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Comparison of RDW PLR value with CRP and NLR values in patients with postoperative leakage and abscess after pancreatectomy

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Abstract

Aim: New studies show red cell distribution width (RDW) to be altered by inflammatory cell wall changes in acute pancreatitis, sepsis and critical illness. We aimed to evaluate the efficacy of RDW, platelet lymphocyte ratio (PLR) and neutrophil lymphocyte ratio (NLR) values in patients who underwent pancreatectomy.

Materials and Methods: Fifty patients who underwent pancreatectomy were retrospectively compared. The study group consisted of patients who were followed up with clinical or laboratory evidence of either leakage or infection, with proof of infection being culture positivity and associated fever, tachycardia, and elevated laboratory values. The control group, on the other hand, comprised of 25 patients with uneventful postoperative course. RDW, neutrophil, platelet (PLT), aspartate aminotransferase (AST), alanine transaminase (ALT), C reactive protein (CRP), PLR and NLR values of the patients were compared among and between groups at 4 different time points (1: admission, 2: postoperative first week prior to infection, 3: at the time of infection and 4: discharge).

Results: Statistically significant results were obtained for ALT, CRP, neutrophil, and PLR ratios (p=0.003, p=0.002, p=0.028, p=0.032, respectively). Significant differences were also observed in RDW 2, RDW 3 and RDW 4 (p=0.034, p=0.010, p=0.031, respectively). Regarding CRP levels, significant differences were found for CRP 1 and CRP 3 levels (p=0.001, p=0.025, respectively). A significant difference was detected only for the PLR 4 value (p=0.009).

Conclusion: In patients who underwent pancreatic resection and were suspected of having infection that progressed to a septic state, the levels of RDW, CRP, PLT, and PLR were observed to be correlated with infection and increased at various intervals before the culture results and evidence of infection emerged. Due to their association with the emergence of infections, these parameters have been proven to be effective and affordable tools in clinical decision-making.

Introduction

Rapid and efficient intervention during the development of infection in postoperative patients has a direct impact on their recovery and survival. It is crucial to identify and intervene during the onset of the inflammatory process before it advances to sepsis. Additionally, the early detection and intervention of the inflammatory process in frail and elderly patients enhance survival rates and reduce hospitalization length.

Red cell distribution width (RDW) measures the heterogeneity (anisocytosis) of circulating red blood cell (RBC) width. It can be easily, quickly and inexpensively determined by all modern devices. Recent studies have found that inflammatory signals from acute pancreatitis, sepsis and critical illness alter the RBC cell walls leading to changes in RDW. Additionally, changes in cell wall structure affect RDW [1-2]. RDW is cost-effective compared to other specific laboratory tests and are easy to incorporate into daily practice because they are already a part of routine complete blood count (CBC) tests.

Elevation of RDW post-operation has been linked to poor prognosis through various mechanisms. Although the precise pathophysiology is not known, evidence suggesting a link between RDW and inflammation hints at its association with systemic inflammatory response syndrome and associated markers of inflammation [3-4]. Inflammatory

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processes directly affect the blood-forming stem cells in the bone marrow, which control the production of RBCs. Changes in the erythrocyte membrane lead to an increase in the RDW's measurable size spectrum.

Platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) have also been evaluated in several studies as indicators of infection severity and prognosis [5]. The aim of this study was to examine the potential of RDW, PLR, NLR values in identifying infectious processes in patients who have undergone pancreatic surgery resulting in abscess and/or anastomotic leakage during the postoperative phase, in comparison to established parameters [6-8].

Materials and Methods

Twenty-five patients who underwent pancreatic resections (Whipple procedure, distal or total pancreatectomy) at our tertiary university hospital and had infection between the first and second week of hospitalization proven by their intra-abdominal or catheter culture positivity and were later followed up with clinical or laboratory findings of either a leak or infection with accompanying fever, tachycardia, and worsening of laboratory values were compared with 25 patients in the control group who were discharged with no infection. Ege University ethics committee approved this study with the file number 23-9T/41 on 07.09.2023.

Age, sex, type of operation, length of hospital stay, presence of at least one recurrent postoperative fever (above 38°C), tachycardia, persistent peripancreatic drainage (more than 3 weeks), increased amylase level in drainage fluid (3 times higher than serum level), red blood cell distribution width, white blood cell count, C-reactive protein, aspartate transaminase, alanine transaminase, platelet count, and neutrophil values of all patients were analyzed retrospectively from electronic medical records.

Pancreatic leakage was defined as the presence of postoperative recurrent fever, tachycardia, and persistent drain leakage with elevated amylase levels. All patients were operated due to malignancy and were followed up for a period of minimum 9, maximum 44 months. Patients with clinically insignificant leaks that showed elevated amylase levels without persistence or any accompanying signs of infection, as wel as group C patients with organ failure or need for reoperation, in accordance with the international Study Group for Pancreatic Surgery (ISGPS) definition of pancreatic fistula were excluded from the study. Our study group consisted of patients who could be categorized as group B with present clinical signs of leak and complicating infection [9].

After initial review, 66 patients who underwent pancreatic resection between 2020 and 2022 at our tertiary university hospital were identified. Of these, 16 did not meet our inclusion criteria, and were thus excluded. The study includes 50 eligible patients. Twenty-five patients were monitored after surgery for either pancreatic leakage or abscess in the radiology imaging with culture-proven infection according to the inclusion criteria, while the remaining twenty-five patients served as the control group with an uneventful postoperative course.

White blood cell (WBC), C reactive protein (CRP), aspartate aminotransferase (AST), alanine transaminase (ALT), RDW, platelets, neutrophils, and platelet and neutrophil counts, and PLR, NLR values of the patients were analyzed at 4 different time points (1: admission, 2: postoperative first week prior to infection, 3: at the time of infection, and 4: discharge), PLR as well as NLR values were computed and their correlations were compared. The relevant parameter at a certain time interval was appropriately shortened, for example, the CRP level at admission is abbreviated as CRP1, and the RDW value at the time of infections is shortened to RDW3.

Statistical analysis

The data obtained was analyzed with the Statistical Package for the Social Sciences, version 26.0 (IBM SPSS Corp., Armonk, NY, USA). Normality of continuous data was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For comparisons between two independent groups, normally distributed data were analyzed using Student's t-test, while non-normally distributed data were subjected to the Mann-Whitney U-test. Categorical data were compared using the chi-squared test. In cases where more than two dependent groups were present, the Friedman test was employed, with Wilcoxon rank tests used to identify differences between subgroups. Cox regression test was used to analyze the relation between the parameters and a longer duration of hospitalization. Throughout the study, a p-value <0.05 was considered as statistically significant.

Age, sex, type of operation, hospital stay were compared between groups. RDW, WBC, CRP, AST, ALT, PLT, neutrophil counts and calculated PLR-NLR ratios at four different time points were analyzed to investigate any relationship with pancreatic leakage and/or infection within group. Wilcoxon rank test and Friedman test were used to identify time-based differences within-group for RDW1-2-3-4, WBC 1-2-3-4, CRP 1-2-3-4, AST 1-2-3-4, ALT 1-2-3-4, platelets, neutrophils counts and calculated PLR 1-2-3-4, NLR 1-2-3-4 ratios. The same procedure was applied to the control group. Mann-Whitney U test was used to identify any difference between study and control group. Cox regression test was used the determine the effect of all parameters on prolongation of hospital stay.

Results

In the study group there were 20 male (40%) and 5 female (10%), while in the control group there were 17 male (34%) and 8 female (16%) and there was no statistically significant difference between groups (p=0.333).

The mean age in the study group was 59,52 (±5,95), while it was 60,44 (±7,76) in the control group. There was no statistically significant difference between groups in terms of age (p=0.641)

In the study group, 16 patients had Whipple surgery (32%), 4 had total pancreatectomy (8%), and 5 had distal pancreatectomy (10%). In the control group, 13 patients (26%) had undergone Whipple surgery, 7 had (%14) total pancreatectomy and 5 patients (10%) had distal pancreatectomy. There was no statistically significant difference between groups in terms of type of operation (p=0.569)

Table 1. Comparison of parameters over four different time periods in the study group.

		IQR 25th	MEDIAN	IQR 75th	
RDW1	25	13.9000	15.0000	16.8000	p=0.449
RDW2	25	14.2000	15.2000	17.8000	
RDW3	25	14.5000	15.4000	18.8000	
RDW4	25	14.7500	15.4000	17.2500	
AST 1	25	22.0000	45.0000	82.5000	p=0.134
AST 2	25	24.5000	42.0000	48.5000	
AST 3	25	14.5000	21.0000	95.0000	
AST 4	25	16.0000	30.0000	46.0000	
ALT 1	25	25.0000	50.0000	118.0000	**p=0.003**
ALT 2	25	37.0000	48.0000	80.5000	
ALT 3	25	17.5000	31.0000	76.0000	
ALT 4	25	14.0000	25.0000	37.0000	
CRP 1	25	12.1000	30.1000	97.4150	**p=0.002**
CRP 2	25	25.8200	138.3500	172.9000	
CRP 3	25	48.7500	75.4600	216.0000	
CRP 4	25	9.9750	31.7100	91.0650	
WBC 1	25	6.3500	9.1100	14.2350	p=0.138
WBC 2	25	6.1700	9.2400	14.6000	
WBC 3	25	6.7850	10.2000	12.7400	
WBC 4	25	6.6050	8.3100	10.7150	
NEUTROP 1	25	3.5300	6.0200	11.9700	p=0.028*
NEUTROP 2	25	4.0900	8.8200	12.3850	
NEUTROP 3	25	5.3100	5.7500	11.3600	
NEUTROP 4	25	3.4100	5.1000	7.5200	
PLT 1	25	209.0000	287.0000	430.5000	p=0.073
PLT 2	25	172.5000	233.0000	325.0000	
PLT 3	25	165.5000	231.0000	322.5000	
PLT 4	25	197.0000	230.0000	342.5000	
PLR 1	25	22.3497	35.6295	45.0217	p=0.032*
PLR 2	25	16.6369	24.0587	42.3708	
PLR 3	25	15.4568	20.3777	33.5370	
PLR 4	25	20.7216	29.1415	37.9282	
NLR 1	25	.5981	.6853	.8347	p=0.078
NLR 2	25	.6495	.7897	.8683	
NLR 3	25	.5358	.7526	.8514	
NLR 4	25	.5161	.6113	.7678	

1: Admission, 2: Pre-infection, 3: During infection, 4: At discharge
*Posthoc tests showed no significant association in pairwise comparisons.

When the length of stay was investigated, the median duration for hospitalization was 30 days [28,12-45,24] in the study group, and the median hospitalization was 16 days in the control group [16,30-25,78]. This difference of longer hospitalization in the study group was found statistically significant (p=0.003).

RDW, AST, ALT, CRP, WBC, PLT, PLR, and NLR values were assessed at four different time points (hospitalization, pre-infection, infection, discharge) for both the study and control groups who underwent pancreatectomy. Both within and between group analyses were conducted. RDW, AST, ALT, CRP, WBC, PLR, NLR neutrophils, platelets (PLT), values of infection group are summarized in Table 1, and sub-analysis of values found to be different during hospital stay are shown in Table 2.

Table 2. Subgroup analysis of statistically significant parameters in the study group.

ALT 1-2	p=0.527
ALT 2-3	p=0.356
ALT 3-4	p=0.113
ALT 1-4	**p=0.008**
CRP 1-2	p=0.058
CRP 2-3	p=0.819
CRP 3-4	**p=0.002**
CRP 1-4	p=0.456

1: Admission, 2: Pre-infection, 3: During infection, 4: At discharge.

In the study group with infection, we observed significant differences in ALT, CRP, neutrophil count, and PLR ratios within the study group (p=0.003, p=0.002, p= 0.028, p=0.032, respectively), while RDW, AST, WBC, PLT, and NLR ratios did not differ significantly (p=0.449, p=0.134, p=0.138, p=0.073, p=0.078). ALT, CRP, neutrophil count, and PLR ratios exhibited statistically significant changes over time as patients stayed in the hospital after the operation. Culture positivity in samples resulted within one week after collection and therefore these parameters can help predict the occurrence of leakage and infected collections.

Since significant changes were found in the study group's ALT, CRP, neutrophil counts, and PLR ratio during the hospital stay, the difference between the two different sample time periods was evaluated. The levels of ALT between hospitalization (ALT1) and discharge (ALT4) showed a significant difference (p=0.008), while no significant differences were observed in the other time periods. A significant difference (p=0.002) was found between the levels of CRP at infection and discharge,while no difference was found in the other time periods. Although there was statistical significance in the neutrophil and PLR values over time, no statistically significant difference was found in the two pairwise comparisons between the hospitalization-pre-infection-infection-discharge periods (Table 2).

We also monitored these values in the control group to determine any additional differences and potential correlations. In the control group, we observed significant differences in CRP, WBC, neutrophil counts, platelet counts, PLR ratio, and NLR ratio (p=0.002, p=0.006, p=0.019, p<0.001, p<0.001, p=0.003, respectively). However, we found no significant differences in RDW, AST, and ALT values (p=0.259, p=0.081, p=0.230, respectively). Changes in the WBC, neutrophil count, and CRP levels in the control group may be linked to the surgical stress, as these markers significantly increased from the time of hospital admission to one week post-operation. Furthermore, these changes decreased significantly between the two-week mark and pre-discharge. Two groups, the study group with leakage/infection and control group, were compared and we found significant differences between groups in the values of CRP1-3 (p=001, p=0.25), PLT1-3-4 (p=0.003, p=0.013, p=0.002), RDW2-

Table 3. Comparison of parameters between the study and control groups.

	INFECTION (MEDIAN – IQR)	CONTROL (MEDIAN – IQR)	P value
AST 1	45 [60.50]	56.72 [57.50]	0.218
AST 2	42.00 [24.00]	32.00 [57.00]	0.845
AST 3	21.00 [80.50}	26.00 [27.50]	0.923
AST 4	30.00 [30.00]	20.00 [36.50]	0.362
ALT 1	50.00 [93.00}	24.00 [72.00]	0.277
ALT 2	48.00 [43.50]	45.00 [110.50]	0.522
ALT 3	31.00 [58.50]	35.00 [70.00]	0.669
ALT 4	25.00 [23.00]	28.00 [29.50]	0.801
WBC 1	9.11 [7.89]	7.87 [3.09]	0.200
WBC 2	9.24 [8.43]	11.68 [7.87]	0.190
WBC 3	10.20 [5.96]	10.73 [5.58]	0.509
WBC 4	8.31 [4.11]	8.05 [7.16]	0.884
NEUTROP 1	6.02 [8.44]	5.61 [2.27]	0.535
NEUTROP 2	8.82 [8.30]	8.65 [7.97]	0.337
NEUTROP 3	5.75 [6.05]	7.53 [4.76]	0.648
NEUTROP 4	5.10 [4.11]	5.95 [5.25]	0.528
NLR 1	0.68 [0.24]	0.69 [0.16]	0.839
NLR 2	0.79 [0.22]	0.81 [0.19]	0.808
NLR 3	0.75 [0.32]	0.71 [0.17]	0.839
NLR 4	0.61 [0.26]	0.61 [0.18]	0.516

1: Admission, 2: Pre-infection, 3: During infection, 4: At discharge.

3-4 (p=0.034, p=0.014, p=0.031), and PLR4 (p=0.009).

The factors that changed over time along with the hospital stay in the study group and the factors that did not change over time were compared with those in the control group. No statistically significant difference was found between the two groups in AST, ALT, WBC, neutrophil count, and NLR ratio. The corresponding parameters are summarized in Table 3.

On the other hand, while there was no significant difference between the two groups in RDW 1 (p=0.123), statistically significant differences were found in RDW 2, RDW 3, and RDW 4 (p=0.034, p=0.010, p=0.031, respectively). For CRP levels, CRP 1 and CRP 3 levels showed a significant difference between the two groups (p=0.001, p=0.025, respectively). CRP 2 and CRP 4 levels did not show a significant difference (p=0.299, p=0.479, respectively). For platelet levels, PLT 1, PLT 3 and PLT 4 levels showed a significant difference between the two groups (p=0.003, p=0.013, p=0.002, respectively), while no significant difference was found for PLT 2 (p=0.705). In PLR values, a significant difference was found only in PLR 4 (p=0.009) and no significant difference was found in PLR 1, PLR 2, PLR 3 (p=0.090, p=0.273, p=0.059, respectively). The associated parameters are summarized in Table 4.

Cox regression test was used to analyze the change of parameters in relation with length of stay in the hospital. It was found that RDW3, WBC3, neutrophil3, and NLR4 values were statistically significant and associated with a longer hospitalization (p=0.002, 0.015, 0.017, 0.007, respectively).

Table 4. Statistically significant parameters between the study and the control group.

	INFECTION (MEDIAN – IQR)	CONTROL (MEDIAN – IQR)	P value
RDW1	15.00 {2.90]	13.70 [2.90]	0.123
RDW2	15.20 [3.60]	13.90 [2.75]	**0.034**
RDW3	15.40 [4.30]	14.00 [2.05]	**0.010**
RDW4	15.40 [2.50]	14.47 [2.50]	**0.031**
CRP 1	30.10 [85.32]	3.96 [85.32]	**0.001**
CRP 2	138.35 [147.08]	69.21 [164.95]	0.299
CRP 3	75.46 [167.25]	56.42 [99.47]	**0.025**
CRP 4	31.71 [81.09]	44.49 [86.11]	0.479
PLT 1	287 [221.50]	223 [75.00]	**0.003**
PLT 2	233 [152.50]	219 [107.00]	0.705
PLT 3	231 [157.00]	335 [282.50]	**0.013**
PLT 4	230 [145.50]	428 [266.00]	**0.002**
PLR 1	35.62 [22.67}	26.66 [9.59]	0.090
PLR 2	24.05 [25.73]	18.66 [19.45]	0.273
PLR 3	20.37 [18.08]	31.04 [18.70]	0.059
PLR 4	29.14 [17.21]	43.11 [30.11]	**0.009**

1: Admission, 2: Pre-infection, 3: During infection, 4: At discharge.

Discussion

Conventional markers of inflammation such as white blood cell count, CRP, and erythrocyte sedimentation rate are commonly employed in clinical practice. However, while providing guidance in the case of infection, these traditional markers have low sensitivity and specificity, and do not provide actionable insights for rapid intervention and treatment revision in patients with sepsis. While parameters such as procalcitonin, galectin-3, interleukin-6, interleukin-8, and tumor necrosis factor-alpha have diagnostic value for sepsis, they are costly and not widely available for routine use. In patients who have undergone a major surgery, such as pancreatic surgery, the course of infection may be more catastrophic and can lead to high mortality. Without evidence of the causative pathogen and a bacteriogram showing its susceptibility to specific drugs, infectious disease specialists are often hesitant to initiate broad-spectrum antimicrobial therapy. Delaying for culture results, particularly in patients undergoing high-stress procedures like pancreatic surgery, leads to a postponement in preventing unfavorable consequences.

Sepsis is a disease with high mortality and morbidity, the pathogenesis of which is not fully understood. Current theories suggest that it is characterized by an excessive release of cytokines as a result of stimulation of the immune system against endogenous or exogenous pathogens. Endothelial injury is a result of excessive cytokine release. Impaired organ function and hypoperfusion arise from endothelial damage. Because the inflammatory process progresses so quickly in septic patients, the treatment requires a rapid and effective change without waiting for the results of blood, urine or sputum cultures. If the treatment of these patients is not modified as promptly as possible, the septic process can result in organ dysfunction and organ failure, and the infectious process can result in the patient's death [10-12]. In addition to traditional inflammatory markers including CRP, white blood cell, neutrophil and lymphocyte counts in the complete blood count, we also examined RDW, NLR and PLR values and their variations throughout 4 different time intervals. In a comparative manner, these parameters were studied primarily at the time of hospitalization, secondarily in the pre-infection period, in the post-infection recovery period, and in the discharge period. Our study group consisted of patients with a confirmed infection, while our control group consisted of patients who had undergone pancreatic surgery and were discharged without any complications.

Our study showed that the RDW in the study group with infection did not result in a statistically significant difference during the hospital stay within group, while the RDW at periods 2,3,4 (pre-infection, during the infection, at the time of discharge) displayed a significant difference in comparative studies between the control and study groups. Thus, it may be concluded that RDW could serve as a valuable predictive indicator or warning signal prior to the positive growth of cultures. Although our results did not allow us to determine the exact timing and underlying causality of RDW's response to infection, it is evident that RDW undergoes changes in the presence of infection. Therefore, it is recommended to monitor RDW and incorporate it into clinical practice.

There was a notable disparity in CRP levels between the two groups at the periods of hospitalization and infection. It was discovered that the relationship between CRP levels measured in the preoperative period and CRP levels at the time of infection in the hospital stay of current patients may be an early indicator of postoperative infection before culture results are determined. Additionally, the difference between the two groups in platelet levels at the time of hospital infection and discharge was also considered valuable in hospital stay.

Significant increases and decreases in CRP values were observed in both groups over time during CRP evaluation. A significant difference was found between the two groups, particularly in CRP values at the time of hospitalization and infection. Additionally, during PLT evaluation, there were no significant fluctuations observed over time within study group with infection. However, the control group showed significant changes during hospitalization-discharge and infection-discharge time periods within group. The lack of change in the study group during similar time periods suggests a link to the inflammatory process caused by the leak/infection. Indeed, a statistical difference was observed in PLT values at the time of hospitalization, infection, and discharge between the study group and the control group. However, there was no notable difference found in the change of RDW during the hospital stay within both groups. When evaluating the control and study groups together, a difference in RDW values was observed before infection, at infection, and at discharge. While RDW did not significantly change over time in within group in hospital stay for both group, the statistically significant difference between groups indicates that RDW values may serve as an early warning for leakage/infection, without awaiting culture results.

Significant changes in PLR were observed at various points in time during the evaluation process. Nevertheless, there was a noticeable difference in the values of PLR upon discharge when comparing the changes between the two groups. Since there were significant changes observed within the group during the course, but only a statistically significant difference was found in the discharge values when compared to the control group, it would be incorrect to consider it a warning factor for infection. Future prospective studies with a larger sample size are needed for further examination.

There is a need for a reliable, rapid and cost-effective method for prompt diagnosis and monitoring of sepsis. This parameter will have an impact on the reduction of the length of stay in the intensive care unit and the reduction of the mortality rate. RDW is both an effective and inexpensive parameter for determining prognosis during patient postoperative hospital stay. The normal range of RDW may vary depending on gender, age, race and the machine utilized. The low end of the range lies at 11.5% and the high end at 15%. While a drop in RDW may not be clinically meaningful, a rise in RDW usually is. The cause of the increase is the degradation of cell membrane structure of mature red blood cells and the early release of reticulocytes into circulation [13-15]. RDW has long been used to diagnose thalassemia and iron deficiency anemia, however, recent research indicates that it may also serve as a monitoring tool for non-hematologic conditions including cardiovascular disease, autoimmune disease, and sepsis. Although the exact timing and underlying causality of why and how RDW responds to infection could not be deduced from our findings, it is evident that RDW changes in the presence of infection and should therefore be monitored and incorporated into clinical practice. We have shown the statistically significant change in RDW, CRP, PLT and PLR levels in patients progressing to sepsis. The application of a composite of these markers in a rating system or mathematical model warrants further investigation.

Conclusion

In patients with suspicion of having an infection and developing sepsis, the levels of RDW, CRP, PLT, and PLR are found to correlate with infection and increase at different time intervals before culture results and infection evidence are present in patients who have undergone pancreatic resection. To establish RDW, CRP, PLT and PLR parameters as diagnostic markers, that are easy to use in the clinic due to their low cost and wide application, prospective studies with large sample sizes are necessary.

Ethical approval

Ege University ethics committee approved this study with the file number 23-9T/41 on 07.09.2023.

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