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The Ratio of Red Blood Cell Distribution Width to Serum Calcium Level in Predicting the Severity of Acute Pancreatitis

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ABSTRACT

Background & Objective: The present study was designed to investigate the ratio of red blood cell distribution width (RDW) to serum calcium level as a predictor of acute pancreatitis severity.

Materials & Methods: In this cross-sectional study, 336 acute pancreatitis patients referred to the emergency rooms of Valiasr and Mousavi hospitals were investigated during the period from 2022 to 2023. Demographic, clinical and laboratory data were obtained from patient records. The data were analyzed using STATA16, and the area under the ROC curve was applied to determine the best cutoff point for the ratio of RDW to serum calcium level.

Results: 188 patients had mild pancreatitis and 148 had moderate/severe pancreatitis. The mean age of patients with mild and moderate/severe acute pancreatitis was 60.22 (±17.84) and 58.68 (±18.53) years, respectively. The frequency of women in mild and moderate/severe pancreatitis was 53.2% and 52%, respectively. The multiple logistic regression model showed that for every one unit increase in the mean RDW to calcium ratio, the odds of developing moderate/severe pancreatitis increased 4.30-fold (OR= 4.30; P<0.001). The best cutoff for the ratio of RDW to serum calcium in predicting moderate/severe acute pancreatitis was 1.69. The sensitivity, specificity, positive predictive value, negative predictive value, and area under the ROC curve for this cutoff were 83.45%, 85.47%, 85.17%, 83.77%, and 0.8698, respectively.

Conclusion: The ratio of RDW to serum calcium can be a rapid, accessible, inexpensive, sensitive, and reliable indicator for predicting the severity of acute pancreatitis.

Keywords: Red Blood Cell Distribution Width (RDW), Serum Calcium, Acute Pancreatitis, Prediction

1. Introduction

One of the important inflammatory diseases of the pancreas that may be associated with fibrosis is acute pancreatitis (AP). Clinical manifestations range from mild attacks of abdominal pain to severe disease. Symptoms of this condition can include hypotension, sepsis, metabolic disorders, third-space fluid accumulation, organ failure, and even death (1, 2). The causes of acute pancreatitis vary depending on the epidemiological characteristics of different regions. In the United States and European countries, most cases of AP are due to alcohol consumption, while in Iran, most cases (50%) of AP are due to gallstones (3, 4). Multiple factors, such as gallstones, bile duct stones, alcohol consumption, trauma, infection, hyperlipidemia, hypercalcemia, ERCP, infections, and medications are involved in its development (5, 6). The highest prevalence is in the 41–50 age group. The incidence of pancreatitis varies greatly

across different countries. Its incidence rate in England and The United States of America is 12 and 79 per 100,000 people, respectively, but there are no accurate statistics for it in Iran (4, 7). Studies have shown that 12-42 % of AP deaths are diagnosed only after autopsy. The basis for the diagnosis of acute biliary pancreatitis is clinical symptoms accompanied by elevated pancreatic enzymes (amylase, lipase, trypsin, and elastase) and sonography to confirm biliary pathology (8, 9).

The death rate for acute pancreatitis has been estimated at about 10%. The high mortality rate of acute pancreatitis has made early diagnosis of the severity of the disease very important for timely decision-making (10). Therefore, various methods have been suggested to determine the prediction of the severity of the disease. Ranson criteria, APACHE, Balthazar, and EWS are among these methods, and each of them uses different types of clinical, laboratory, and imaging criteria. However, each of these criteria has shortcomings that have led to ongoing studies to find the best criteria for diagnosing the severity of the disease (11, 12). Therefore, an ideal system and index for determining the severity and prognosis of the disease should be simple, economical, non-invasive, accurate, and quantitative. Since changes in blood biomarkers begin in the early stages of acute pancreatitis, it seems that these biomarkers can be used as a measure of the severity of acute pancreatitis. Therefore, in recent studies, their measurement has been considered as a criterion for determining the severity of the disease (13, 14).

Among biomarkers, red blood cell distribution width (RDW) is a common parameter of the CBC that measures the heterogeneity of RBC size. This indicator is simple and inexpensive 2 (15). RDW is associated with inflammatory markers such as CRP, interleukin-6, and fibrinogen, which can be a good predictor of the mortality risk of heart and respiratory diseases. However, some studies have shown that RDW and serum calcium (Ca) alone are not used as predictors for acute pancreatitis severity; because these indicators have low accuracy (16, 17). On the other hand, to our knowledge, studies that have examined both parameters simultaneously in predicting the severity of this disease are limited; therefore, our aim was to determine the role of the ratio of RDW to serum calcium level in predicting the severity of AP.

2. Materials and Methods

2.1 Design and subjects

The study was conducted as a census and all patients with AP referred to the emergency room of Valiasr and Mousavi hospitals during 2022-2023 were included (n=336). The inclusion criteria were being suffering from AP and over 18 years old. The exclusion criteria were chronic pancreatitis, history of tumor, pancreatitis caused by a trauma, pregnant mothers, liver failure, history of blood disease and a medical record with incomplete information.

2.2 Data collection

The data were extracted from the patient records by referring to the medical records department of Valiasr and Mousavi hospitals in Zanjan. Then, patients with acute pancreatitis were divided into two groups: mild acute pancreatitis and moderate/severe. The revised Atlanta classification in 2012 was used for the diagnosis and severity of AP.

According to (18), two of the three criteria are required to confirm the diagnosis: 1. Persistent epigastric abdominal pain that may radiate to the back 2. A threefold increase in serum amylase and/or lipase 3. Abdominal imaging findings consistent with AP. Also, mild AP was considered as the lack of organ failure and local or systemic complications. Moderate AP was considered to be the lack of persistent organ failure (<48 hours), and severe AP was considered to be persistent organ failure (>48 hours) (18, 19).

2.3 Statistical analysis

The data were analyzed using STATA 16 software. An independent sample t-test was applied to compare the quantitative variables between the mild and moderate/severe acute pancreatitis groups. A chi-square test was also used to compare the qualitative variables. Then, a multiple logistic regression analysis was carried out to determine the role of the ratio of RDW to calcium level in predicting the severity of AP, and finally the adjusted odds ratio (adjusted OR) with a 95% confidence interval (CI) was calculated. Finally, the area under the ROC curve was applied to determine the optimal cut off point for the ratio of RDW to calcium level in predicting the severity of AP.

2.4 Ethics considerations

Despite the retrospective nature of the study, the researchers committed themselves to adhering to the Declaration of Helsinki. In addition, this study was conducted under the supervision of the Ethics Committee of Zanjan University of Medical Sciences (IR.ZUMS.REC.1403.002).

3. Results

A total of 336 AP patients were investigated, of which 188 had mild AP and 148 had moderate/severe pancreatitis. The mean age of patients with mild and moderate/severe AP was 60.22 (±17.84) and 58.68 (±18.53) years, respectively. The frequency of women in mild and moderate/severe pancreatitis was 53.2% and 52%, respectively. The mean duration of hospitalization was 4.65 (±2.61) and 6.47 (±3.78) days, respectively. The most common etiology in patients with mild and moderate/severe pancreatitis was biliary- related with 60.2% and 56.3%, respectively. The mean serum calcium was 8.35 (±1.36) and 6.12 (±1.53); respectively. The mean RDW was 12.78 (±1.61) and 15.92 (±1.47) in mild and moderate/severe AP, respectively. Additionally, RDW to calcium ratio was 1.53 (±0.27)

and 2.61 (±0.22) in mild and moderate/severe AP, respectively.

The frequency of cardiovascular diseases, hospitalization, alcohol consumption, history of surgery, history of respiratory diseases, hypertension, fatty liver, mortality rate, ICU admission, and need for surgery in moderate/severe AP were significantly higher than mild (P<0.05). Also, the mean laboratory parameters of WBC, FBS, BUN, Cr, AST, ALT, INR, and CRP were significantly higher in moderate/severe AP than mild (P<0.05). The mean serum calcium level in patients with moderate/severe AP was significantly lower than mild (P<0.05). In contrast, the mean RDW and RDW to calcium ratio was significantly higher in moderate/severe pancreatitis than mild (P<0.05) (Tables 1 & 2).

In order to determine the role of the serum RDW to calcium ratio in predicting moderate/severe acute pancreatitis, a multiple logistic regression model was used. The results of this model showed that alcohol consumption, WBC, and RDW to calcium ratio were the most important predictors of acute pancreatitis severity (P-value < 0.05). The odds ratio (OR) for RDW to Calcium ratio was 4.30, indicating that if the effects of other variables remain constant, for every one unit increase in the mean RDW to calcium ratio, the odds of developing moderate/severe pancreatitis increase 4.30 times (Table 3).

The best cutoff for the ratio of RDW to serum calcium in predicting moderate/severe acute pancreatitis was 1.69. The sensitivity, specificity, PPV, NPV, and area under the ROC curve for this cutoff were 83.45%, 85.47%, 85.17%, 83.77%, and 0.8698, respectively (Table 4). Figure 1 also shows the area under the ROC curve.

Table 1. Demographic and clinical characteristics of mild and moderate/severe pancreatitis patients

Variable		Mild pancreatitis (N= 188)	Moderate/severe pancreatitis (N= 148)	P-Value
Age (year)		60.22 (±17.84)	58.68 (±18.53)	0.440
Hospitalization (day)		4.65 (±2.61)	6.47 (±3.78)	<0.001
Sex	Male	88 (48.8)	71 (48)	0.832
	Female	100 (51.2)	77 (52)	
Cardiovascular disease	No	181 (96.3)	116 (78.4)	<0.001
	Yes	7 (3.7)	32 (21.6)	
Bile duct diseases	No	185 (98.4)	143 (96.6)	0.308
	Yes	3 (1.6)	5 (3.4)	
Kidney failure	No	186 (98.9)	145 (98)	0.658
	Yes	2 (1.1)	3 (2)	
Viral diseases	No	184 (97.9)	141 (95.3)	0.244
	Yes	4 (2.1)	6 (4.7)	
Diabetes	No	174 (92.6)	129 (82.7)	0.099
	Yes	14 (7.4)	19 (17.3)	
Hyperlipidemia/hyperglyceridemia	No	174 (92.6)	141 (95.3)	0.307
	Yes	14 (7.4)	6 (4.7)	
History of ERCP	No	180 (95.7)	145 (98)	0.359
	Yes	8 (4.3)	3 (2)	
Vasculitis	No	187 (99.5)	146 (98.6)	0.411
	Yes	1 (0.5)	2 (1.4)	
Stroke	No	187 (99.5)	146 (98.6)	0.411
	Yes	1 (0.5)	2 (1.4)	
Trauma	No	187 (99.5)	146 (98.6)	0.411
	Yes	1 (0.5)	2 (1.4)	

Variable		Mild pancreatitis (N= 188)	Moderate/severe pancreatitis (N= 148)	P-Value
Smoking	No	162 (86.2)	118 (79.7)	0.116
	Yes	26 (13.8)	30 (20.3)	
Alcohol consumption	No	180 (95.7)	127 (85.8)	0.001
	Yes	8 (4.3)	21 (14.2)	
Surgical history	No	151 (80.3)	101 (68.2)	0.011
	Yes	37 (19.7)	47 (31.8)	
Respiratory diseases	No	181 (96.3)	129 (87.2)	0.003
	Yes	7 (3.7)	19 (12.8)	
Gallstones	No	158 (84)	113 (76.4)	0.076
	Yes	30 (16)	35 (23.6)	
History of dialysis	No	187 (99.5)	145 (98)	0.324
	Yes	1 (0.5)	3 (2)	
Thyroid disorders	No	176 (93.6)	130 (87.8)	0.065
	Yes	12 (6.4)	18 (12.2)	

Table 2. Laboratory and biochemical parameters of mild and moderate/severe pancreatitis patients

Variable	Mild pancreatitis (N= 188)	Moderate/severe pancreatitis (N= 148)	P-Value
WBC	11.95 (± 5.50)	24.02 (± 5.27)	0.005
RBC	4.82 (± 0.70)	4.91 (± 0.80)	0.274
HGB	13.80 (± 2.08)	14.08 (± 1.82)	0.208
HCT	40.71 (4.80)	41.37 (± 4.60)	0.206
MCV	84.64 (±7.83)	84.58 (± 8.29)	0.953
MCH	29.92 (±5.27)	28.06 (± 5.06)	0.802
MCHC	33.60 (±2.35)	23.93 (± 1.92)	0.558
PLT	236.82 (± 86.42)	223.71 (± 74.14)	0.143
PDW	13.40 (± 2.40)	13.62 (± 2.30)	0.748
MPV	10.15 (± 0.87)	10.40 (± 0.93)	0.128
FBS	135.89 (± 8.52)	161.06 (± 9.60)	0.033
BUN	16.55 (± 10.01)	23.65 (± 14.97)	0.019
Cr	0.99 (± 0.43)	1.51 (± 0.67)	0.045
AST	116.58 (± 52.91)	196.22 (± 78.76)	0.012
ALT	121.29 (± 72.68)	184.60 (± 92.46)	0.017
Bill T	1.66 (± 0.38)	1.81 (± 0.32)	0.362
Bill D	0.74 (± 0.70)	0.81 (± 72)	0.385
Amylase	1051.95 (± 274.70)	1037.80 (± 258.60)	0.924
CPK	112.74 (± 94.17)	122.52 (± 97.68)	0.421
CK-MB	13.18 (± 7.54)	11.54 (± 7.05)	0.109
LDH	428.94 (± 78.15)	457.12 (± 68.72)	0.445
Mg	2.01 (± 0.41)	2.10 (± 0.39)	0.941

Variable	Mild pancreatitis (N= 188)	Moderate/severe pancreatitis (N= 148)	P-Value
P	3.15 (± 1.12)	3.25 (± 1.17)	0.593
Alb	4.01 (± 0.76)	4/10 (± 0.78)	0.638
Total pro	6.90 (± 0.70)	7.10 (± 0.60)	0.056
Na	139.21 (± 3.111114)	139.37 (± 3.10)	0.644
K	4.01 (± 0.68)	4.11 (± 0.60)	0.669
Triglyceride	202.04 (± 24.80)	268.05 (± 29.90)	0.243
Cholesterol	141.92 (± 44.96)	143.08 (± 41.16)	0.907
HDL	41.72 (± 9.43)	40 (± 10.71)	0.768
LDL	95 (± 34.13)	91.52 (± 32.27)	0.692
CRP	23.69 (± 2.42)	35.03 (± 3.81)	0.044
ESR	28.66 (± 4.14)	30.64 (± 3.84)	0.620
PT	14.11 (± 2.01)	13.84 (± 1.76)	0.213
PTT	33.05 (± 6.26)	32.47 (± 6.13)	0.405
INR	1.11 (± 0.19)	2.18 (± 0.17)	0.036
PH	11.02 (± 5.05)	12.65 (± 7.84)	0.619
PCO2	42.80 (± 10.37)	42.49 (± 14.29)	0.902
PO2	41.18 (± 19.43)	51.02 (± 27.85)	0.064
HCO3	24.30 (± 2.91)	7.10 (± 0.60)	0.626
Calcium	8.35 (± 1.26)	6.12 (± 1.53)	<0.001
RDW	12.78 (± 1.61)	15.92 (± 1.47)	<0.001
RDW to Calcium ratio	1.53 (± 0.27)	2.61 (± 0.22)	<0.001

Table 3. The role of RDW to serum calcium ratio in predicting the severity of acute pancreatitis by multiple logistic regression model

Variable		Adjusted Odds Ratio	CI 95%	P-Value
Age		1.21	0.95 – 1.35	0.062
WBC		1.09	1.02 – 1.13	0.033
FBS		0.99	0.97 – 1.02	0.357
BUN		0.94	0.85 – 1.04	0.215
Cr		0.56	0.07 – 4.34	0.578
AST		0.99	0.92 – 1.05	0.885
ALT		1.05	0.88 – 1.12	0.874
CRP		0.98	0.97 – 1.01	0.163
RDW to Calcium Ratio		4.30	3.45 – 6.84	<0.001
Sex	Male	Reference	-	0.404
	Female	1.42	0.62 – 3.22	
Cardiovascular disease	No	Reference	-	0.820
	Yes	0.82	0.16 – 4.21	

Variable		Adjusted Odds Ratio	CI 95%	P-Value
Hypertension	No	Reference	-	0.326
	Yes	1.66	0.60 – 4.56	
Fatty liver	No	Reference	-	0.541
	Yes	1.33	0.53 – 3.30	
Alcohol consumption	No	Reference	-	0.022
	Yes	2.86	1.25 – 5.85	

PPV: positive predictive value
NPV: negative predictive value

Table 4. Laboratory and biochemical parameters of mild and moderate/severe pancreatitis patients

Cutoff RDW to Calcium	Sensitivity	Specificity	PPV	NPV	Are under ROC curve (95% CI)
1.69	83.45	85.47	85.17	83.77	0.8698 (0.8265 – 0.9131)

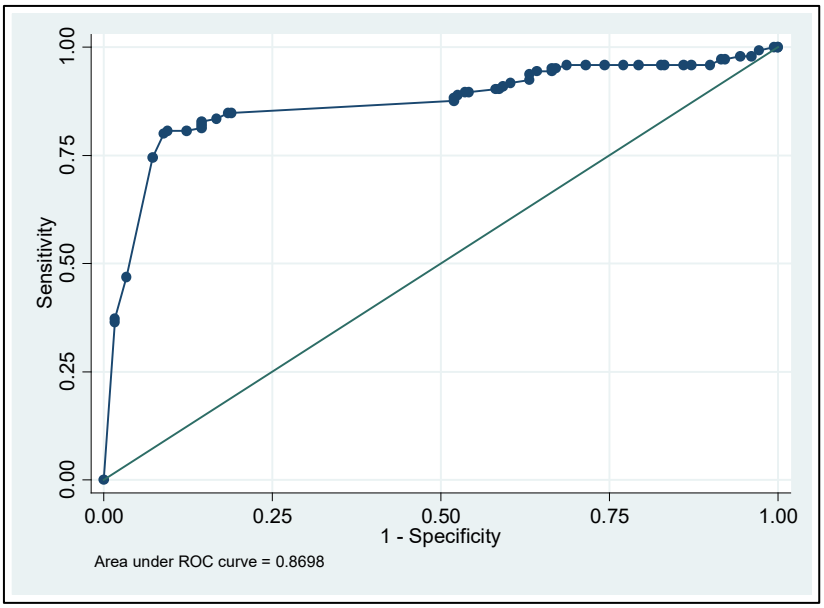

Figure 1. Area under the ROC curve for the best cutoff ratio of RDW to serum calcium in predicting moderate/severe acute pancreatitis

4. Discussion

Early diagnosis of severe AP is of great importance in managing the treatment process, reducing complications, and subsequent deaths (20, 21). Various scoring systems and laboratory markers have been proposed to determine the prognosis of AP, however, none of them have been effective predictors of the severity and outcome of AP (22, 23). Additionally, many biochemical markers have been introduced to determine the severity of AP; however, their use has been challenging due to high costs and low sensitivity (24, 25). In recent years, several clinical signs and imaging procedures have emerged to detect pancreatic necrosis early, monitor its progression, and assess response to the treatment. However, 20-30% of cases of severe AP are misdiagnosed based on clinical, imaging, and biochemical data (26). Important features of an ideal biomarker for predicting the severity and prognosis of AP include being inexpensive, readily available, simple, and insensitive to interindividual differences; however, none have yet been able to predict the severity of AP with sufficient accuracy (27, 28).

Evidence suggests that RDW may be an important prognostic marker for determining the risk of mortality

in patients with pancreatitis, reflecting their inflammatory status (17, 29-31). A systematic review showed that the RDW was independently related to mortality in acute pancreatitis (32). A review of previous studies shows that RDW has been widely used for the differential diagnosis of anemia.

However, in recent years, RDW has been associated with systemic inflammation due to elevated oxidative stress and inflammatory cytokines, increased release of newer and larger RBCs into the peripheral circulation, alterations in membrane glycoproteins and RBC ion channels with subsequent morphological changes (33). However, most previous studies have included RDW only as a predictor of the severity of AP. For example, a study by Han et al (13) in India involving 666 patients with AP showed that AUC for the RDW/Ca ratio (0.912) was significantly greater than the AUC for RDW (0.768) and Ca (0.875) alone. The value of 7.04 with a sensitivity and specificity of 88% and 83%, respectively, was the best cutoff point for the RDW/Ca ratio for predicting severe AP. Finally, this study concludes that RDW/Ca may be used as an accurate marker in predicting AP severity, however, further studies in this area are recommended (13).

A cross-sectional study by Varun Gupta, Narang (14) in India showed that the best cutoff point for the RDW/total serum calcium (TSC) ratio in predicting the severity of AP was 2.42 with sensitivity, specificity, PPV, NPV, and AUC of 100%, 100%, 100%, 100%, and 1.00, respectively. Additionally, the best cutoff point for the RDW/TSC ratio in predicting mortality in AP was 2.90 with sensitivity, specificity, PPV, NPV, and AUC of 100%, 96.6%, 70%, 100%, and 0.975, respectively (14). The latest similar study was a case-control study by Gravito-Soares, Gravito-Soares (34) in Portugal on 312 patients with AP that showed the best cutoff point for RDW in predicting the severity of AP to be 13, with sensitivity, specificity and AUC of 92.7, 84.3% and 0.960, respectively. Moreover, the best cutoff point for RDW/Ca ratio in predicting the severity of AP was 1.4, with sensitivity, specificity and AUC of 96.3, 84.3% and 0.973, respectively. This study suggested that the RDW/Ca ratio is an accessible parameter at admission and can be a good predictor of the severity of AP (34).

Overall, the findings and similar studies suggest that RDW can reflect the degree of inflammation that occurs in AP, and therefore, can be used to predict the severity of the disease. In addition, the ratio of RDW to calcium is an excellent predictor of the severity of AP and its associated mortality. Indeed, hypocalcemia in the first 24 hours is associated with the severity of AP, although its etiopathogenesis is not clearly understood, However, it is hypothesized that hypocalcemia may be related to the formation of calcium soaps and a decrease in parathyroid hormone (35).

The present study had the following limitations: 1- The first limitation was the cross-sectional nature of the study, because in cross-sectional studies, exposure and outcome are examined simultaneously, and cause-and-effect relationships cannot be judged with certainty. Therefore, we need to design cohort and prospective studies to accurately examine cause-and-effect relationships. 2- The possibility of selection bias due to the single-center nature of the study, which could limit the generalizability of the results. 3- The possibility of information bias due to incomplete recording of information in patients' medical records 4- Failure to consider other confounding variables, such as patients' nutritional status or other underlying medical conditions, which could affect RDW and calcium levels and thus influence the relationship between these variables and pancreatitis severity.

Finally, we suggest that future studies investigate the predictive factors of the ratio of RBC distribution width to calcium level in AP. Also, examining the ratio of RBC distribution width to total serum calcium (TSC) level in predicting mortality in AP could be another suggestion.

5. Conclusion

Our study suggests that the ratio of RDW to serum calcium can be a rapid, accessible, convenient, inexpensive, sensitive, and reliable indicator for predicting the severity of AP.

6. Declarations

6.1 Acknowledgments

The authors appreciate the sincere cooperation of the staff of Valiasr and Ayatollah Mousavi hospitals during the conduct of this study.

6.2 Ethical Considerations

The study was approved by the Deputy of Research and Ethics Committee of Zanjan University of Medical Sciences (IR.ZUMS.REC.1403.002).

6.3 Authors' Contributions

Conceptualization, supervision, funding acquisition and resources: Mohsen Salehi and Faezeh Barhgi; Methodology: Kamyar Mansori and Sattar Jafari; Data collection: Faezeh Barhgi; Data analysis: Kamyar Mansouri; Investigation and writing: All authors.

6.4 Conflict of Interest

The authors declare that there are no conflicts of interest.

6.5 Fund or Financial Support

This study was funded by Zanjan University of Medical Sciences, Zanjan, Iran.

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

6.7 Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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