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Red blood cell distribution width as a prognostic factor in critically ill dogs

M. Garcia Arce, A. Gow, I. Handel, W. Ngoi, E. Thomas

ABSTRACT

Objective: To evaluate the association between red blood cell distribution width (RDW) and in-hospital mortality, length of hospitalization and leukocyte count in critically ill dogs.

Design: Retrospective study.

Setting: University teaching hospital.

Animals: One hundred and twenty-seven dogs admitted to the ICU from December 2016 to April 2017. Patients were included if they had a CBC performed within the first 24 hours of admission.

Interventions: None.

Measurements and Main Results: The overall in-hospital mortality rate was 29% (37/127) and median length of hospital stay was 3 days (IQR 1-6). The median RDW value was 13.8% (IQR 13.1-14.7%; reference range 11.9-14.5 %). The canine acute patient physiologic and laboratory evaluation (APPLE) fast score was calculated in 81/127 (64%) patients, the median score was 24/50 (IQR 20-29). There was no significant correlation between RDW and APPLE fast score ($P = 0.163$). Sub-group analysis was performed according to the following diagnostic categories: abdominal (36%; 46/127), hematological (13%; 16/127), respiratory (13%; 16/127), neurological (12%; 15/127), cardiovascular (11%; 14/127), integument (3%; 4/127), trauma (3%;

4/127), musculoskeletal (2%; 3/127) and other (7%; 9/127). Elevated RDW was not associated with in-hospital mortality overall ($P = 0.381$) nor in any individual sub-group analysis. No association was found between length of hospitalization and RDW values in either survivors ($P = 0.548$) or non-survivors ($P = 0.083$). The correlation between RDW and leukocyte count was non significant ($P = 0.12$).

Conclusions: In this study admission RDW was not associated with in-hospital mortality or length of hospitalization in critically ill dogs. The correlation between RDW and leukocyte count was non significant.

Abbreviations

APACHE II: Acute physiology and chronic health evaluation II

APPLE: Acute patient physiologic and laboratory evaluation

CRP: C-reactive protein

IQR: Interquartile range

MCV: Mean corpuscular volum

PIM-2: Pediatric Index of Mortality 2

RDW: Red blood cell distribution width

SAPS: Simplified Acute Physiology Score

INTRODUCTION

Red blood cell distribution width reflects erythrocyte heterogenicity providing a quantitative measure of anisocytosis¹. This parameter is calculated automatically by

dividing the standard deviation of erythrocyte volume by the mean corpuscular volume (MCV). This number is then multiplied by 100 and expressed as a percentage which indicates the degree of variation in the erythrocyte volume compared to MCV, which is a measure of the mean volume of the erythrocyte population². Thus, the higher the RDW, the greater the size variability which generally indicates defective erythropoiesis, reduced RBC lifespan, or premature release of reticulocytes³.

Although originally used as an index for regenerative anemia in both human⁴ and veterinary medicine⁵, in humans RDW has also been proposed as a predictive biomarker of adverse outcome in multiple conditions and different groups of diseases⁶ such as cardiovascular disease^{2,7-9}, cancer^{10,11}, sepsis¹²⁻¹⁴ and critical illness¹⁵⁻²¹. Moreover, several studies have found an association between RDW and all-cause mortality²²⁻²⁴. Although the physiologic mechanisms that underlie the association between RDW and outcome remain unknown, inflammation has been proposed as the main contributing factor and RDW has been associated with an increased C-reactive protein (CRP) level^{12,18,25} and leukocyte count^{7,12}.

Erythropoietin regulates production, maturation and viability of RBCs and is one of the main determinants of RDW⁶. Proinflammatory cytokines impair the erythropoietin-induced maturation process of the RBCs²⁶ affecting the differentiation and proliferation of erythroid progenitors in the bone marrow, shortening erythrocyte life-span and causing functional and structural alterations in the RBC contributing to an increase in RDW²⁷.

Other factors such as oxidative stress, malnutrition, dyslipidemia, abnormal erythropoietin function and hypertension which are all prognostic factors for morbidity and mortality in humans, can also contribute to an increase in RDW⁶. Human literature suggests that RDW is as good^{7,18} or even better^{14,28} at prognosticating mortality compared to other inflammatory markers such as CRP and WBC. Thus, RDW provides valuable information about the general health status of the patient and in humans also provides prognostic information. This parameter is a component of the CBC reported by most modern hematology analyzers, which makes it inexpensive and routinely available.

Studies evaluating the prognostic value of RDW in veterinary patients are sparse²⁹⁻³². Red blood cell distribution width was found to be higher in dogs with pulmonary hypertension when compared to controls^{30,32} and higher in cats with hypertrophic cardiomyopathy and congestive heart failure compared to controls³¹. In another study, RDW was not significantly different between healthy dogs and dogs with chronic degenerative valvular disease, or, in the diseased dogs, between those with compensated and decompensated heart failure²⁹. To the authors' knowledge, the use of RDW as a biomarker in critically ill dogs has not previously been investigated.

The aims of this study were to determine whether increased RDW admission values were associated with increased in-hospital mortality, a longer length of hospitalization and a higher leukocyte count in canine ICU patients. Acute patient physiologic and laboratory evaluation (APPLE) fast score was used to assess severity of illness, and the association between RDW and APPLE fast score was also analyzed. Our hypotheses were that the RDW would be higher in patients that died in hospital

and that a higher RDW would predict longer hospitalization. We also hypothesized that there would be a positive correlation between RDW and the leukocyte count and between RDW and APPLE fast score.

MATERIALS AND METHODS

This was a retrospective observational study where the medical records database of a university teaching hospital was searched to identify all dogs admitted to the ICU between December 30th, 2016 and April 26th, 2017. The study was approved by the School of Veterinary Medicine Ethical Review Committee.

Patient selection and data collection

The inclusion criteria for this study were admission to the ICU and a CBC^a sent to an external laboratory which included RDW values obtained within 24 hours of admission and prior to any blood transfusion. In this study, “critically ill dogs” were defined as dogs admitted to the ICU.

For all study patients, data regarding signalment, physical examination on admission, diagnosis, length of ICU and overall hospitalization, outcome (defined as survival to discharge or in-hospital mortality), CBC results and, when available, blood biochemistry^b parameters were collected. Biochemistry analysis was performed in an external laboratory whereas blood glucose and lactate measurements used for the APPLE fast score calculation were obtained using point of care devices^{c,d}. When pos-

sible, the APPLE fast score was calculated. This is a validated score for the stratification of illness severity in hospitalized dogs and is calculated from the values of blood glucose, albumin, lactate, platelet count and mentation score³³. Thorough revision of the medical records was performed in order to determine the mentation score (responsive vs unresponsive and ambulatory, standing with support or recumbent). Calculations were all performed retrospectively by the same investigator. Patients with insufficient data, or those with platelet clumps noted on pathologist review of the blood smear were excluded from APPLE fast score calculation.

Patients were divided into nine diagnostic categories based on full medical records and final diagnosis code: abdominal, hematological, respiratory, neurological, cardiovascular, integument, trauma, musculoskeletal and others. Diagnostic categories were determined prior to data collection and were based on similar human studies^{16,20}. The abdominal category included all patients diagnosed with a non-traumatic disease related to the gastro-intestinal and urinary tracts and also patients with hepatic and splenic disorders. When more than one final diagnosis was made, the main disease process was used for patient classification. Patients that did not fit into any of the above categories, were assigned to the “others” group. For consistency, categorization was performed by the same investigator in all patients.

Statistical analysis

Median and interquartile range (IQR) were calculated for age, in-hospital mortality, length of ICU hospitalization, length of overall hospitalization (including ICU and

wards days), RDW value and APPLE fast score. Correlation and *P* value were assessed between RDW and APPLE fast score, overall outcome, outcome for each diagnostic category, length of hospitalization and leukocyte count.

Spearman's rank correlation test was used to describe the relationship between the RDW and APPLE fast score. The Mann Whitney U Test was used to compare RDW values between patients that survived and patients that died as RDW values were not normally distributed. The same test was used to compare RDW and APPLE fast score between survivors and deceased patients. Statistical significance level was set at $P \leq 0.05$. Data introduction, analysis and graphs were undertaken with commercial software packages^c.

RESULTS

A total of 247 dogs were admitted to the ICU within the study period. Of these, 127 dogs met the inclusion criteria. None of the dogs had a blood transfusion prior to blood collection for CBC analysis. The study population comprised 23 entire males, 53 neutered males, 13 entire females and 38 neutered females. The Labrador Retriever was the most commonly represented breed (16%; 21/127), followed by cross-breed (15%; 19/127), Cocker Spaniel (5%; 7/127), Yorkshire Terrier (5%; 7/127), Greyhound (4%; 5/127), Springer Spaniel (4%; 5/127), Bearded Collie (3%; 4/127), French Bulldog (3%; 4/127) and Jack Russell Terrier (3%; 4/127). Thirty-six other breeds were represented at low numbers (< 3% each of the study population). The

median age of patients included in the study was 8 years (IQR 3.4-10.3). RDW did not correlate with age ($r = -0.002$; $P = 0.982$) (Figure 1).

The overall in-hospital mortality rate was 29% (37/127). Of these, 8% (3/37) of the dogs died and the remainder were euthanized (92%; 34/37). The reason for euthanasia was recorded in 94% (32/34) of cases and was due to poor prognosis in 78% (25/32) of the dogs, and financial concerns in one case. Finally, 19% (6/32) of clients declined to pursue further investigations or specific treatment (e.g. chemotherapy, surgery, other), after initial investigations and supportive treatment, given the eventual poor prognosis of the disease process.

The RDW for the study population ranged from 11.0% to 40.2% with a median value of 13.8% (IQR 13.1-14.7). The hematology analyzer's reference range for RDW was 11.9 to 14.5%. Seventy-three per cent (93/127) of the dogs included in the study had a RDW value within the reference range and from these, 27% (25/93) died. Twenty-six per cent (33/127) of dogs had a RDW above the reference range. This group of patients had a mortality rate of 36.4% ($P = 0.2$). Only one dog had a RDW value below the reference range (11%). A higher RDW was not associated with increased in-hospital mortality overall ($P = 0.381$) (Figure 2).

The median length of ICU hospitalization was 2 days (IQR 1-3.25). The median length of overall hospitalization was 3 days (IQR 1-6). No significant correlation was found between ICU hospitalization length and RDW ($r = -0.1$; $P = 0.263$), nor between overall length of hospitalization and RDW ($r = 0.053$; $P = 0.554$) (Figure 3) in either survivors ($r = 0.064$; $P = 0.548$) or non-survivors ($r = 0.548$; $P = 0.083$).

There was sufficient data to calculate an APPLE fast score in 64% (81/127) of cases. The median APPLE fast score was 25 (IQR 19.5-29). A weak, positive, non-significant association was found between RDW and APPLE fast score overall ($r = 0.147$; $P = 0.163$). RDW in this subset of patients and APPLE fast score were not found to be significantly different between survivors and deceased dogs.

Finally, there was a weak, positive but non-significant correlation ($r = 0.139$; $P = 0.118$) between RDW and leukocyte count (Figure 4).

Sub-group analysis

Patients were sub-grouped as follows: abdominal disease (36%; 46/127), hematological (13%; 16/127), respiratory (13%; 16/127), neurological (12%; 15/127), cardiovascular (11%; 14/127), integument (3%; 4/127), trauma (3%; 4/127), musculoskeletal disorders (2%; 3/127) and other disorders (7%; 9/127). No association between RDW and APPLE fast score was identified in any of the subgroups (Table 1). A higher RDW was not associated with in-hospital mortality in any individual diagnostic category (Table 2).

DISCUSSION

To the authors' knowledge, this is the first study evaluating the prognostic value of RDW in critically ill canine patients. Limited studies have evaluated the use of RDW in veterinary medicine, and to date all have focused on specific disease processes.

Swann et al³⁰ found no association between RDW values and mortality in dogs with pulmonary hypertension, whereas Stanzani et al³¹ found that greater RDW values in cats with hypertrophic cardiomyopathy were associated with a higher risk of death. Our study did not find a significant correlation between RDW values and in-hospital mortality in critically ill dogs overall, or within diagnostic sub-group categories, which agrees with Swann et al³⁰ in not finding an association.

Red blood cell distribution width has been shown to be a useful adjunct to illness severity scores in both pediatric and adult critically ill people. Ramby et al²⁰ found that RDW provided similar prognostic information to the Pediatric Index of Mortality 2 (PIM-2) score and other studies in adult ICU patients found that RDW increased the Acute Physiology And Chronic Health Evaluation (APACHE II) predictive power for mortality^{16,17} and improved the Simplified Acute Physiology Score (SAPS) for risk stratification of critically ill patients³⁴. In this study, the APPLE fast score was calculated for 64% (81/127) of the patients and was used as a measure of severity of illness in the study population. The association between RDW and APPLE fast score was found to be non significant. When the APPLE fast score was compared between survivors and non-survivors, no significant difference was found between groups. This may indicate lack of positive correlation between RDW and severity of illness, but could be the consequence of a low study sample size or the retrospective nature of the study as we rely on the accuracy of the data collected. Prospective studies with a larger study sample are needed to further evaluate this association.

Studies in people have shown that increased RDW values predicted a longer length of ICU stay or overall hospitalization in critically ill patients^{16,18,20}. However, no

correlation was found between RDW and length of hospitalization in our study population. In veterinary medicine, length of hospital stay tends to be much shorter compared to humans. This is likely to be biased by financial limitations and also euthanasia as a possibility when a poor prognosis or poor quality of life is expected in a patient. To avoid this bias, the correlation between length of hospitalization and RDW in the survivor group was assessed. However, this also revealed no association. Due to the retrospective nature of the study, it was not possible to determine if some patients might have been discharged early from ICU against veterinary recommendation due to financial concerns.

This study evaluated the prognostic value of a single RDW measurement within 24 hours of admission in critically ill dogs. In people, limited data suggests that serial RDW measurements may provide more valuable prognostic information, although studies show inconsistent results. Zhang et al¹⁸ found an association between RDW on admission to ICU and in-hospital mortality but repeated RDW measurements did not add additional prognostic value. Meynaar et al¹⁷ found no difference between admission RDW values among ICU patients that died or survived. However, the last recorded RDW value was found to be significantly higher in patients who died in hospital compared to survivors. This suggests that RDW may increase when the patient's condition worsens. In our study, serial RDW measurements were not considered.

Finally, in people, RDW has been shown to increase with age, likely due to nutritional deficiencies, myelodysplasia and other comorbidities such as neoplasia and anemia of chronic disease³⁵. In our study, there was no correlation between RDW and

age. However, the study population was middle aged to elderly, with a median age of 8 years, which might have contributed to the lack of correlation.

Studies in both people and dogs have assessed the correlation between RDW and markers of inflammation such as CRP and WBC count^{12,17,23,25,32} with conflicting results. Whereas some studies showed a positive association between RDW and CRP^{23,25} and a positive correlation between RDW and WBC^{12,32}, other studies did not establish an association between them¹⁷. In veterinary medicine, Mazzotta et al³² found an association between RDW and WBC in dogs with pulmonary arterial hypertension. In contrast, our results showed no significant correlation between RDW and leukocyte count. Inflammation may, therefore, not be the only factor causing RDW to increase.

Other factors such as oxidative stress and nutritional deficiencies have also been linked to an increase in RDW^{28,36}. Oxidative stress in particular increases RBC fragility, has a negative effect on erythroid maturation and accelerates erythrocyte senescence contributing to an elevated RDW³⁷⁻³⁹. Critically ill patients tend to have increased formation of reactive oxygen species as well as a decreased antioxidant response leading to oxidative stress⁴⁰. Many of these patients also suffer from malnutrition due to an increased metabolic demand combined with delayed or inadequate nutritional support in hospital due to inherent difficulties in accurately estimating the nutritional needs of the patient and providing these adequately⁴¹. This can lead to a low concentration of cobalamin, folate, and iron, all required for normal RBC development. Thus, nutritional deficiencies may also cause alterations in both erythropoiesis and erythrocyte maturation^{25,35} leading to changes in RDW.

Limitations of this study are largely due to its retrospective nature. We adapted the subgroup classification from the ones used in critically ill human patients and aimed to classify our patients as accurately as possible. The ICU population is very heterogenous, with many patients suffering from multiple disease processes. To minimize inconsistency, one investigator performed all diagnostic categorization using the full medical record as well as the final diagnosis code to determine the primary disease process. Nevertheless, some patients such as dogs diagnosed with cancer and seizing dogs were occasionally more difficult to allocate to one of the diagnostic groups due to the involvement of multiple organs or intra-cranial versus extra-cranial causes. Data on treatment prior to blood collection for CBC analysis was not collected in this study due to the heterogenous nature of the study population. This could be a confounding factor, and should be considered in any future studies. The association between RDW and inflammation was evaluated by assessing its correlation with the leukocyte count. However WBC may be low or high in inflammatory processes. Future studies are needed to evaluate the association between RDW and other markers of inflammation such as CRP. In this study, a single RDW value within 24 hours of admission was assessed as timing of serial measurements would have been inconsistent.

In common with many veterinary studies, the small sample size may mean that statistical power was insufficient to detect an association between the assessed parameters. This would be compounded in subgroup analysis with a higher likelihood of type II error. There were insufficient septic cases to classify these patients as a unique group and the retrospective nature of the study would have made it difficult to correctly

identify these patients. Patients with sepsis or septic shock represent a group of critically ill patients that often requires long hospitalization periods and whose treatment can be expensive. That is why future studies assessing RDW as a prognostic factor in this group of patients might be interesting in order to help clinicians and clients to direct their decisions based on prognosis.

Human studies differ regarding inclusion and exclusion criteria when it comes to patients with recent blood transfusions or anemia. In this study, none of the patients were transfused prior to admission or in hospital prior to blood collection for CBC analysis. Anemic dogs were not excluded as we aimed to determine if RDW, regardless of the underlying cause of elevation, was predictive of outcome. However, patients with regenerative anemia are likely to have a higher RDW value by virtue of the regeneration, and this might have biased our results.

In common with many veterinary ICUs, our ICU not only houses patients requiring specialist treatment under the care or supervision of a boarded criticalist, but also patients that are less critically ill but require constant nursing supervision such as those requiring close post-operative monitoring, or patients at risk of seizures. The inclusion of these patients may also have affected our results as some dogs might have had increased RDW but were hospitalized in the ICU for reasons other than being critically ill. Their inclusion was a pragmatic decision in order to provide information that can be readily applied to a large, heterogenous population.

CONCLUSIONS

Red blood cell distribution width is a component of the CBC, and is thus both widely available and inexpensive. In human medicine, RDW has been associated with outcome in multiple disease processes as well as in the general and critically ill patient populations. To our knowledge, this is the first study evaluating the association between RDW and critically ill dogs. In this study, RDW was not associated with in-hospital mortality or length of hospitalization in the canine ICU population. Also, the association between RDW and leukocyte count was not significant. Further prospective studies are needed to evaluate any correlation between RDW and outcome in subsets of the most critically ill patients as well as the prognostic value of serial RDW values.

FOOTNOTES

^a ADVIA 2120 Hematology System, Siemens Healthcare Limited, Frimley, United Kingdom

^b AU480 Chemistry Analyser, Beckman Coulter, High Wycombe, United Kingdom

^c AlphaTrak2 Blood glucose monitoring system, Abbott, Zoetis UK Limited, Leatherhead, United Kingdom

^d StatStrip Xpress® Lactate Systems, Nova Biomedical, Runcorn, United Kingdom

^e Numbers, version 4.3 (5046), ©The R Foundation for Statistical Computing, Vienna, Austria

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Table 1: Correlation and *P* value for RDW and APPLE fast score in each diagnostic category.

Diagnostic category	Cases	RDW: mean (IQR)	APPLE fast: mean (IQR)	Correlation (<i>r</i>)	P value (<i>P</i>)
Abdominal	34 (42%)	13.8% (13.1-14.4)	25.5 (22-29)	0.203	0.215
Hematological	10 (12%)	20.9% (17.5-27.7)	24 (21-31)	0.297	0.349
Respiratory	6 (7%)	13.8% (12.9-14.1)	17.5 (13-20)	0.157	0.686
Neurological	9 (11%)	13.3% (2.95-13.55)	23 (15.5-26)	0.278	0.470
Cardiovascular	8 (10%)	14.2% (13.15-14.45)	19.5 (15-24.5)	-0.417	0.304
Integument	3 (4%)	13.9% (NA)	29 (NA)	-0.470	-0.688
Trauma	4 (5%)	13.2 (12.35-15.2)	26 (21-32)	-0.301	-0.699
Musculoskeletal	3 (4%)	12.7% (NA)	29 (NA)	0.126	0.920
Others	4 (5%)	13.65% (13.1-13.9)	20.5 (17-25)	0.767	0.130
OVERALL	81	13.8 (12.95-14.65)	25 (19.5-29)	0.146	0.162

Table 2: RDW comparison between survivors and non survivors for each diagnostic category.

Diagnostic category	Cases	Survivors	RDW (%) survivors: mean (IQR)	Non-survivors	RDW (%) non-survivors: mean (IQR)	P value (P)
Abdominal	46 (36%)	35 (76%)	13.8 (13.1-14.4)	11 (24%)	13.6 (13-14)	0.606
Hematological	16 (13%)	9 (56%)	18.8 (13.7-27.25)	7 (44%)	18.7 (15-27.7)	0.634
Respiratory	16 (13%)	12 (75%)	13.95 (13-14.3)	4 (25%)	13.8 (13.45-14.6)	0.808
Neurological	15 (12%)	11 (73%)	13.3 (13.1-13.5)	4 (27%)	13.1 (12.95-13.95)	0.599
Cardiovascular	14 (11%)	9 (64%)	14.3 (13.1-14-65)	5 (36%)	14.2 (13.1-14.7)	0.738
Integument	4 (3%)	2 (50%)	13.9 (NA)	2 (50%)	13.45 (NA)	0.439
Trauma	4 (3%)	4 (100%)	13.2 (12.35-15.2)	0 (0%)	NA	NA
Musculo-skeletal	3 (2%)	1 (33%)	NA	2 (67%)	12.8 (NA)	0.221
Other	9 (7%)	7 (77%)	13.1 (12.7-14)	2 (22%)	14.2 (NA)	0.240

Diagnostic category	Cases	Survivors	RDW (%) survivors: mean (IQR)	Non-survivors	RDW (%) non-survivors: mean (IQR)	<i>P</i> value (<i>P</i>)
OVERALL	127	90 (70%)	13.75 (13.1-14.4)	37 (29%)	13.8 (13.1-14.85)	0.381

Figure 1: Correlation of RDW (%) and age (months); ($r = -0.002$; $P = 0.982$).

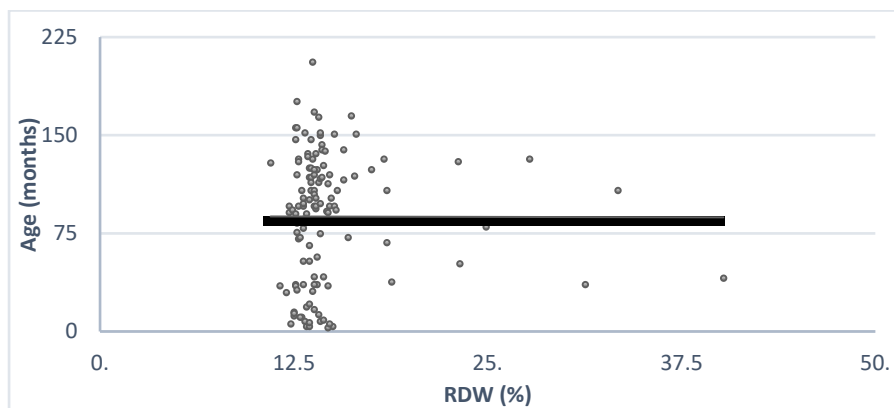


Figure 2: RDW (%) and in-hospital mortality; ($P = 0.381$).

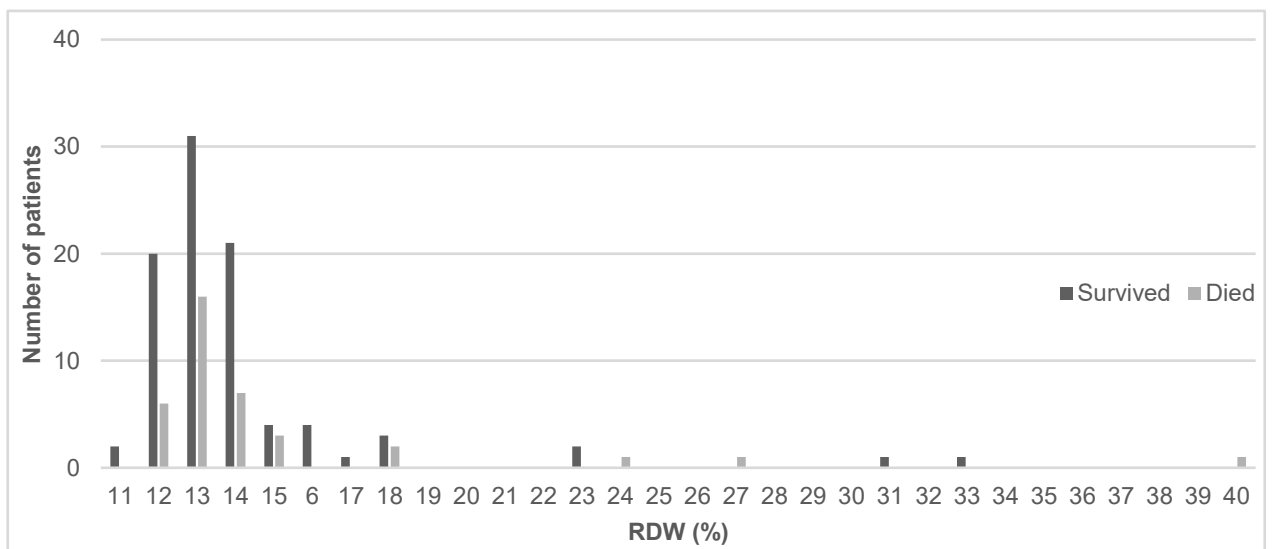


Figure 3: Correlation between length of overall hospitalization (days) and RDW (%); ($r = 0.053$; $P = 0.554$).

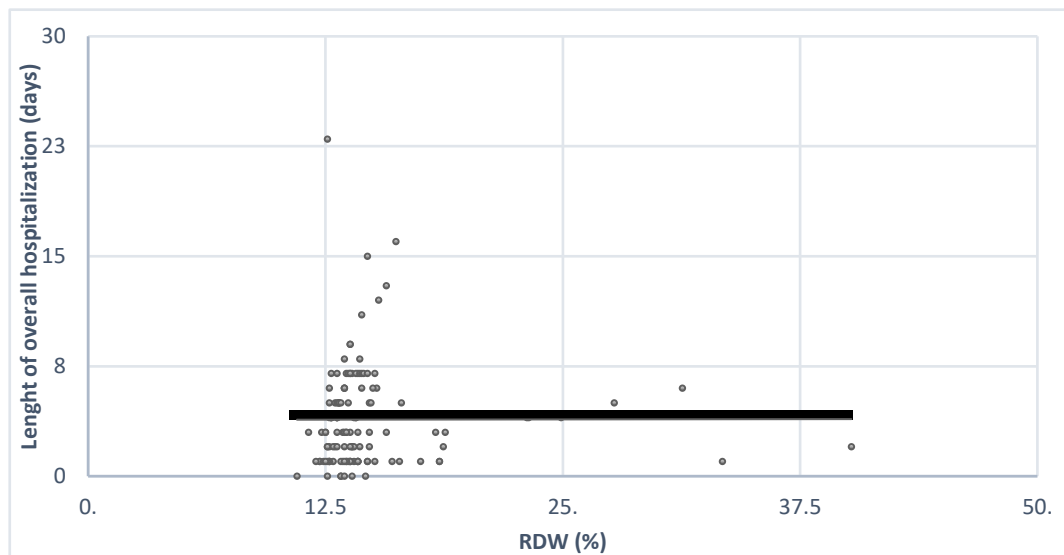


Figure 4: Correlation between leukocyte count ($\times 10^9/L$ [$\times 10^3/\mu L$]) and RDW (%); ($r = 0.139$; $P = 0.118$).

