagnostic accuracy of 84.71%. AUROC for BISAP was 0.968 ($p < 0.0001$) for a cutoff of >1 with a sensitivity of 96.67%, specificity of 85.45%, PPV of 78.4%, NPV of 97.9%, and diagnostic accuracy of 89.4%. AUROC for MM score was 0.932 (p <

0.0001) for a cutoff of >0 with a sensitivity of 86.67%, specificity of 98.18%, PPV of 96.3%, NPV of 93.1%, and diagnostic accuracy of 94.12%. BISAP index followed by MM score were the best predictors of severity, followed by RDW/TSC ratio. Multivariate regression analysis showed that none of the variables included in our study was an independent significant risk factor for SAP.

Table 2: Receiver operating characteristic curve of RDW, serum calcium, RDW/TSC ratio, BISAP, and MM for predicting SAP

SAP	*RDW at 0 hour*	*RDW at 24 hours*	*Serum calcium (mg/dL)*	*RDW/TSC ratio*	*BISAP*	*MM*
AUROC	0.794	0.821	0.87	0.884	0.968	0.932
SE	0.0598	0.05	0.0403	0.0437	0.0142	0.0322
95% CI	0.693–0.874	0.723–0.896	0.780–0.933	0.796–0.943	0.905–0.994	0.856–0.975
p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Cutoff	>13	>13	≤8.7	>1.5	>1	>0
Sensitivity (95% CI)	83.33% (65.3–94.4%)	76.67% (57.7–90.1%)	83.33% (65.3–94.4%)	86.67% (69.3–96.2%)	96.67% (82.8–99.9%)	86.67% (69.3–96.2%)
Specificity (95% CI)	72.73% (59.0–83.9%)	83.64% (71.2–92.2%)	80% (67.0–89.6%)	83.64% (71.2–92.2%)	85.45% (73.3–93.5%)	98.18% (90.3–100.0%)
PPV (95% CI)	62.5% (45.8–77.3%)	71.9% (53.3–86.3%)	69.4% (51.9–83.7%)	74.3% (56.7–87.5%)	78.4% (61.8–90.2%)	96.3% (81.0–99.9%)
NPV (95% CI)	88.9% (75.9–96.3%)	86.8% (74.7–94.5%)	89.8% (77.8–96.6%)	92% (80.8–97.8%)	97.9% (88.9–99.9%)	93.1% (83.3–98.1%)
Diagnostic accuracy	76.47%	81.18%	81.18%	84.71%	89.41%	94.12%

4. Discussion

In the present study on 85 patients of AP, there was no significant difference between the two groups regarding age. All patients above 70 years had MSAP/SAP. There was no significant association with age in studies by Zhang et al., 7 Gravito - Soares et al., 3 and Peng et al.8 However, age is an important implication in AP as advanced age is associated with more severe form of the disease and worse prognosis.

Our study did not show any gender predilection for SAP. Similar results were observed in studies by Peng et al.8 Zhang et al., 7 and Karabuga et al.9 who did not find any gender differentiation in cases of MAP, MSAP, and SAP.

In our study, alcohol abuse was the most common cause of AP in male patients whereas gallstone pancreatitis was the most common in female patients. Majority of cases were of gallstone origin irrespective of gender in studies by Ye et al.10 and Gülen et al.11 Mean TLC (cell/mm3) in our study was 10247.27 in MAP and 14858.33 in MSAP/SAP which was statistically significant ($p = 0.0004$). Similar results were seen in a study by Bedel et al., 12 wherein mean TLC (per mm3) was 15.2 in nonsurvivors and 12.1 in survivors which was significantly higher in nonsurvivors ($p < 0.05$).

Mean platelet count was 331.7 in nonsurvivors and 253.4 in survivors, respectively ($p < 0.05$). In our study, mean urea in patients with MAP (mg/dL) was 30.47 and in MSAP was 100.07 which was statistically significant ($p < 0.0001$). Mean creatinine (mg/dL) in patients with MAP was 0.72 and in MSAP was 2.25 which was statistically significant ($p < 0.0001$). In a study by Zhang et al., 7 RDW values positively correlated with the patient blood urea nitrogen (BUN) ($p = 0.02$). Mean bilirubin (mg/dL) in patients with MAP was 1.61 and 2.27 in patients with MSAP/ SAP which was not significant ($p = 0.631$). Mean serum glutamic oxaloacetic transaminase (SGOT) (IU/L) was 99.09 in patients with MAP and 89.2 in patients with MSAP/SAP which was not significant ($p = 0.679$). Mean serum glutamic pyruvic transaminase (SGPT) in patients with MAP was 209.16 and 170.37 in patients with MSAP/SAP which was not significant. In a study by Zhang et al., 7 no significant correlation was seen between RDW and alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Red Cell Distribution Width

RDW0h

In our study, RDW was measured in all patients at admission. The median for MAP and MSAP/ SAP was 13 and 15, respectively. The mean of RDW was found to be 12.96 in patients with MAP while it was 15.3 in patients with MSAP/SAP ($p = 0.001$). Significant association was seen in RDW (%) at 0 hour with severity ($p < 0.05$). Similar results were seen in studies by Gravito - Soares et al., 3 Han et al., 13 and Yao and Lv, 14 wherein RDW was significantly higher in patients with MSAP/SAP when compared to MAP. They also observed that in all patients with AP, RDW correlated inversely with calcium, serum albumin, RBC count, and hemoglobin, and directly with age and LDH.

However, contrary results were seen in a study by Gülen et al., 11 who observed that median RDW in mortality and nonmortality groups was found to be statistically nonsignificant ($p = 0.201$). In another study by Ye et al., 10 a regression analysis of RDW as a single predictive factor for severity of AP showed a regression coefficient of 0.177 ($p > 0.05$) with an odds ratio (OR) of 1.193 implying that RDW was not a prediction index of AP severity. However, they attributed this finding to the monocentric nature of the study, the limited sample size, and the regionalism of the case source.

In our study, ROC curve of RDW (Fig.1) at 0 hour for predicting SAP was 0.794 with a sensitivity of 83.3% and specificity of 72.5% for a cutoff of >13 and PPV of 62.5% and NPV of 88.9%. Similarly, Gravito - Soares et al.3 suggested that RDW0h (AUROC: 0.960; $p > 0.001$) was a major predictor of SAP to a cutoff value of 13.0 (sensitivity—92.7%; specificity—84.3%). A study by Peng et al.8 also showed that for RDW cutoff for persistent organ failure in AP of 13.05%, area under the curve (AUC) was 0.791 (sensitivity—97.4%; specificity—55.8%) with a PPV of 0.411 and NPV 0.985 implying that RDW on admission is an

independent prognostic factor for persistent organ failure in AP. Another study by Yao and Lv14 revealed that RDW had a sensitivity of 75% and specificity of 89.8% in predicting mortality and suggested that RDW levels were notably elevated in nonsurvivors of AP compared to both healthy individuals and survivors of AP patients. Similar results were also seen in a study by Zhang et al.7 The AUC for RDW was found to be 0.677 ($p < 0.000$). When RDW was combined with albumin, the AUC increased slightly to 0.693 [95% confidence interval (CI) 0.625–0.761, $p < 0.000$], surpassing the AUC of RDW alone. The optimal cutoff value for RDW to differentiate between MSAP and SAP was determined to be 13.55, with a sensitivity of 54.5% and specificity of 73.6%.

RDW24h

In our study, the mean ± SD of RDW at 24 hours following admission was 12.47 ± 1.35 and 14.79 ± 2.16 in patients with MAP and MSAP/ SAP, respectively ($p < 0.001$). The median was 13 and 15 in MAP and MSAP/SAP, respectively. Significant association was seen in RDW (%) at 24 hours with severity ($p < 0.05$). The AUROC analysis of RDW 24 hours with severity of pancreatitis was 0.821 with a sensitivity of 76.67%, specificity of 83.64%, PPV of 71.9% and NPV of 86.8% for cutoff >13. Study by Gravito - Soares et al.3 showed that RDW24h (%) was 14.3 ± 1.9 and 12.8 ± 0.5 in patients in MAP and MSAP/SAP, respectively ($p < 0.001$). AUROC of RDW 24hrs with severity of AP was 0.848 ($p < 0.001$; cutoff 13.8) suggesting that RDW0h and RDW at 24 hours were excellent predictors of mortality in AP.

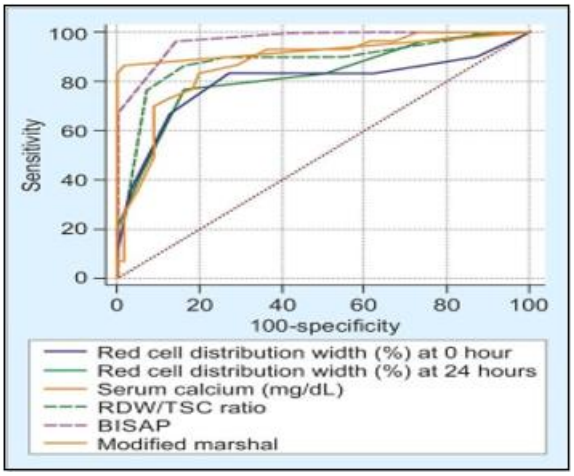

Figure 1: Receiver operator characteristics curves

Total Serum Calcium

In our study, mean ± SD of serum calcium (mg/dL) in MAP was 9.09 ± 0.62 which was significantly higher compared to MSAP/ SAP (8.18 ± 0.57) ($p < 0.0001$). Similar results were seen in a study by Yao and Lv, 14 serum calcium (mmol/L) was found to be 2.11 ± 0.24 and 2.03 ± 0.19 in patients with MAP and MSAP/SAP, respectively ($p < 0.001$). AP with RDW >13.3% had lower levels of calcium and higher mortality (6/8). The nonsurvivors of AP had lower levels of calcium. Regression analysis of a study by Ye et al.10 showed that the regression coefficient of serum calcium was −5.706 ($p < 0.01$) with an OR of 0.003. Multifactor logistic regression analysis showed that serum calcium was an independent predictor of severity of AP.

In a study by Han et al., 13 TSC, in mmol/L was 2.12 ± 0.18 and 1.77 ± 2.74 in patients of MAP and MSAP/SAP, respectively ($p < 0.001$). The TSC in ICU patients was 1.85 while in non - ICU patients was 2.10 and in the survivors and nonsurvivors was 2.09 and 1.83, respectively. Above studies showed similar results comparable to our study.

In our study, AUROC analysis of calcium as a predictor of severity of AP was 0.870 for cutoff of ≤8.7 mg/dL with a sensitivity of 83.33%, specificity of 80%, PPV of 69.4%, NPV of 89.8%, and diagnostic accuracy of 80%. Study by Han et al.13 showed that AUROC for TSC in AP patients of 0.773 in patients requiring ICU admission, and 0.809 in hospital deaths. The ROC AUCs for BISAP, serum calcium, and serum calcium and BISAP were 0.779, 0.797, and 0.852, respectively ($p < 0.01$) in the study by Ye et al.10

Red Cell Distribution Width/Total Serum Calcium Ratio

In our study, mean ± SD of RDW/TSC was 1.38 ± 0.2 and 1.83 ± 0.33 in patients with MAP and MSAP/SAP, respectively. The median RDW/TSC was 1.4 in patients with MAP and 1.8 in patients with MSAP/SAP ($p < 0.001$). GravitoSoares et al.3 also showed a similar RDW/TSC of 1.8 ± 0.4 and 1.3 ± 0.1 in patients with MAP and MSAP/SAP, respectively ($p < 0.001$). A study by Bedel et al.12 showed that RDW/TSC of 2.3 ± 0.5 and 1.7 ± 0.3 in nonsurvivors and survivors, respectively ($p < 0.001$). This was in concordance with our study.

Area under the receiver operating characteristic for RDW/TSC as predictor of severity in AP was 0.884 for a cutoff of >1.5 ($p < 0.001$) with a sensitivity of 86.67%, specificity of 83.64%, PPV of 74.3%, NPV of 92%, and diagnostic accuracy of 84.71%. In study by Gravito - Soares et al., 3 AUROC of RDW/TSC was 0.973 for a cutoff of 1.4 ($p < 0.001$), with a sensitivity of 96.3% and specificity of 84.3% and stated that RDW0h/TSC >1.4 were excellent predictors for AP severity. Han et al.13 showed RDW/TSC AUROC of 0.824 for patients requiring ICU care, 0.768 in patients needing surgery and 0.855 inhospital deaths ($p < 0.001$). Bedel et al.12 showed an RDW/TSC AUROC of 0.880 for a cutoff of >2.0 with a sensitivity of 91.9%, specificity of 81.1%, PPV of 82.9%, NPV of 91.1%, and diagnostic accuracy of 86.5%. These studies were in concordance with our results.

Bedside Index for Severity in Acute Pancreatitis

In our study, the mean BISAP index in patients with MAP was 0.62 ± 0.73, while in patients with MSAP/SAP it was 2.93 ± 0.87, which was significant ($p < 0.0001$). In a study by GravitoSoares et al., 3 mean ± SD of BISAP for MSAP/SAP and MAP was 1.7 ± 0.9 and 1.0 ± 0.7 ($p < 0.001$), respectively. In a study by Ye et al., 10 the regression coefficient for BISAP as single factor of AP severity predictor was 1.373 [standard error (SE) 0.184] with OR of 3.948 ($p < 0.01$).

In our study, AUROC for BISAP as predictor of severity of AP was 0.968 for a cutoff of >1, with a sensitivity of 96.67%, specificity of 85.45%, PPV of 78.4%, NPV of 97.9%, and diagnostic accuracy of 89.41%, showing that it was the best predictor of severity of AP. GravitoSoares et al.3 showed an AUROC for BISAP to be 0.732 for a cutoff of >1.5 with a sensitivity and specificity of 57.3 and 55.1%, respectively.

Modified Marshall Score

In our study, mean MM score in patients with MAP was 0.02 ± 0.13 and 2 ± 1.05 in patients with MSAP/SAP which was statistically significant ($p < 0.0001$). In a study by GravitoSoares et al., 3 mean MM score was 0.0 ± 0.0 in patients with MAP and 0.8 ± 0.7 in patients with MSAP/SAP ($p < 0.0001$).

Area under the receiver operating characteristic for MM score was 0.932 ($p < 0.0001$) for a cutoff of >0 with a sensitivity of 86.67%, specificity of 98.18%, PPV of 96.3%, NPV of 93.1%, and diagnostic accuracy of 94.12%. In a study by Gravito - Soares et al., 3 AUROC of MM score was 0.756 ($p < 0.001$) for a cutoff of 1.0 with a sensitivity of 51.2% and specificity of 100%.

In our study, BISAP index followed by MM Score were the best predictors of severity followed by RDW/TSC ratio. There is always a trade - off between sensitivity and specificity so we chose the variable with the maximum predictive value which in our study was BISAP index. RDW/TSC ratio was a better predictor of AP when compared to serum calcium and RDW at admission and at 24 hours. RDW at 24 hours was a better predictor of severity in AP than RDW at admission. On multivariate analysis, no individual parameter was an independent significant predictor of AP.

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