Received: 25 March 2021 / Accepted: 29 May 2021 / Published online: 30 June 2021

DOI 10.34689/SH.2021.23.3.008

UDC 616-07:616.15

THE PROGNOSTIC SIGNIFICANCE OF RED CELL DISTRIBUTION WIDTH IN TRAUMATIC PATIENTS WITH ACTIVE HEMORRHAGE: IS SERIAL MEASUREMENT A NEW PERSPECTIVE?

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Abstract

Aim: Trauma takes an important place among all causes of death. Red cell distribution width (RDW) is associated with mortality in trauma, and upper gastrointestinal bleeding. Our aim in this study is to show whether RDW value is important in trauma cases.

Methods: The patients were divided into 2 groups as alive and deceased. Bleeding foci were determined from the radiological and surgical results of the patients. The results were analyzed together with the RDW.

Results: 854 of the patients, 79.5% were male (n=679). The mean age was 42.1±18.7 years. Of all patients, 42.7% (n=365) were treated inpatiently. Of these patients, 16.7% (n=143) were hospitalized and followed up by orthopedics. Of the patients, 0.9% (n=8) left voluntarily and 0.2% (n=2) died in the ED, while 1.8% (n=15) died in the hospitalized clinic. Accordingly, the AUC was 0.781 for RDW. For the 13.6 RDW value, the sensitivity was calculated as 84.6% and the specificity was 63.4%.

Conclusion. The decrease in hemoglobin and hematocrit values that were measured for the second time was considered to be very good for predicting mortality, while the increase in PDW and RDW was acceptable in predicting mortality. We think that the serial measurements of RDW yield more significant results in the light of the studies conducted so far.

Keywords: *Trauma; red cell distribution width; hemorrhage*

Резюме

ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ ШИРИНЫ РАСПРЕДЕЛЕНИЯ ЭРИТРОЦИТОВ У ТРАВМАТИЧЕСКИХ ПАЦИЕНТОВ С АКТИВНЫМ КРОВОТЕЧЕНИЕМ: ЯВЛЯЕТСЯ ЛИ СЕРИЙНОЕ ИЗМЕРЕНИЕ НОВОЙ ПЕРСПЕКТИВОЙ?

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Цель: травма занимает важное место среди всех причин смерти. Ширина распределения эритроцитов (RDW) связана со смертностью от травм и кровотечением из верхних отделов желудочно-кишечного тракта. Наша цель в этом исследовании - показать, насколько важна величина RDW в случаях травм.

Методы. Пациенты были разделены на 2 группы: выжившие и умершие. Источники кровотечения определяли по рентгенологическим и хирургическим данным. Результаты обследования были проанализированы параллельно с RDW.

Результаты: В исследование включены 854 пациента, 79,5% - мужчины (n = 679). Средний возраст составил 42,1 ± 18,7 года. Из всех пациентов 42,7% (n = 365) лечились стационарно. Из этих пациентов 16,7% (n = 143) были госпитализированы и находились под наблюдением ортопедов, 0,9% (n = 8) выписались добровольно, 0,2% (n = 2) умерли в отделении неотложной помощи, а 1,8% (n = 15) умерли в профильном отделении. Соответственно, AUC для RDW составила 0,781. Для значения RDW 13,6 чувствительность составила 84,6%, а специфичность - 63,4%.

Заключение. Снижение значений гемоглобина и гематокрита, которые были измерены двукратно, считалось хорошим предиктором для прогнозирования смертности, в то время как увеличение PDW и RDW было приемлемым для прогнозирования смертности. Мы думаем, что серийные измерения RDW дают более значимые результаты в свете проведенных исследований.

***Ключевые слова**: травма; ширина распределения эритроцитов; кровоизлияние.*

Түйіндеме

БЕЛСЕНДІ ҚАН КЕТУМЕН ЖАРАҚАТТЫҚ НАУҚАСТАРДАҒЫ ЭРИТРОЦИТТЕРДІ БӨЛУ КЕҢДІГІНІҢ БОЛЖАЛДЫ МӘНІ: СЕРИЯЛЫҚ ӨЛШЕМ ЖАҢА ПЕРСПЕКТИВА БОЛЫП ТАБЫЛА МА?

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Мақсаты: Жарақат өлімнің барлық себептері арасында маңызды орын алады. Эритроциттердің таралу ені (RDW) жарақаттанудан болатын өліммен және асқазан-ішек жолдарының Жоғарғы бөліктерінен қан кетумен байланысты. Бұл зерттеудегі біздің мақсатымыз-жарақат алған жағдайда RDW мәні қаншалықты маңызды екенін көрсету.

Әдістері. Науқастар 2 топқа бөлінді: тірі қалғандар мен өлгендер. Қан кету көздері рентгенологиялық және хирургиялық мәліметтер бойынша анықталды. Зерттеу нәтижелері RDW-мен қатар талданды.

Нәтижелер: Зерттеуге 854 науқас, 79,5% ер адамдар (n = 679) кіреді. Орташа жасы 42,1 ± 18,7 жыл болды. Барлық пациенттердің 42,7% (n = 365) стационарлық емделген. Бұл пациенттердің 16,7% (n = 143) ауруханаға жатқызылды және ортопедтердің бақылауында болды, 0,9% (n = 8) ерікті түрде шығарылды, 0,2% (n = 2) жедел жәрдем бөлмесінде қайтыс болды, ал 1,8% (n = 15) мамандандырылған бөлімде қайтыс болды. Тиісінше, RDW үшін AUC 0,781 болды. RDW мәні үшін 13,6 сезімталдық 84,6% құұрады, ал ерекшелігі - 63,4%.

Қорытынды. Екі рет өлшенген гемоглобин мен гематокрит мәндерінің төмендеуі өлімді болжау үшін жақсы болжам болып саналды, ал PDW және RDW жоғарылауы өлімді болжау үшін қолайлы болды. Біздің ойымызша, RDW сериялы өлшеулер жүргізілген зерттеулерге байланысты айтарлықтай нәтиже береді.

***Түйінді сөздер**: жарақат; эритроциттердің таралу ені; қан кету.*

Bibliographic citation:

Erdem Ah.B., Çelikel E., Kavak N., Yılmaz M.S., Kavalcı G., Güngör İ., Tümer M., Kavalcı C. The prognostic significance of red cell distribution width in traumatic patients with active hemorrhage: is serial measurement a new perspective? // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2021, (Vol.23) 3, pp. 69-77. *doi 10.34689/SH.2021.23.3.008*

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Introduction

While trauma is the third leading cause of death worldwide, it accounts for 9% of all deaths [1,2]. The injury occurs with the impacts of trauma such as direct or tensile, compressive, and shaking impacts. This may result in hollow organ perforation, solid organ injury, vascular injury, bone fractures, or retroperitoneal bleeding. In particular, retroperitoneal injuries may not manifest clinical symptoms in the early period [3].

The care of major trauma patients remains a challenge for emergency physicians and surgeons. Uncontrolled hemorrhagic shock is the major cause of trauma-related death in the first 2-3 hours. About 20% of patients are lost in this group [4].

The red cell distribution width (RDW) is one of the indicators in hemogram measurement. It is obtained by dividing the percentage of the standard deviation of the erythrocyte volume by the mean corpuscular volume [5]. This parameter is known to be correlated with coronary artery disease, stroke, heart failure, trauma, sepsis, pneumonia, hip fracture, chronic obstructive pulmonary disease, and pulmonary hypertension-related mortality [6-15]. However, the pathogenesis of elevated RDW levels in such conditions is not fully known. It is commonly used to determine the etiology of anemia. In upper gastrointestinal bleedings, elevated levels of RDW is also associated with mortality and morbidity [16]. Normally, erythrocyte volumes are often equal to each other. An increased RDW value indicates anisocytosis. This means that the amount of reticulocyte rapidly released into the bloodstream before maturation increases and erythrocyte volumes vary [17]. It is considered that rather than baseline RDW values, follow-up values may give more significant results [18].

The aim of this study was to determine whether RDW has significance in cases of trauma causing acute hemorrhage, which are increasing in the emergency department (ED). Elevated RDW levels may determine the severity of hemorrhage in asymptomatic trauma-related hemorrhages. We retrospectively evaluated major trauma patients presenting to our ED with trauma. Of these, patients who had a trauma-related hemorrhage underwent surgery, and were discharged from the emergency department were included in the study.

Materials and methods

Study design and participants

The study was conducted retrospectively after obtaining the ethics committee approval (decision of the Clinical Research Ethics Committee of Ankara Numune Training and Research Hospital dated 16/11/2016 and numbered E-16-1076). Records of 903 patients admitted to the ED between 2012 and 2014 due to trauma were scanned. 49 patients were excluded from the study because of minor trauma, incomplete data, pregnancy, and under 18 years of age. The study included 854 patients who were brought with blunt trauma, firearm, and penetrating stab wounds. Of these patients, 224 whose follow-up hemogram values were not studied were excluded from the study. Epidemiological data of 854 patients were used in the study. Since 224 patients had no control hemogram value, serial hemogram analysis was performed on 630 patients (Fig. 1). 630 patients were divided into two groups as those who died and survived. The survivors were determined as group 1 and the patients who died as group 2. With isolated head trauma, isolated small bone fractures or large bone fractures without haemorrhage, small skin incisions, isolated spinal injuries, burn patients, simple orthopedic injuries were not included in the study.

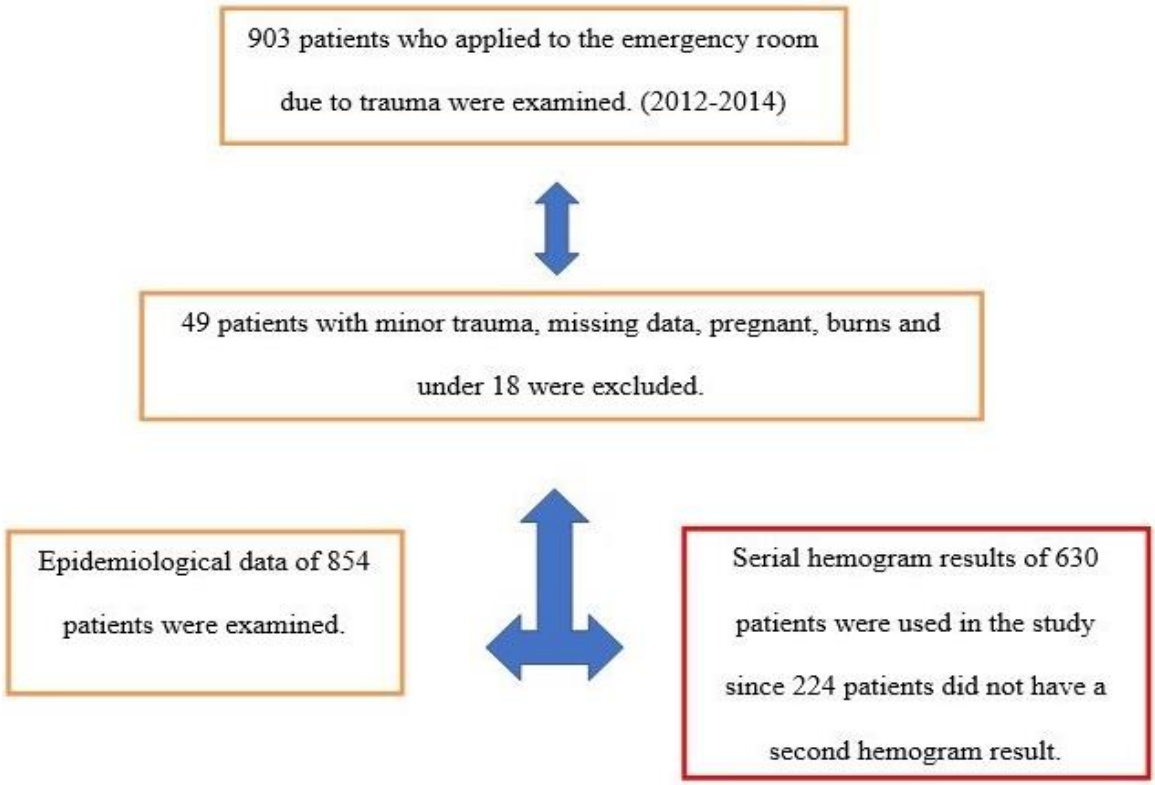

Figure 1. Flow chart of trauma patients.

Definitions

Of these, major trauma patients were determined according to the 2011 Guidelines for Field Triage of Injured Patients classification (Table 1), including a firearm, penetrating stab wounds, and blast injuries. According to this classification, patients with severe and high energy trauma were accepted as major trauma [19]. Patients outside this classification were considered minor trauma and were excluded from the study.

Table 1.

2011 Guidelines for Field Triage of Injured Patients Classification.

Serious trauma	High energy trauma
Glasgow coma score <13	Falling from a height of 6 m
Respiratory rate <10 or >29	Jumping out of the vehicle
Systolic blood pressure <90 mmHg	Mortal passenger in the vehicle
Need for endotracheal intubation	Crashing vehicle faster than 32 km/h
Penetrating traumas	Motorcycle accident higher than 32 km / h
2 or more long bone fractures	
Hand and ankle amputation	
Fragmented or pulsed limb	
Pelvic fracture	
Open or displaced skull fracture	
Paralysis	
Chest wall instability and deformity	

Data collection

We determined age, gender, and trauma type (blunt, penetrating-stab, firearm) from the demographic data of the patients. Trauma patients who were admitted to the ED between 2012 and 2014 were retrospectively scanned through the information processing system of our hospital. Hemoglobin (Hgb), hematocrit (Htc), platelet distribution width (PDW), and RDW values were obtained from the initial hemogram (1st Hemogram) measurements of the patients at the time of admission via the system. In addition, X-ray, ultrasonography (USG), and computed tomography (CT) images taken from the patients were analyzed. Organ injuries detected in the radiological reports were recorded. Of these patients, those who were hospitalized, transfused blood, operated, discharged, and died were determined. Hgb, Htc, PDW, RDW values of control hemogram (2nd Hemogram) parameters before discharge were re-recorded. Organ injuries and bleeding foci were determined from the discharge summaries according to the operative notes and progress notes. Finally, the 30-day mortality status of the patients was evaluated from the hospital records. The data were recorded by 2 specialist doctors. A specialist doctor checked this data.

Sample collection

Venous blood samples were collected in the Becton Dickinson (BD diagnostics, Plymouth, UK) Vacutainer tubes compatible with Potassium EDTA. The specimens were analyzed on XT-2000i (Sysmex corporation of America, Long Grove, Illinois, USA). RDW CV% value was used in the study. Its normal range was 12.1-14.3. The normal range of Hgb was 12-16 g/dL, the normal range of Htc was 36-46%, and PDW was 9-17%. Blood was drawn from the patients upon arrival at the emergency department. In our study, we determined the first admission values of the patients as the result of the 1st Hemogram and the control hemogram parameters before discharge hemogram as the 2nd Hemogram result.

Outcomes

Symptoms and findings of the patient, laboratory data, X-Ray, USG and CT findings, consultation notes, surgery notes and epicrisis information were evaluated together. As a result of all these data, the conditions of patients causing active blood loss were determined. According to this information, the patients who were decided to die from patients' active blood loss due to trauma constituted the second group of our study (dead patient).

Statistical data analysis

The study data were analyzed with SPSS for Windows v.17 and MedCalc trial version 23. The data were presented as frequency (n), percentage (%), median, and interquartile range. The distribution of continuous data was evaluated by the Kolmogorov-Smirnov test. It was found that they were non-normally distributed. Therefore, the Mann-Whitney U test, one of the non-parametric tests, was used. The patients divided two groups. Group 1 is survival after posttrauma in 30-day (n=613), Group 2 has died after post-trauma in 30-day (n=17). Multiple linear regression analysis was performed to determine independent factors affecting mortality. According to the groups, 1st and 2nd Hgb, Htc, RDW, and PDW measurements were evaluated by the Wilcoxon-Sign test.

In order to determine the role of Hgb, Htc, PDW, and RDW measured for the second time in predicting mortality, a receiver operating characteristic (ROC) curve was generated. Accordingly, the values with an Area Under the Curve (AUC) of 0.7-0.8 were considered acceptable, 0.8-0.9 very good, and the values above 0.9 were considered excellent. Sensitivity and specificity were calculated. The power of the study calculated 0.65. A p-value of <0.05 was considered statistically significant.

Results

854 of the patients, 79.5% were male (n=679). The mean age was 42.1±18.7 years. Of the patients, 81.4% (n=695) had blunt trauma, 18.5% (n=158) had penetrating stab injury, and 0.1% (n=1) had firearm injury. Of these

patients, 746 had USG result. The USG examination of 94.2% of the patients was reported to be normal (n=703). Of the patients, 4% (n=30) had free fluid in the abdomen and 0.9% (n=8) had subcutaneous hematoma. In addition, one patient (0.1%) had splenic laceration, intraabdominal hematoma, renal laceration and pleural effusion. In one patient, intraabdominal free fluid and pleural effusion were simultaneously present. Of the 854 patients, 33% (n=282) underwent CT. The CT result of 54.9% of these patients was reported to be normal. The most common pathologic findings in patients with CT were hemothorax (11.3%, n = 32) (Table 2).

Table 2.

Epidemiological data.

		Number (n)	Percentage (%)
Gender	Male	679	79.5
	Female	175	20.5
Type of trauma	Blunt	695	81.4
	Penetrating	158	18.5
	Firearm	1	0.1
Ultrasonography (n=746)	Normal	703	94.2
	Free fluid	30	4
	Other*	13	1.8
Computed tomography (n=282)	Normal	155	54.9
	Hemothorax	32	11.3
	Hemopneumothorax	29	10.2
	Pneumothorax	18	6.3
	Other**	48	17.3

Other:* Splenic laceration, intraabdominal hematoma, renal laceration and pleural effusion

Other**: Lung Contusion, pelvic fracture, esophageal rupture, subcutaneous hematoma, splenic laceration, liver laceration, aortic thrombus, pericardial fluid, kidney laceration

Of all patients, 42.7% (n=365) were treated inpatiently. Of these patients, 16.7% (n=143) were hospitalized and followed up by orthopedics and traumatology, 9.5% (n=81) by thoracic surgery, 7.5% (n=64) by general surgery, 3.9% (n=33) by intensive care, 3.5% (n=30) by neurosurgery, 1.3% (n=11) by plastic surgery, and 0.4% (n = 3) were hospitalized and followed up by cardiovascular surgery clinics. Of the patients, 55.2% (n=471) were discharged from the emergency department and 0.9% (n=8) were referred. Of the patients, 0.9% (n=8) left the ED voluntarily and 0.2% (n=2) died in the ED, while 1.8% (n=15) died in the hospitalized clinic.

The values in the laboratory results of the patients were non-normally distributed. The initial and second Hgb, Htc, PDW, RDW values of the patients by mortality are shown in Table 2. Accordingly, to table 3 there was a statistically significant difference between the two groups with and without mortality in terms of the second values.

Wilcoxon-Sign test results between the 1st and 2nd hemogram parameters of the patients are shown in table 4. Accordingly, while there was a significant difference between Hgb, Htc, and RDW first and second values, there was no significant difference between PDW values (Table 3).

Table 3.

Laboratory values according to the mortality status of the patients.

Variable	Group 1 (n=613) Median (IQR)	Group 2 (n=17) Median (IQR)	p
1. Hemoglobin (g/dL)	14.7 (2.1)	13.2 (2.4)	0.045
1. Hematocrit (%)	43.2 (5.3)	38.5 (6.8)	0.029
1. Platelet distribution width (%)	11.6 (2.2)	12.2 (5.9)	0.118
1. Red cell distribution width (%CV)	13.3 (1.1)	13.3 (0.9)	0.809
2. Hemoglobin (g/dL)	13.5 (3.3)	9.3 (4.5)	<0.001
2. Hematocrit (%)	40.1 (8.4)	28.2 (11.7)	<0.001
2. Platelet distribution width (%)	11.5 (2.1)	12.8 (5.6)	0.01
2. Red cell distribution width (%CV)	13.3 (1.2)	14.8 (2.2)	0.001

The 1st RDW median of men was 13.10 (1.0) whereas the median of women was 13.9 (1.6). The 2nd RDW the median of men was 13.30 (1.1) whereas median of women is 14.20 (1.8). There was a significant positive correlation between the age of the patients and RDW ($p < 0.001$; $r = 0.319$). In the analysis using the Mann-Whitney U test, there was a statistically significant difference between the 1st RDW and 2nd RDW levels and gender ($p < 0.001$ in both).

A ROC curve was generated for Hb, Htc, PDW and RDW values obtained from the patients for the second time. Accordingly, the AUC was 0.822 for Hgb and 0.822 for Htc, while it was 0.708 for PDW and 0.781 for RDW. For the 13.6 RDW value, the sensitivity was calculated as 84.6% and the specificity was 63.4%. The sensitivity for the 12.3 PDW value was 69.2% and the specificity was 70.1% (Fig 2).

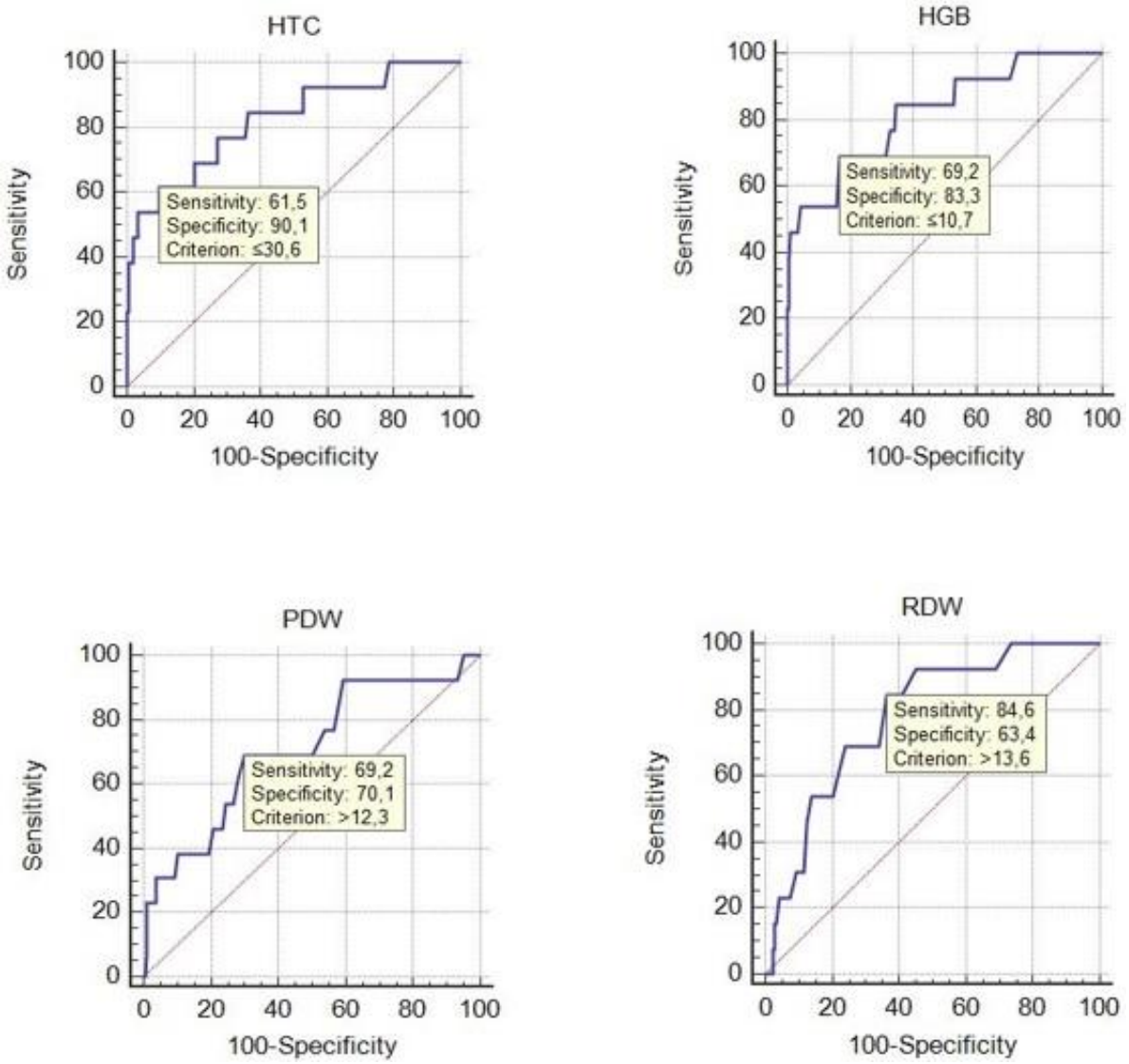

Figure 2. Sensitivity and specificity graphs for hemoglobin, hematocrit, platelet distribution width, red cell distribution width values taken from patients for the second time.

According to the AUCs, the decrease in Hgb and Htc values that were measured for the second time was considered to be very good for predicting mortality, while the increase in PDW and RDW was acceptable in predicting mortality.

Table 4.

Serial measurement of the hemoglobin, hematocrit, platelet distribution width and red cell distribution width.

Variable	1st measurement	2nd measurement	p
Hemoglobin (g/dL)	14.36±1.8	13.12±2.2	<0.001*
Hematocrit (%)	42.34±4.7	38.95±5.9	<0.001*
Platelet Distribution Width (%)	11.91±1.8	11.90±1.9	0.39
Red Cell Distribution Width (%CV)	13.57±1.3	13.66±1.4	0.003*

** Wilcoxon-Sign test*

Discussion

In our study, we found that increasing RDW value is an acceptable parameter in predicting mortality. The first measured value of RDW may be normal especially in trauma with bleeding. This study reveals that RDW has increased as a follow-up parameter.

There are challenges in predicting acute blood loss in the early period. Although various scoring systems have been developed for this, patients still die because of trauma, gastrointestinal bleedings, or spontaneous bleedings due to coagulopathies are still lost. In the absence of early symptoms of shock, a precursor to hemorrhage will become important for emergency physicians and surgeons.

RDW is a followed up parameter in iron deficiency anemia. It is a good indicator of anisocytosis. When iron

deficiency occurs, erythropoiesis is impaired and erythrocytes with abnormal shapes, and sizes are formed. This shows up as an increased RDW. Chronic infection, malignancy and inflammation may also increase [20]. In a previous study on RDW, its independent prediction of mortality was found to be significant. However, its etiopathogenesis could not be demonstrated [21]. It has been most commonly investigated in chronic diseases and thromboembolic events, observed in head trauma, hip fracture, and multiple trauma in trauma patients and found to be significant [21-24]. RDW value was found to be significantly increased in patients who died in studies related to head trauma [1,24]. In another study, only one week of serial Hgb value was examined. The decrease in Hgb value in these patients was found valuable in terms of mortality. However, this study did not include RDW values [25]. Contrary to these studies, Lippi et al. found that RDW values that were examined once in mid-head injuries were not significantly [26]. Increased RDW value in trauma-related acute hemorrhage can be explained by impaired erythropoiesis as a result of increased cell and indirect iron loss [5]. There are studies showing that RDW increases in hemorrhages after coagulopathy, in patients with post-traumatic hemorrhage requiring transfusion and in patients with upper gastrointestinal bleeding [16]. In our study, we found that the initial RDW value was not significant. However, the initial Hgb and Htc values were significant. Moreover, the initial PDW value was insignificant. This may be due to the fact that blood loss and inflammation may not be reflected in hemogram results in the early period. It will take time for the distribution width to increase due to the loss of Hgb after blood loss. Although the etiopathogenesis has not been fully demonstrated, some inflammatory processes may be effective in RDW elevation. Suppressed erythropoiesis by inflammation, a decreased number of red blood cells activates the angiotensin system because of reduced arterial filling, resulting in the release of immature erythrocytes into the bloodstream and accordingly the elevation of RDW. In summary, the infectious and inflammatory process that some who begins disrupt erythrocyte production. Resulting in an inadequate arterial filling, it accelerates the mortality process [27].

There are not many studies done in trauma patients with PDW value. It was found that PDW value increased significantly in patients with traumatic brain injury and was associated with awareness and mortality [28]. In studies with patients with Crimean Congo hemorrhagic fever [29,30] and patients with gastrointestinal bleeding [31], they found that PDW value increased. They showed that this result was significant in terms of prognosis. In this studies [29-30] as in our study (p=0.01), the 2nd PDW value gave significant results. Senel et al. showed that Forrest 1 class patients had higher PDW and PDW value decreased in the serial measurements after the treatment was completed. Again, in this study, the RDW value was found to be significantly higher than the control group [31]. As in our study (AUC was 0.708 for PDW and 0.781 for RDW), this shows that PDW and RDW values are important in terms of prognosis if there is active bleeding in traumatic or non-traumatic patients.

RDW has been shown to be associated with mortality in many conditions, and then the significance of hemorrhage with mortality has been demonstrated. However, the number of studies showing the value of RDW in serial measurements are limited in the literature. In the present study, we aimed to demonstrate the significance of RDW in predicting mortality regardless of the post-traumatic bleeding focus. In the study of 360 cases by Lee et al., it was found that the RDW values measured in the first hour for patients with upper gastrointestinal bleeding admitted to the ED indicated high-risk patients [16]. However, this is a study conducted on a single value of RDW. Moreover, in the trauma study of 305 patients by Kong et al. it was shown that RDW measurements on day 2 and day 3 were more valuable in predicting mortality than day 0 [18]. The second RDW value measured in our study was significant in terms of mortality but not more significant than Hgb and Htc.

Our study was that the hemogram follow-ups of the patients varied in terms of the time period and was not standardized because of the retrospective nature of the study. For this reason, we considered the hemogram results at the time of admission as the initial value, and the hemogram values measured immediately before discharge as the second value. We also found that the second value of PDW was significant but not as valuable as RDW. However, in a recent study of 200 cases by Habibpour et al. on the serial measurement of RDW in trauma, the initial RDW value was insignificant, as in our study [27]. Unlike our study, the RDW value measured on day 1 was also insignificant. However, RDW results may have been affected since patients who died before day 1 and received transfusion were excluded from the study. Our study included every patient who died and the 30-day mortality was evaluated. This may be the reason for the difference between the two studies. Moreover, considering the detail of the study by Habibpour et al., the values of day 0 and day 1 were insignificant [27]. In other words, it can also be speculated that rather than the initial values, the serial measurements of RDW value approximated the significant range in trauma patients with hemorrhage. Furthermore, considering the AUC in our study, the RDW values obtained during the follow-up were measured to be s 0.781 and found to be acceptable in predicting mortality.

In the study by Paulus et al. on 3994 trauma patients, RDW was significant in predicting the requirement for massive blood transfusion within 24 hours of hospitalization [22]. Moreover, this study supports the study of Majercik et al. [13] and contains more powerful data. In our study, the initial RDW value measured at the time of admission did not yield a significant result in predicting the requirement for transfusion. However, 93 of our patients required transfusion in the later period. This suggests that RDW can yield more significant results with serial measurements. If a prospective study is conducted with hourly serial measurements on trauma patients and a parabola can be generated, we can obtain more significant results.

Limitations

Since our study was retrospective, there was no standard in hemogram follow-up hours. In our hospital, RDW values gave a single reference interval according to age and gender. Routine C reactive protein (CRP) is not observed in trauma patients. For this, we could not examine

the relationship between CRP and RDW. These were the points that limited our work.

Conclusion

RDW is considered as a valuable parameter in predicting mortality in trauma patients. We are of the opinion that the serial measurements of this simple and inexpensive parameter yield more significant results in the light of the studies conducted so far. RDW is a candidate to be a part of trauma scoring systems with further prospective studies to be conducted.

Acknowledgment

Declaration of conflicting interests: The authors declared no potential conflict of interests in respect of the research, authorship and/or publication of this article.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Informed consent: All subjects gave informed consent for participation.

Author contribution statement: A.B.E. and E.Ç. conceived the presented idea. A.B.E., M.S.Y., N.K., M.T. and C.K. developed the theory and performed the computations. A.B.E., C.K., N.K. and M.S.Y. verified the analytical methods, M.T., E.Ç. and İ.G. supervised the findings of this work. All authors discussed the results and contributed to the final manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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