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

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Abstract

Background: Although serum calcium (Ca) and red cell distribution width (RDW) can be used to predict the severity of acute pancreatitis (AP), their sensitivity and specificity are limited. The goal of this study is to see how well the serum calcium ratio of RDW, which may be measured at presenta-tion, predicts the severity of AP in patients with AP.

Materials and methods: AP patients admitted to a tertiary hospital's emergency department between 14 February 2021 and 14 February 2022 were screened retrospectively. According to the 2012 Atlanta classification guidelines, AP severity was classified as mild acute pancreatitis (MAP), moderate acute pancreatitis (MSAP), and severe acute pancreatitis (SAP). During admittance to the emergency department, vital signs, laboratory exams, and imaging findings were gathered from the database.

Results: This study comprised 384 AP patients, including 166 males (56.8%), 239 patients with MAP, and 145 patients with MSAP or SAP. The mean RDW/Ca changes considerably according to pancreatitis severity ($p<0.05$). Pancreatitis severity rises considerably when RDW/Ca value increases (odds ratio: 2.27; lower(95 % CI):1.07; upper(95 % CI):4.83; $p<0.05$).

Conclusion: RDW/Ca can be a valuable indicator to predict the severity of patients with AP.

Keywords: Acute pancreatitis, red cell distribution width, serum calcium, disease severity

Introduction

Acute pancreatitis (AP) is parenchyma inflammation of the pancreas that can cause local and systemic complications[1,2]. Revised Atlanta Classification in 2012 defined mild acute pancreatitis (MAP) as the absence of organ failure and the absence of local or systemic complications. Moderate acute pancreatitis (MSAP) was defined as the presence of local or systemic complications and/or organ failure with no indication of chronic organ failure, whereas severe acute pancreatitis (SAP) was defined as persistent organ failure lasting more than 48 hours[3]. Although the majority of patients have a modest illness, around 20% of AP patients develop a clinical picture linked with mortality and morbidity[4]. Early diagnosis and rapid medical or endoscopic therapy can improve the prognosis in people with fatal or clinically severe AP[5]. As a result, the best marker/prognostic score for diagnosing clinically severe AP should be simple, inexpensive, noninvasive, easily accessible, accurate, and quantitative[5,6]. Many prognostic grading methods and biomarkers have been developed to identify patients with severe and fatal AP in the early stages [4]. However, the majority of them are difficult and cannot be efficiently applied early on. Ranson and Bedside Index severity in AP (BISAP) are the most often utilized grading systems due to their availability within the first 24 hours and ease of evaluation[6].

RDW, a common parameter in the complete blood count test, is a simple, affordable, and widely accessible parameter that evaluates the variance in the size of peripheral red blood cells (RBC)[7]. RDW is linked to elevated inflammatory markers such as interleukin-6, fibrinogen, and C-reactive protein (CRP)[8]. RDW has been demonstrated to be an accurate predictor of death in the elderly and in individuals suffering from a systemic illness[9-11]. It has also been demonstrated that RDW predicts death in AP patients[12]. Low calcium levels have been found to be a significant signal for diagnosing patients with severe AP, risk of mortality, and an indicator of severity[13]. However, several studies revealed contradictory results when evaluating the association between RDW, total serum calcium (TSC),

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and AP-specific prognostic ratings in patients with AP[14,15]. Although RDW and Ca can be used to predict AP severity and death on their own, their sensitivity and specificity are limited.

The purpose of this study was to determine the predictive usefulness of the red blood cell distribution width to serum calcium (RDW/Ca) ratio in determining the severity of acute pancreatitis patients.

Materials and Methods

Study design and settings: This clinical study is a retrospective cohort study conducted in the emergency department of a tertiary hospital. The study was approved by the Local Ethics Commission (protocol code: 29, decision no: 29, issue: E-48670771-514.99 date: 29 February 2022). The institutional review board waived informed consent to conduct this retrospective study. The current study was carried out in accordance with the Helsinki Declaration.

Selection of participants:

Inclusion criteria;

- Age ≥ 18 years;
- Meeting the diagnostic criteria for AP in the 2012 revised international consensus on the classification and definition of Atlanta pancreatitis. According to the revised Atlanta Classification for AP, at least two of the three characteristics are required for diagnosis: persistent abdominal pain and a threefold increase in serum levels of amylase and/or lipase or characteristic findings on abdominal imaging[3,16].

Exclusion criteria;

- Age < 18 years;
- Time from onset of abdominal pain to admission to hospital ≥ 72 hours
- Chronic pancreatitis;
- History of malignant tumor;
- AP resulting from poisoning, surgery, and trauma;
- Postoperative pancreatic lesions;
- Women during pregnancy or perinatal period
- Diseases affecting the hematological system (lymphoma, leukemia, and bone marrow malignancies) or other chronic inflammatory diseases (including tuberculosis, Henoch-Schönlein purpura)
- Chronic use of erythropoietin
- recent history of transfusion
- Complicated with chronic essential liver diseases and kidney failure;
- Missing clinical data and follow-up.

Study protocol

AP patients admitted to a tertiary hospital's emergency department between February 14, 2021, and February 14, 2022 were screened retrospectively. The severity of AP was divided into 3 groups as MAP, MSAP, and SAP using Atlanta classification standards[3]. During admittance to the emergency department, vital signs, laboratory exams, and imaging findings were gathered from the database.

Out-come

The value of RDW's serum calcium ratio (RDW/Ca) in predicting AP severity

Statistical analysis

Parametric tests were used without the normality test due to the Central Limit Theorem compatibility[17]. In the analysis of the data, the mean and standard deviation were used while the continuous data statistics were made in the scales, and the frequency and percentage values were used when defining the categorical variables. The student's t-test statistic is given to compare the means of two independent groups. Chi-square test statistics were used to evaluate the relationship between categorical variables. Risk factors associated with pancreatitis severity were evaluated with an odds ratio and 95% confidence interval. The statistical significance level of the data was taken as $p<0.05$. In the evaluation of the data, www.e-picos.com New York software and MedCalc statistical package program were used.

Results

This study comprised 384 AP patients, including 166 males (56.8 %), 239 patients with MAP, and 145 patients with MSAP or SAP. Table 1 shows the baseline and clinical characteristics of the groups.

The mean RDW/Ca changes considerably depending on the severity of the pancreatitis ($p<0.05$). While RDW/Ca was 1.56±0.22 in patients with mild pancreatitis and 11.63±0.34 in patients with moderate-to-high severity, those with moderate-to-high severity had a higher mean RDW/Ca. The factors affecting the severity of pancreatitis are evaluated in table 2.

It is statistically significant that it is 1.74 times more likely to be male in those with moderate-to-high pancreatitis severity than in those with low pancreatitis severity. (odds ratio:1.74; lower(%95 CI):1.15;upper(%95 CI):2.65; $p<0.05$).

Age, SpO2, HCT, HGB, LYM, MCV, MONO, MPV, NEU, PLT, WBC, GLUCOSE, ALT, AST, ALP, CRP, CA, and RDW factors were found to have no effect on estimating the severity of pancreatitis ($p>0.05$).

As the systolic blood pressure value increases, the severity of pancreatitis decreases significantly. (odds ratio:0.64; lower(%95 CI):0.56;upper(%95 CI):0.71;$p<0.05$).

As the diastolic blood pressure value increases, the severity of Pancreatitis decreases significantly. (odds ratio:0.75; lower(%95 CI):0.71;upper(%95 CI):0.8;$p<0.05$).

Table 1: Difference and Relationship Evaluation of Pancreatitis Severity and Characteristics

		Total (n=384)	MAP (n=239)	MSAP + SAP (n=145)	
Features		x̄±SD	x̄±SD	x̄±SD	**p-value**
Age		62,5±17,8	61,7±17,8	63,8±17,9	0,27
Systolic Blood Pressure(mmHg)		131,25±19	142,68±8,84	112,41±16,95	**<0,0001**
DiastolicBloodPressure (mmHg)		79,63±11,2	86,41±5,48	68,48±9,25	**<0,0001**
Heart Rate(Pulse/min)		95,16±16,04	84,94±8,09	112±10,84	**<0,0001**
Respiratory Rate /min / min(Respiratory/min)		20,2±1,7	19,7±1,8	21,1±1,1	**<0,0001**
Fever(°C)		36,55±0,32	36,47±0,13	36,68±0,47	**<0,0001**
SpO_2(%)		96,04±1,03	95,99±0,62	96,11±1,46	0,27
HCT(%)		40,02±5,53	40,08±5,17	39,94±6,11	0,81
HGB(g/L)		13,31±2,04	13,32±1,91	13,28±2,24	0,85
LYM(10^3mcL)		1,46±0,95	1,51±0,93	1,39±0,98	0,23
MCV(fL)		87,62±6,32	87,36±6,88	88,04±5,27	0,31
MONO(10^3mcL)		0,57±0,31	0,56±0,26	0,61±0,37	0,09
MPV(fL)		10,59±1,32	10,58±1,35	10,61±1,27	0,82
NEU(10^3mcL)		9,52±4,06	9,34±3,79	9,82±4,46	0,25
PLT(10^3mcL)		248,67±83,49	249,28±82,51	247,69±85,37	0,86
WBC(10^3mcL)		11,69±4,11	11,53±3,84	11,96±4,51	0,32
Glucose(mg/dL)		145,78±69,61	142,3±57,88	151,51±85,43	0,21
ALT(U/L)		178,28±148,08	195,13±165,48	150,97±120,29	**0,04**
AST(U/L)		186,59±180,89	198,13±154,48	167,73±135,24	0,17
Albumin(g/dL)		40.18±5.81	40.76±5.48	39.23±6.23	**0,01**
ALP(U/L)		190,02±138,25	178,92±131,59	208,33±148,56	0,24
Creatinine(mg/dL)		1,23±1,02	1,04±0,83	1,54±1,32	**<0,0001**
Na(mmol/L)		137,49±4,78	138,02±3,91	136,64±5,85	**0,006**
Ure (mg/dL)		46,81±35,84	40,92±23,25	56,56± 38,68	**0,001**
CRP(mg/L)		38,35±29,99	35,94±30,21	42,27±40,56	0,32
CA(mg/dL)		9,04±0,73	9,09±0,62	8,98±0,87	0,13
RDW(fL)		14,23±1,73	14,13±1,41	14,41±2,14	0,12
RDW/Ca		1,59±0,28	1,56±0,22	1,63±0,34	**0,03**
		n(%)	n(%)	n(%)	
Gender (famela/male)	Famela Male	218(56,8) 166(43,2)	148(61,9) 91(38,1)	70(48,3) 75(51,7)	**0,009**
Mortality (No/Yes)	No Yes	361(94) 23(6)	239(100) -	122(84,1) 23(15,9)	**<0,0001**

Student's t / Chi-square p<0.05 significance
SpO_2: Blood oxygen saturation, **HCT:** Hematocrit, HGB: Hemoglobin, **LYM:** lymphocyte, **MCV:** Mean cellular volume, **MONO:** monocyte, MPV: mean platelet volume, **NEU:** Neutrophil, **PLT:** Platelets, **WBC:** White blood cells**, ALT: Alanine** aminotransferase, **AST:**Aspartate aminotransferase, **ALP:** Alkaline phosphatase, **Na:** sodium, **CRP:** C reactive protein, **CA:** Calcium, **RDW:** Red Cell Distribution Width)

As the heart rate value increases, the severity of pancreatitis increases significantly (odds ratio:1.33; lower(%95 CI):1.26;upper(%95 CI):1.42;p<0.05).

As the respiratory rate value increases, the severity of pancreatitis increases significantly. (odds ratio:1.76; lower(%95 CI):1.52;upper(%95 CI):2.04;p<0.05).

As the fever measurement value increases, the severity of pancreatitis increases significantly. (odds ratio:17.11; lower(%95 CI):5.03;upper(%95 CI):58.16;p<0.05). In other words, it can be said that a 1 unit increase in the fever measurement value increases the severity of pancreatitis 17.11 times.

As the albumin value increases, the severity of pancreatitis decreases significantly. (odds ratio:0.96; lower(%95 CI):0.92;upper(%95 CI):0.99;p<0.05).

As the creatinine value increases, the severity of pancreatitis increases significantly. (odds ratio:1.39; lower(%95 CI):1.14;upper(%95 CI):1.69;p<0.05).

As the Na value increases, the severity of pancreatitis decreases significantly. (odds ratio:0.94; lower(%95 CI):0.89;upper(%95 CI):0.98;p<0.05).

As the urea value increases, the severity of pancreatitis increases significantly. (odds ratio:1.02; lower(%95

Table 2: Relationship between baseline variables and Pancreatitis Severity (n = 384)

Variable	Odds Ratio	Lower (%95 CI)	Upper (%95 CI)	p-value
Age	1,01	0,99	1,02	0,26
Gender	1,74	1,15	2,65	**0,009**
Systolic Blood Pressure(mmHg)	0,64	0,56	0,71	**<0,0001**
Diastolic Blood Pressure (mmHg)	0,75	0,71	0,8	**<0,0001**
Heart Rate(Pulse/min)	1,33	1,26	1,42	**<0,0001**
Number of Breaths(Respiratory/min)	1,76	1,52	2,04	**<0,0001**
Fever (°C)	17,11	5,03	58,16	**<0,0001**
SpO2(%)	1,12	0,92	1,37	0,27
HCT(%)	0,99	0,96	1,03	0,81
HGB(g/L)	0,99	0,89	1,09	0,85
LYM(10^3mcL)	0,87	0,69	1,09	0,23
MCV(fL)	1,02	0,98	1,05	0,31
MONO(10^3mcL)	1,76	0,9	3,46	0,09
MPV(fL)	1,02	0,87	1,19	0,82
NEU(10^3mcL)	1,03	0,98	1,08	0,25
PLT(10^3mcL)	1,01	0,99	1,02	0,86
WBC(10^3mcL)	1,03	0,98	1,08	0,32
Glukose (mg/dL)	1,02	0,99	1,03	0,21
ALT(U/L)	0,98	0,97	1,01	0,06
AST(U/L)	0,99	0,98	1,02	0,17
Albumin (g/dL)	0,96	0,92	0,99	**0,01**
ALP(U/L)	0,99	0,98	1,01	0,25
Creatinine(mg/dL)	1,39	1,14	1,69	**0,001**
NA(mmol/L)	0,94	0,89	0,98	**0,008**
URE(mg/dL)	1,02	1,01	1,03	**0,004**
CRP(mg/L)	1,01	0,99	1,02	0,32
Ca(mg/dL)	0,8	0,6	1,07	0,12
RDW(fL)	1,1	0,97	1,24	0,13
RDW/Ca	2,27	1,07	4,83	**0,03**

** It is significant at the p<0.05 level. (Odds ratio)*
SpO_2: blood oxygen saturation, **HCT**: Hematocrit, **HGB**: Hemoglobin, **LYM**: lymphocyte, **MCV**: average volume, **MONO**: monocyte, **MPV**: mean platelet volume, **NEU**: Neutrophil, **PLT**: Platelets, **WBC**: White blood cells, **ALT**: Alanine aminotransferase, **AST**: Aspartate aminotransferase, **ALP**: Alkaline fosfataz, **Na**: sodium, **CRP**: C reactive protein, **CA**: Calcium, **RDW**: Red Cell Distribution Width)

CI):1.01;upper(%95 CI):1.03;p<0.05).

As the RDW/Ca value increases, the severity of pancreatitis increases significantly. (odds ratio:2.27; lower(%95 CI):1.07;upper(%95 CI):4.83;p<0.05). In other words, it can be said that a 1 unit increase in the RDW/Ca value increases the severity of pancreatitis 2.27 times.

Discussion

AP has an important place in gastrointestinal system emergencies. Although the majority of AP patients have a modest and favorable prognosis, people with a severe clinical course who suffer organ failure (OF) account for around 20-30%

of all AP patients[18]. The development of OF in individuals with AP has a significant impact on their clinical course and death[5,19-22]. As a result, it demonstrates the critical need of identifying predictors of illness severity and mortality in AP. Several grading methods have been developed to define individuals with AP who are at high risk of morbidity and death[6]. Ranson and BISAP are two commonly used scoring systems[6,23].

The accuracy of Ranson and BISAP scores was determined to be 0.69 and 0.74, respectively[6]. At presentation, the prognosis of severe AP (e.g. MSAP and SAP) is still difficult to predict. Because major AP problems develop as a consequence of a worsening of pre-existing morbidity upon hospitalization[24]. As a result, serum indicators such as RDW, hematocrit, creatinine, BUN, TSC, lactate, and CRP have been intensively researched for early detection of severe AP (ie MSAP and SAP) and improved prognosis[5,25-28].

RDW, which has been linked to high levels of inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and interleukin (IL), has been recognized as a significant prognostic factor for AP mortality risk[8,29-31]. AP may raise RDW levels by boosting inflammatory cytokines, which limit erythrocyte maturation and hasten the entrance of immature erythrocytes into the peripheral blood circulation[32]. RDW was shown to be independently linked with AP mortality in a comprehensive study[33].

The majority of AP-related mortality occurs in patients with severe AP, implying that, in addition to predicting mortality in AP, finding predictors of AP severity is critical[5,21]. In our study, all 23 patients who died had MSAP-SAP. Another research indicated that RDW, unlike TSC, was not a predictor of AP severity, while being a more helpful sign of AP severity than serum glucose or serum calcium[14,15]. In our study, no significant difference was found in terms of RDW, calcium and glucose averages, and pancreatitis severity. ($p>0.05$). However, the RDW/Ca mean differed significantly according to the severity of Pancreatitis. ($p<0.05$).

Hypocalcemia in AP patients frequently means the development of pancreatic parenchymal tissue necrosis, indicating the probability of SAP. According to one study, there is a link between the severity of AP and the degree of calcium clearance[34].

Serum calcium levels are often low during pancreatitis, and the presence of hypocalcemia is factored into the AP prognostic score system[35]. Hypocalcemia in AP patients frequently implies pancreatic necrosis, which is a significant predictor of the potential of SAP. A study found that the blood calcium level in MSAP and SAP patients was significantly lower than in MAP patients[36]. In our study, there was no significant relationship between mean serum calcium and pancreatitis severity ($p>0.05$). Research demonstrated a substantial and independent connection between RDW/TSC ratio and AP mortality, with a 0.820 AUROC[37]. Furthermore, in determining AP mortality, this research was shown to be superior to the RDW/TSC ratio and RDW conventional prognostic ratings at admission[37]. A study evaluating the usefulness of RDW/Ca within 24 hours for predicting MSAP and SAP found that RDW/Ca (AUC = 0.912) had better predictive power than single factors in predicting MSAP and SAP in acute pancreatitis[37]. RDW (AUC = 0.768, $P < 0.05$) and Ca (AUC = 0.875, $P < 0.05$)[24]. In addition, this study demonstrated that RDW/Ca is an independent risk factor for clinical worsening in AP. APACHE-II scoring system, Ranson scoring system, etc. Compared with RDW/Ca, there was a significant advantage in the early prediction of clinical worsening[36]. In our study, the severity of pancreatitis increases significantly as the RDW/Ca ratio increases (odds ratio:2.27; lower(%95 CI):1.07;upper(%95 CI):4.83;$p<0.05$). In other words, a 1 unit increase in RDW/Ca value increased the severity of pancreatitis 2.27 times.

The severity of pancreatitis increases dramatically as the fever measurement value rises. (odds ratio:17.11; lower(%95 CI):5.03;upper(%95 CI):58.16;$p<0.05$). With the increase in the severity of pancreatitis, fever occurs secondary to the increased inflammation. Therefore, fever is an important parameter as an indicator of severity.

Limitations

There are some limitations to our study. Some patients were not included in the study because of the patients whose data could not be accessed in the registry system and the patients who were referred to other hospitals. In addition, RDW samples were collected from a single center and therefore there may have been minor differences in RDW levels in other populations studied. Future prospective and multicenter studies are needed for more reliable results.

Conclusion

RDW and TSC are simple, inexpensive, non-invasive, and quantitative serum indicators that are included in complete blood count and biochemistry tests and are therefore easily accessible at the time of admission. In conclusion, RDW/Ca be a valuable indicator to predict the severity of patients with AP.

Ethics Committee Approval: *The study was approved by Prof.Dr.Cemil Taşcıoğlu City Hospital Ethics Committee and the requirement for informed consent was abandoned (protocol code: 29, decision no: 29, issue: E-48670771-514.99 date: 29 February 2022). The present study was conducted in line with the Declaration of Helsinki.*

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