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Original Article

Prognostic Value of Initial Red Cell Distribution Width and its Platelet-derived Ratio in Critically Ill Adult Patients

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ABSTRACT

Background: Increased red cell distribution width (RDW) reflects a severe dysregulation of erythrocyte homeostasis and has been linked to poor prognosis in various clinical hematological and non-hematological conditions. Additionally, the RDW to platelet ratio (RPR) is a novel inflammatory index and has gained considerable attention as a prognostic marker on critically ill patients.

Aim: Evaluation of the prognostic usefulness of RDW and its derived ratio (RPR) at the time of admission in patients of intensive care units (ICU).

Methods: This prospective cohort study was conducted on 42 patients admitted to the medical ICU of the internal Medicine Department, at Zagazig University Hospitals, during the period from October 2022 to March 2023. The baseline RDW and RPR were measured and patients were followed during the hospital stay then divided into 2 groups according to the survival outcome and proper statistical analyses were used for the detection of the prognostic relevance of the studied parameters.

Results: The optimal cutoff of RDW for prediction of mortality was 16.25 ($p<0.05$), while the RPR was 0.0723 and Higher RDW was significantly associated with lower overall survival ($p= 0.025$), and on multivariate analysis was the only factor significantly associated with mortality ($p= 0.002$), whereas the RPR did not affect the patient outcome.

Conclusion: RDW is an affordable CBC-based parameter that can be used as an independent predictor of mortality in critically ill ICU patients.

Keywords: Red Cell Distribution Width, RDW to platelet ratio, Critically Ill, mortality

INTRODUCTION

The red cell distribution width (RDW) is considered a CBC-derived parameter that can reflect RBCS anisocytosis and is usually used to differentiate types of anemia, particularly iron-deficiency anemia [1].

Its prognostic value was demonstrated in different conditions including community-acquired pneumonia, septic shock, acute kidney injury (AKI), pulmonary hypertension, pulmonary embolism, peripheral artery disease, and cardiovascular disorders [2-4].

The mechanism by which the RDW indicates mortality is not fully elucidated and the high oxidative state linked to the release of inflammatory cytokines, may explain the raised levels of RDW due to iron immobilization in these different conditions [5], suggesting its value in demonstrating the

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presence of an underlying, intricate hyper-inflammatory pathologic process [6].

Platelets provide a fundamental linkage between coagulation and inflammation, and Changes in both RDW and platelet count are complementary rather than isolated and considered as important components of hematological pathophysiology in the course of critical illnesses. In addition, a novel risk predictor known as the RDW-to-platelet ratio (RPR) has been linked recently to the prognosis of a variety of disorders and is thought to be a simple measure of inflammation [7].

To the best of our knowledge, there is a lack of prospective cohort studies that evaluate both the RDW and RPR in adult critically ill patients with no agreement on the cutoff value for detection of mortality especially in the Egyptian population.

So, our work aims to evaluate the prognostic value of RDW and its platelets-derived ratio (RPR) in assessing the adverse outcomes in ICU patients and to define their best cutoff value for the detection of mortality.

METHODS

This prospective cohort study was carried out in the medical ICU of Internal Medicine and clinical pathology departments, Faculty of Medicine, Zagazig University, during the period from October 2022 to March 2023 and included a total of 42 critically ill adult patients.

Pregnant females, patients receiving blood transfusion in the three months preceding the ICU admission, and those maintaining on immunosuppressive therapy were excluded from the study.

Samples:

Peripheral blood samples were collected from all patients at the time of presentation. Venous blood samples were aseptically withdrawn from each patient. One ml of the sample was delivered into a sterile container

containg EDTA for complete blood count (CBC) examination, and 1.5 ml was delivered into a plan vacutainer tube for analysis of liver and kidney function tests. 2 ml was delivered into a citrated vacutainer for analysis of PT/INR and PTT..

Methods:

Participants enrolled in the study were subjected to the following: full history taking, clinical examination and proper radiological assessment as abdominal ultrasonography. Complete blood count was identified by cell counter (Sysmex XN1000, Japan), liver and kidney function tests were done on Cobas 6000 auto analyzer (Roche diagnostic, Germany), and PT/INR, PTT were measured on blood coagulation analyzer, model CA1500 (Sysmex, Japan).

Additionally, the RPR was calculated by dividing the RDW (%) by the platelet count (109/L) [7].

Also, the Illness severity was assessed using the sequential organ failure assessment score (SOFA), which provides a simple method of assessing and monitoring organ dysfunction in critically ill patients giving a score based on the data obtained in each category [8].

Besides, the Glasgow coma scale (GCS), which is the most widely used tool for measuring the disturbance in the level of consciousness was used [9].

Ethical approval:

Informed written consents were taken from all the patients and the study's ethical principles were following the Declaration of Helsinki. Also, approval of the ethical committee in the Faculty of Medicine, Zagazig University was done (ZU- IRB#:9359-27-3-2022).

Statistical analysis:

Analysis of data was performed using the SPSS computer program, version 26. Qualitative data were compared by χ2-test. While, quantitative data were compared by Mann– Whitney and t-tests. Shapiro-Wilk test was used to test data distribution and normally distributed data was expressed as mean ± Standard Deviation (SD), while the non-normally distributed data was expressed as median (range). Spearman's, test was used for correlations. The receiver operating characteristic curve (ROC) analysis was used to detect a best cutoff value for the prediction of hospital mortality. Kaplan-Meier method was used to estimate survival. A $P<0.05$ was considered statistically significant, and a $P<0.001$was highly significant.

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RESULTS

This prospective cohort study was carried out on 42 critically ill adult patients, including 16 (38.1%) males and 26 (61.9%) females, their ages ranged from 38 to 78 years and 9 (21.4%) patients were smokers. In addition, the mean values ± SD for the SOFA score and RDW were 7±2 & 15.71 ± 2.16, respectively, whereas the median value (range) for the RPR was 0.07 (0.06 – 0.11), other baseline clinic-laboratory data are presented in table 1.

The main patient comorbidities included diabetes mellitus and hypertension (each represents 38.1% of cases), followed by cardiac diseases (31%), whereas other comorbidities include chronic kidney diseases (CKD) (14.3%), chronic liver diseases (CLD) (7.1%), COPD (7.1%), cancer (4.8%) and rheumatoid arthritis (4.8%.)

The RDW had a statistically significant positive correlation with age, RPR, TLC, ANC and MCHC. On the other hand, there was a statistically significant negative correlation with hematocrit, hemoglobin and MCV [Table 2].

By applying linear regression analysis for factors correlated to the RDW, only MCHC and PTT (p= 0.001& p=0.002, respectively) had a statistically significant association [Table 3].

The RPR had a statistically significant positive correlation with age, INR, mean platelets volume (MPV), absolute lymphocytic count (ALC), and MCHC. On the other hand, there was a statistically significant negative correlation with absolute monocytic count (AMC), platelets to lymphocyte ratio (PLR) and hemoglobin.

Among factors correlated to the RPR, the PLR, ALC, AMC, hemoglobin and ejection fraction ($p<0.001$, $p<0.001$, $p<0.001$, $p=0.01$ & $p=0.026$, respectively) had a statistically significant association [Table 3].

The best cutoff value of RDW for prediction of mortality among critically ill patients using the ROC curve was ≥16.25 with the area under curve (AUC) 0.767, sensitivity 66.7%, specificity 76.7%, positive predictive value 53.3%, negative predictive value 85.2%, and overall accuracy 73.8% (p= 0.008). while, the optimal cutoff of RPR was ≥0.0723 with the AUC 0.614, sensitivity 58.3%, specificity 56.7%, positive predictive value 35%, negative predictive value 77.3%, and an overall accuracy of 57.1% ($p>0.05$) [Figure 1].

Regarding survival, 12 out of 42 patients (28.5%) didn't survive after the ICU admission, while 30 patients (71.5 %) survived and were discharged. The non-survivors were slightly older, had more co-morbidities and higher SOFA score and RPR than the survivors although not reaching a statistically significant level. However, the RDW was significantly higher among the non-survivors (p= 0.012) [Table 4]. In addition, the higher RDW was found to have a significant association with lower overall survival (OS) (p= 0.025), as by the Kaplan-Meier analysis. While the RPR and OS were not significantly associated [Table 5 and Figure s1].

Finally, by using the Cox regression analysis for the prediction of mortality among critically ill patients, the higher RDW was found to significantly increase hazard by 2.1 folds and is the only independent predictor of mortality (p= 0.002), while other parameters including the RPR did not reach such significance [Table 6].

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Table (1): Baseline clinic-laboratory data of the studied group.

Parameter	Value
	Mean ± SD
Age (year)	58.24 ± 19.98
Sex **Female** **Male**	 26 (61.9%) 16 (38.1%)
Smoking: **No** **Yes**	 33 (78.6%) 9 (21.4%)
SOFA:	7 ±2
laboratory data:	
Hemoglobin (g/dl)	10.52 ± 2.42
Platelet	214.79 ± 95.21
Hematocrit	28.2 ± 10.27
MCV	75.16 ± 8.54
MCH (pg)	26.06 ± 3.04
MCHC (g/dl)	33.98 ± 3.55
RDW (%)	15.71 ± 2.16
	Median (Range)
RPR	0.07 (0.06 – 0.11)
TLC	10.5(7.9 – 16.8)
ANC	7.55(6 – 11.7)

RDW: Red cell Distribution Width, RPR: red blood cell distribution width-to-platelet ratio, TLC: Total leucocytic count, SD: standard deviation, SOFA: sequential organ failure assessment score, ANC: Absolute Neutrophil count, MCV: Mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration.

Table (2): Correlation between RDW and different clinic-laboratory parameters of the studied group

	R	P
Age (years)	0.334	0.002
Ejection Fraction	-0.221	0.159
INR	0.172	0.276
Albumin	-0.224	0.154
Total protein	-0.104	0.513
Total bilirubin	0.206	0.191
ALT	0.16	0.312
AST	-0.012	0.941
Creatinine	-0.187	0.236
ICU stay (days)	-0.014	0.929
GCS	0.143	0.365
SOFA	0.018	0.911
RPR	0.374	<0.001
TLC	0.324	0.003
ANC	0.32	0.003
Hemoglobin	-0.396	<0.001
Hematocrit	-0.559	<0.001
MCV	-0.469	<0.001
MCH (pg)	-0.039	0.726
MCHC (g/dl)	0.417	<0.001

R: Pearson correlation coefficient, *p<0.05: statistically significant, **p≤0.001: statistically highly significant TLC: Total leucocytic count, ANC: Absolute Neutrophil count, SOFA: sequential organ failure assessment score, GCS: Glasgow Coma Scale, RDW: Red cell Distribution Width, RPR: RDW to platelet ratio, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, INR: international normalized ratio.

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Table (3): Linear regression analysis of factors affecting the RDW and RPR.

		Unstandardized Coefficients		Standardized Coefficients	P	95.0% Confidence Interval
		β	Slandered Error	Beta		
RDW	(Constant)	-1.23	3.600		0.733	-8.518 to 6.047
	MCHC #	0.28	0.078	0.474	0.001**	0.130 to 0.445
	PTT #	0.22	0.068	0.415	0.002*	0.083 to 0.359
RPR	(Constant)	0.458	0.059		<0.001**	0.338 to 0.578
	PLR #	-0.001	0.000	-0.704	<0.001**	-0.001 to 0.000
	ALC #	-0.053	0.007	-0.942	<0.001**	-0.067 to -0.040
	AMC #	0.020	0.004	0.457	<0.001**	0.011 to 0.028
	Hemoglobin #	-0.007	0.003	-0.243	0.01	-0.012 to -0.002
	Ejection fraction % #	-0.002	0.001	-0.217	0.026*	-0.003 to 0.000

#: t independent sample t test *P<0.05: statistically significant, **P≤0.001: statistically highly significant, AMC: Absolute Monocytic count, RDW: Red cell Distribution Width, RPR: RDW to platelet ratio, MCHC: Mean corpuscular hemoglobin concentration, PLR: Platelet lymphocytic Ratio, PTT: partial thromboplastin time.

Table (4): Comparison of the clinic-laboratory data in both patient groups according to the survival

	Non- survivors	Survivors	p
	Mean ± SD	Mean ± SD	
Age (years) *	63.17 ± 13.12	56.27 ±22.02	0.22
Sex: * **Female** **Male**	 9 (75%) 3 (25%)	 17 (56.7%) 13 (43.3%)	0.316
Comorbidities:			
Diabetes *	5 (41.7%)	11 (36.7%)	>0.999
Hypertension *	7 (23.3%)	9 (30%)	0.158
CLD *	1 (8.3%)	2 (6.7%)	>0.999
COPD *	1 (8.3%)	2 (6.7%)	>0.999
Cardiac *	6 (50%)	7 (23.3%)	0.091
Cancer * **CKD *** **Rheumatoid Arthritis ***	2 (16.7%) 3 (25%) 1 (8.3%)	0 (0%) 3 (10%) 1 (3.3%)	0.024**
SOFA: *	8 ± 1	6 ± 1	0.655
Hemoglobin *	9.36 ± 2.35	10.98 ± 2.33	0.048**
Hematocrit *	20.79 ± 12.91	31.16 ± 7.36	0.02**
RDW *	17.31 ± 2.51	15.07 ± 1.65	0.012**
Platelet count *	200.08 ± 93.82	220.67 ± 96.71	0.533
	Median (Range)	Median (Range)	p
RPR #	0.075 (0.06 – 0.135)	0.068 (0.054 – 0.1)	0.254
Creatinine #	1.35(0.65 – 3.3)	1.13(0.7 – 1.7)	0.817

*: t independent sample t test, #: Mann Whitney test, **p<0.05: statistically significant
RDW: Red cell Distribution Width, RPR: RDW to platelet ratio, SD: standard deviation, SOFA: sequential organ failure assessment score, CLD: Chronic liver disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease.

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Table (5): Kaplan– Meier survival analysis illustrating hospital survival time differences in patients as regard the RDW and RPR.

	Total	Events (Non survivors)	Censored (survivors)	Mean ± SE (Days)	95% Confidence interval	P
RDW:						
≥16.25	15	8	7(46.7%)	11.31 ± 1.37	8.64 – 13.99	0.025*
<16.25	27	4	23(85.2%)	17.17 ± 1.23	14.77 – 19.58	
RPR:						
≤81.11	18	9	9(50%)	13.66 ± 1.51	10.71 – 16.62	0.161
>81.11	24	3	21(87.5%)	15.03 ± 1.05	12.97 – 17.09	
Total	42	12	30	15.03 ± 1.12	12.84 – 17.22	

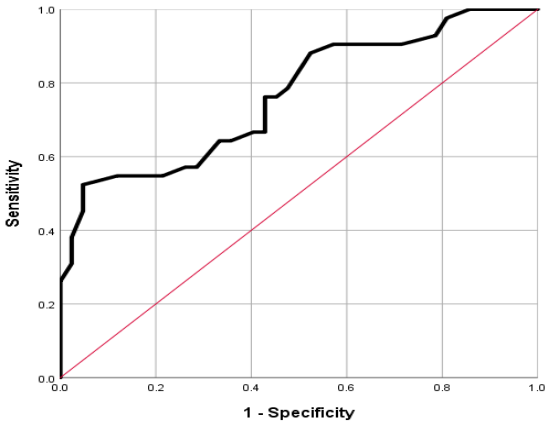
*p<0.05: statistically significant, SE: Standard Error, RDW: Red cell Distribution Width, RPR: RDW to platelet ratio.

Table (6): Regression analysis of predictors of mortality among critically-ill patients:

	B	P	HR	95.0% CI	
				Lower	Upper
PDW	-0.061	0.061	0.941	0.882	1.003
MPV	0.596	0.061	1.814	0.974	3.38
RDW	0.742	0.002*	2.1	1.314	3.357
PRP	-3.969	0.366	0.091	0	103.29
PLR	-0.006	0.481	0.994	0.978	1.011

HR: Hazard ratio, CI: confidence interval, *p<0.05: statistically significant, PDW: Platelet distribution width, MPV: mean platelet volume. RDW: Red cell Distribution Width, RPR: RDW to platelet ratio, PLR: Platelet lymphocytic Ratio.

RDW



(B) RPR

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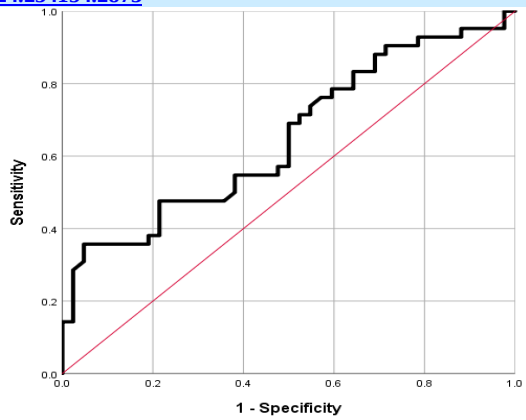

Figure (1): ROC curve showing performance of (a) RDW (B) RPR in prediction of mortality among critically ill patients.

DISCUSSION

The RDW has been identified as a predictive factor in patients with peripheral artery disease, cardiovascular illness, septic shock, acute renal damage, pulmonary hypertension, and various malignant conditions, such as multiple myeloma and solid cancers [10,11]. In addition, the RPR arises when incorporating the RDW and platelets and has been used as an indicator of systematic inflammatory response [12].

The current work represented one of few studies evaluating the prognostic value of both the RDW and RPR in critically ill patients at the time of admission to the medical ICU in a cohort-prospective manner.

In our study, the RDW had a statistically significant positive correlation with age, RPR, TLC, ANC and MCHC and a negative correlation with hematocrit, hemoglobin and MCV and this was in agreement with Vaya et al. [13] who found that RDW was correlated directly with age and inversely with hematologic parameters.

Also, Solak et al. [14] agreed with us in demonstrating the significant positive correlation between RDW and age, TLC and MCHC. However, in contrast to our finding, the hematocrit, hemoglobin, and MCV had a positive correlation with the RDW and this difference might be due to the impact of renal impairment on their selected patients.

While there was no significant correlation between the RDW and SOFA score in our study, confirming the need to incorporate other clinical and laboratory measures to fully assess the severity of the patient's disease and provide an explanation for the exclusion of the RDW as an indicator in the SOFA score.

Our results showed that the best cutoff values of the RDW and RPR in the prediction of mortality among critically ill patients were 16.25 and 0.0723, respectively. However, Jiayuan et al [7] detected these values as 16.25 and 0.0723, respectively, with slightly higher sensitivity and specificity and this is explained by the difference in sample size between the 2 studies and confirming the value of larger studies in better accuracy of results.

Regarding the survival rate, 28.5% of our patients didn't survive after the ICU admission, while 71.5 % survived & discharged and this was different from Safdar et al [15] who found the death rate among the ICU patients was only 19.8% and this might due to difference in patient co-morbidities, disease severity and the level of medical care provided to the patients. However, both studies found that The RDW was significantly higher among the non-survivors group and this suggests the poor outcome of high RDW on the mortality of ICU patients.

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Furthermore, to confirm this effect, the higher RDW was found to be associated with significantly lower OS and interestingly, by using the Cox regression analysis, the higher RDW was found to significantly increase hazard by 2.1 folds and is the only independent predictor of mortality.

Those findings provide RDW as a valid predictor of the prognosis in critical illness and that was consistent with Zhang et al, [2] and Wang et al [5], who reported that OS was significantly shorter with higher RDW.

Also, Vashistha et al., [16]; Zhang et al., [17] and Odutayo et al., [18] agreed with these results and reported that high RDW was an independent predictor of long-term outcomes in the critically ill patients.

According to Han et al., [19], the addition of RDW improves the hospital mortality predictive accuracy of disease severity scores such as the acute physiology score III (APS III) and others. Furthermore, Sun et al., 2023 [20] demonstrated its ability to predict the all-cause mortality of the critical illness and this was independent of severity scores [20].

Additionally, a study by Wang et al., [21] reported that the RDW had superior short-term prognostic value over the APS III and SOFA scores in critically ill patients.

It was uncertain to determine the potential mechanisms by which the RDW affects prognosis in critical illness. Lippi et al, [22] detected several parameters, including age, anemia, renal function, and inflammatory response that had an impact on RDW and these elements might mediate the relationship between the RDW and critical illness prognosis. Disturbance in erythrocyte biology led to increased RDW and was a significant factor in the onset and progression of various disorders, including cancer, heart failure, and liver disease.

The iron metabolism and bone marrow function were suppressed during the process of inflammation and that affects the proliferation and maturation of erythrocytes causing a rise in RDW values [23]. Meanwhile, the systemic inflammatory response syndrome values were increased in the high RDW group. Therefore, RDW could predict the prognosis of critical illness partially by reflecting the levels of inflammation [24].

In our study, the RPR level didn't differ in the survivors from the non-survivors and wasn't found to have a significant relation with OS and this was consistent with Zhang et al, [2] and Wang et al, [5]. Who reported that there was a non-significant relation between OS and RPR.

On the other hand, Liu et al., [25], Tong et al., [26] and Wu et al., [7] found that elevated RPR levels were significantly associated with in-hospital mortality in patients with sepsis, acute myocardial infarction and AKI, respectively. The discrepancy between these studies and the current results might be attributed to the difference in study design, as they were retrospective analyses done on a larger number of patients with differences in the distribution of patient subclasses regarding the critical illness and the RPR cutoff value for prediction of mortality.

Despite the value of the current study, There were some limitations, such as being conducted in a single center on a relatively limited number of patients with a small follow-up period, lack of correlation with other inflammatory markers (e.g. procalcitonin, C-reactive protein, atrial and brain natriuretic peptides) to provide better data about the inflammatory status of the patients and lack of assessment of the dynamic changes in the studied parameters after treatment and stabilization of the critical care condition.

CONCLUSION

RDW is a feasible parameter that can be easily obtained from the CBC and was significantly found to be higher in the non-survivor critically ill ICU patients and considered an independent predictor of mortality, while the RPR lacks this prognostic significance.

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We recommended using the RDW at the time of admission to the ICU as an effective tool for early prognostic assessment to help ameliorate crucial decisions about proper patient management.

Authors' Contributions

HE: designed the study, as well as writing this manuscript in a proper scientific manner with assistance from AE & NZ. AE: performed the statistical analysis, results' interpretation, patients' clinical assessment and follow-up. AF, NZ, AE & HE were responsible for planning, organizing, and reviewing the final manuscript. NZ performed the Laboratory measurements. All authors discussed the results and commented on the manuscript and contributed to the writing of the final manuscript.

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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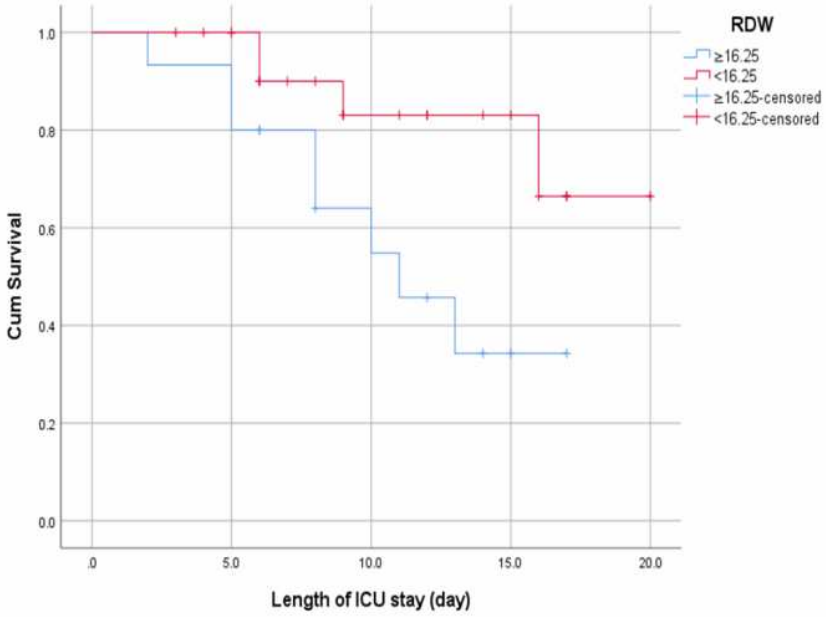

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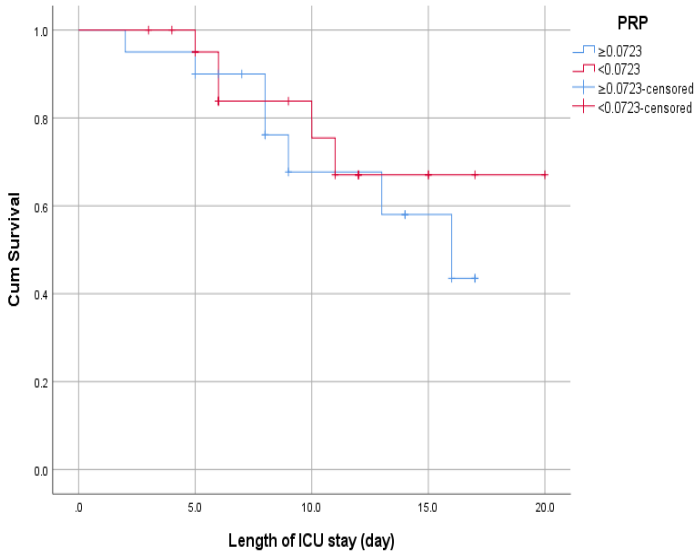

Figure (S1): Kaplan– Meier survival curves illustrating hospital survival time differences (days) in patients as regard RDW and RPR

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