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Predicting mortality rate in elderly patients operated for hip fracture using red blood cell distribution width, neutrophil-to-lymphocyte ratio, and Nottingham Hip Fracture Score

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The ability to identify patients at high risk for poor outcomes before hip fracture operations is clinically important, as hip fractures may result in mortality or insufficiency in daily living activities in the elderly population.[1] Due to the high mortality rates associated with hip fractures, identifying high-risk patients is critical in terms of treatment management and prevention of a substantial economic burden on healthcare services.[2] In addition, preoperative identification of high-risk patients may be helpful for optimal timing of the operation, administration of critical care during the treatment, preparation of patient-specific informed consent, and developing a better understanding of the prognosis.

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ABSTRACT

Objectives: In this study, we aimed to compare the neutrophil-to-lymphocyte ratio (NLR), red blood cell distribution width (RDW), and Nottingham Hip Fracture Score (NHFS) according to one-year mortality estimation after hip fracture surgery in elderly.

Patients and methods: Between January 2015 and December 2019, a total of 190 elderly patients (63 males, 127 females; mean age: 82.8±6.1 years; range, 70 to 98 years) who were diagnosed with collum femoris fractures treated with hemiarthroplasty were included. The cohort was divided into two groups with NHFS ≤4 and >4 as the low- and high-risk patients, respectively and one-year mortality was assessed for both groups. The RDW was evaluated with blood values sampled on the day of admission. A cut-off of 14.5% was considered for the RDW values. The NLR values calculated on admission (NLR-D0) and postoperative Day 5 (NLR-D5) were considered the primary outcome measures.

Results: A total of 46 patients (24.2%) developed any type of complication. The NLR values higher than 5 on Days 0 and 5 were more frequently seen in the complicated patients (p=0.0016 and p<0.001). There were significantly more patients with higher RDW values (>14.5%) in the complicated group (p<0.001). The median NHFS and the rate of patients with NHFS >4 were significantly higher in the complicated patients (p<0.001 for both). The NHFS value higher than 4 had a sensitivity of 87.7% and specificity of 84.0% in predicting mortality (area under the curve [AUC]=0.910, 95% confidence interval [CI]: 0.860-0.947, p<0.001). Estimation of mortality using an RDW cut-off value of >14.5 showed 87.7% and 80.0% sensitivity and specificity, respectively (95% CI: 0.789-0.904, p<0.001). The AUC of the NLR Day 5 using a cut-off value of >6.8 was 0.953 for the prediction of mortality (95% CI: 0.912-0.978, p<0.001).

Conclusion: Age, NLR Day 5 (>5), RDW (>14.5%) and NHFS (>4) were strongly associated with mortality prediction. The NHSF and RDW values had the highest and similar sensitivity merit, while the highest specificity was in NLR-D5. Therefore, NLR, RDW and NHFS values can be used to classify risk factors in estimating one-year mortality rates in elderly patients operated for hip fractures. A multidisciplinary approach should be standardized in determining the risk factors before treatment in patients with hip fractures and in planning appropriate treatment for this risk.

Keywords: Elderly, hip fracture, mortality, predictive value, risk factor.

The neutrophil-to-lymphocyte ratio (NLR), which is defined as the ratio of absolute neutrophil count to absolute lymphocyte count in the peripheral blood, is one of the markers which can be used to identify high-risk patients. Peripheral blood NLR decreases, when the body is under stress or systemic inflammation; therefore, it can be used as a marker reflecting the severity of the disease.[3] In other words, NLR indicates the systemic inflammatory load.[4] Therefore, it has started to be used as a novel inflammatory marker in recent years. Furthermore, several studies have reported that high preoperative NLR values may be associated with the mortality risk after hip fracture surgery.[5,6] However, further large-scale studies are needed to clarify the relationship between NLR and hip fracture mortality in elderly patients.

The red blood cell distribution width (RDW) is an indicator of the range of the volume and size of red blood cells (erythrocytes).[7] The RDW index is often used to distinguish the causes of anemia in the practice of hematology. Recent studies have demonstrated that higher RDW levels are associated with adverse non-hematological health outcomes in elderly, such as cardiovascular disease, in particular, mortality, and worse outcomes in critically ill patients.[8-10] There are also studies reporting that higher RDW levels are associated with the risk of hip fracture.[11,12] In a study, a correlation was reported between the increased RDW values and poor surgical outcomes or higher mortality in patients with osteoporotic fractures.[13] Thus, preoperative RDW levels may be used combined with clinical and laboratory findings to improve the risk stratification of elderly patients who are at risk for proximal femoral fractures.[14]

Various risk parameters have been used to classify high-risk hip fractures in elderly patients.[15-22] The Nottingham Hip Fracture Score (NHFS), a scoring system that predicts both 30-day mortality and one-year mortality in elderly patients after hip fractures, is one of these parameters.[23] It comprises seven independent predictors: age (66-85 and ≥86 years); sex (male); the number of comorbidities (≥2), Mini-Mental Test score on admission (≤6/10), hemoglobin concentration on admission (≤10 g/dL), living in a healthcare facility; and the presence of malignant disease.[24]

To the best of our knowledge, the use of NLR, RDW, and NHFS values in combination to predict the mortality in elderly patients diagnosed with hip fractures has not been investigated before. In the present study, we, therefore, aimed to investigate the utility of NLR, RDW, and NHFS in predicting one-year mortality after hip fracture surgery.

PATIENTS AND METHODS

This single-center, retrospective, cohort study was conducted at Amasya University Faculty of Medicine, Department of Orthopedics and Traumatology between January 2015 and December 2019. A total of 286 consecutive patients who underwent surgery for hip fracture were screened. Inclusion criteria were as follows: aged 65 years and older, having an American Society of Anesthesiologists (ASA) score of 3, and having undergone surgery within 48 h after observation of the fracture. Exclusion criteria were as follows: having any other condition that required surgery on the same or another hip joint, multiple fractures, a pathological fracture pattern, malignancy, using immunosuppressant drugs, and having active foci of infection. Finally, a total of 190 elderly patients (63 males, 127 females; mean age: 82.8±6.1 years; range, 70 to 98 years) who were diagnosed with collum femoris fractures and treated with hemiarthroplasty were included.

All surgeries were performed by a single surgeon under spinal anesthesia. The entire surgical operation was performed using the posterior approach within the first two days of the detection of the fracture. The choice of cemented or cementless partial hip replacement was evaluated case-by-case. Patients' demographic data, preoperative comorbidities, and ASA scores, type, and duration of surgery, type of anesthesia, types of complications (if any), complete blood count (CBC) values on admission, and on a postoperative day five were recorded. NLR was calculated by dividing the absolute total neutrophil count by the absolute lymphocyte count. NLR values calculated on admission (NLR-D0) and postoperative Day 5 (NLR-D5) were identified as the primary outcome measures. Using an NLR cut-off value of 5,[25] the relationship between mortality rates and the increases in NLR-D0 and NLR-D5 values was investigated. Additionally, using an RDW cut-off value of 14.5%,[26] the relationship between mortality rates and the increases in the RDW values calculated on admission was investigated. The NHFS values were used to classify the study cohort into two groups: patients with NHFS ≤4 (low-risk patients) and patients with NHFS >4 (high-risk patients). One-year mortality rates of both groups were

calculated and compared.[23]

Statistical analysis

Statistical analysis was performed using the Jamovi 2.0.0.0 (Jamovi Project, https://www.jamovi.org), JASP 0.14.1.0 (Jeffreys' Amazing Statistics Program, https://jasp-stats.org), and MedCalc (MedCalc Statistical Software Trial Version Software, 2015, MedCalc bvba, Ostend, Belgium, http://www.medcalc.org). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were used to determine whether the numerical variables fit to the normal distribution. The independent samples t-test was used to compare two independent groups in cases where numerical variables were determined to fit to the normal distribution. The Mann-Whitney U test was used to compare two independent groups in cases where variables were determined not to conform to the normal distribution. The Pearson chi-square and Fisher exact tests were used to compare the differences between categorical variables. The Wilcoxon test was used to evaluate the changes over time between the NLR-D0 and NLR-D5, where the variables were determined not to conform to the normal distribution. The univariate and multivariate logistic regression analyses were performed to identify the factors correlated with mortality. The receiver operating characteristic (ROC) analysis using the DeLong method with the Youden index was used to determine the cut-off values of NHFS, RDW, NLR-D0, and NLR-D5 in predicting mortality. The area under the curve (AUC) and the corresponding 95% confidence interval (CI) values were calculated. A p value of <0.05 was considered

TABLE I
Demographic characteristics, laboratory groupings, and clinical outcomes of patients (n=190)

Overall	n	%	Mean±SD	Median	Min-Max
Age (year)			82.8±6.1		
Sex					
Female	127	66.8			
Male	63	33.2			
NLR Day 0					
Patients with					
≤5	38	20.0		6.7	2.3-14.1
>5	152	80.0			
NLR Day 5					
Patients with					
≤5	81	42.6		5.4	1.6-15.8
>5	109	57.4			
RDW (%)					
Patients with					
≤14.5	125	65.8			
>14.5	65	34.2			
NHFS					
Patients with	113	59.5			
≤4	77	40.5			
>4					
Development of complications	46	24.2			
Type of complication					
Cardiovascular	23	50			
Infective	23	50			
Prognosis					
Survive	125	65.8			
Non-survive	65	34.2			

SD: Standard deviation; NLR: Neutrophil-to-lymphocyte ratio; RDW: Red cell distribution width; NHFS: Nottingham Hip Fracture Score.

statistically significant.

RESULTS

Sociodemographic and clinical characteristics of the patients are shown in Table I. There was no significant difference between the sex-based groups in terms of laboratory test results and clinical outcomes (p>0.05).

The median NLR-D0 and NLR-D5 values were calculated as 6.7 and 5.4, respectively. The change in the median NLR value between Day 0 and Day 5 was significant (p<0.001). The number of patients with NLR values >5 was 152 (80%) on Day 0 and 109 (57.4%) on Day 5. Additionally, the rate of patients with RDW ≤14.5% on admission was 68.5%. A total of 113 (59.5%) patients had NHFS ≤4, while 77 (40.5%) patients had NHFS <4. One-year mortality rate of the overall study group was 34.2% (Table I).

At least one type of complication developed in 46 (24.2%) patients. Cardiovascular complications and infections, which were observed in 23 (50%) of the 46 patients, were the most common types of complications. There were significant differences between the patients with and without complications in demographic characteristics, laboratory test results, and clinical outcomes (Table II). The rate of patients with complications significantly increased with age (p=0.005). The median NLR-D0 and NLR-D5 values were significantly higher in patients with complications than those without complications (p<0.001 for both). In addition, the percentage of patients with NLR-D0 and NLR-D5 values higher than 5 in the patient group with complications was

TABLE II
Comparison of the patients' demographic characteristics, laboratory groupings, and clinical outcomes with and without complications

	Development of complications										
	Yes (n=46)					No (n=144)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)					85.2±6.7			82.0±5.8			0.005***
Sex											
Female	30	65.2				97	67.4				0.929*
Male	16	34.8				47	32.6				
NLR Day 0				8.9	4.7-14.1				6.3	2.3-9.9	<0.001**
Patients with											
≤5	3	6.5				35	24.3				0.016*
>5	43	93.5				109	75.7				
NLR Day 5				8.6	3.7-15.8				4.8	1.6-13.6	<0.001**
Patients with											
≤5	1	2.2				80	55.6				<0.001*
>5	45	97.8				64	44.4				
RDW (%)											
Patients with											
≤14.5	16	34.8				109	75.7				<0.001*
>14.5	30	65.2				35	24.3				
NHFS											
Patients with				7.0	2.0-9.0				3.0	2.0-7.0	<0.001**
≤4	9	19.6				104	72.2				<0.001*
>4	37	80.4				40	27.8				
Prognosis											
Survive	18	39.1				107	74.3				<0.001*
Non-survive	28	60.9				37	25.7				

SD: Standard deviation; NLR: Neutrophil-to-lymphocyte ratio; RDW: Red cell distribution width; NHFS: Nottingham Hip Fracture Score; * Pearson chi-square or Fisher exact test; ** Mann-Whitney U test; *** Independent Samples t-test.

TABLE III
Comparison of the demographic characteristics, laboratory groupings, and clinical outcomes of the patients with and without mortality

	Prognosis									
	Survive (n=125)					Non-survive (n=65)				
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			82.1±6.2					84.2±5.8			0.022***
Sex											
Female	86	68.8				41	63.1				0.527*
Male	39	31.2				24	36.9				
NLR Day 0				6.7	2.3-11.2				6.8	3.4-14.1	0.130**
Patients with											
≤5	29	23.2				9	13.8				0.181*
>5	96	76.8				56	86.2				
NLR Day 5				4.6	1.6-8.7				8.6	4.5-15.8	<0.001**
Patients with											
≤5	79	63.2				2	3.1				<0.001*
>5	46	36.8				63	96.9				
RDW (%)											
Patients with											
≤14.5	111	88.8				14	21.5				<0.001*
>14.5	14	11.2				51	78.5				
NHFS				3.0	2.0-7.0				6.0	3.0-9.0	<0.001**
Patients with											
≤4	105	84.0				8	12.3				<0.001*
>4	20	16.0				57	87.7				
Development of complications	18	14.4				28	43.1				<0.001*
Type of complication											
Cardiovascular	9	50.0				14	50.0				0.999*
Infective	9	50.0				14	50.0				

SD: Standard deviation; NLR: Neutrophil-to-lymphocyte ratio; RDW: Red cell distribution width; NHFS: Nottingham Hip Fracture Score; * Pearson chi-square or Fisher exact test; ** Mann-Whitney U test; *** Independent Samples t-test.

significantly higher than the percentage of patients with NLR-D0 and NLR-D5 values higher than 5 in the uncomplicated patient group. Also, there were significantly more patients with RDW values >14.5% among patients with complications than patients without complications (65.2% *vs.* 24.3%, p<0.001). Both the median NHFS and the rate of patients with NHFS >4 were significantly higher among patients with complications than patients without complications (p<0.001 for both). The one-year mortality rate was 60.9% and 25.7% in the patient groups with and without complications, respectively, indicating a significant difference between the groups (p<0.001) (Table II). The two most common complications were cardiovascular complications and infections. However, there were no significant differences between the patients with cardiovascular complications and infections in demographic characteristics, laboratory test results, and clinical outcomes (p>0.05).

Mortality developed in 65 (34.2%) patients. There were significant differences between

TABLE IV
Correlation analysis of the numerical variables

		r	*p*
Age	NLR Day 0	0.380	<0.001
Age	NLR Day 5	0.355	<0.001
Age	NHFS	0.337	<0.001
NLR Day 0	NHFS	0.328	<0.001
NLR Day 5	NHFS	0.691	<0.001

NLR: Neutrophil-to-lymphocyte ratio; NHFS: Nottingham Hip Fracture Score; Spearman's rho correlation coefficient.

TABLE V
Association of RDW and NHFS

	RDW								
	≤14.5 (n=125)				>14.5 (n=65)				
	n	%	Median	Min-Max	n	%	Median	Min-Max	*p*
NHFS									
Patients with			3.0	2.0-9.0			6.0	2.0-9.0	<0.001**
≤4	98	78.4			15	23.1			<0.001*
>4	27	21.6			50	76.9			

RDW: Red cell distribution width; NHFS: Nottingham Hip Fracture Score; * Pearson chi-square test; ** Mann-Whitney U test

TABLE VI
ROC analysis of NHFS, NLR Day 0, and NLR Day 5 in predicting the mortality

	AUC	Sensitivity	Specificity	Cut-off	95% CI	*p*
NHFS	0.910	87.7	84.0	>4	0.860-0.947	<0.001
NLR Day 0	0.567	70.8	44.0	>6.1	0.493-0.639	0.120
NLR Day 5	0.953	86.2	94.4	>6.8	0.912-0.978	<0.001

ROC: Receiver operating characteristic; NHFS: Nottingham Hip Fracture Score; NLR: Neutrophil-to-lymphocyte ratio; AUC: Area under curve; CI: Confidence interval.

the deceased and survived patients in terms of age, NLR-D5, RDW, and NHFS (Table III). The deceased patients were significantly older than the survived patients (84.2±5.8 years *vs.* 82.1±6.2 years, respectively; p=0.022). Both the median NLR-D5 and the rate of patients with NLR values >5 were significantly higher among the deceased patients (p<0.001 for both). The rate of patients with high RDW values (>14.5%) among deceased patients was also significantly higher than that of survived patients (78.5% *vs.* 11.2%, respectively; p<0.001). Both the median NHFS and the rate of patients with NHFS >4 were significantly higher in the deceased patient group (p<0.001 for both) (Table III). There was no significant relationship between the type of complication and mortality (p=0.999), although the deceased patients had significantly more complications than the survived patients (p<0.001). There was a significant correlation between age, NLR-D0, NLR-D5, and NHFS (Table IV).

The median NHFS of patients with RDW values higher than 14.5% was 6. The rate of patients with NHFS >4 among patients with RDW values >14.5% was 76.9%. A comparison of the median NHFS values and the rates of patients with NHFS >4 revealed significant differences between the patients with RDW values >14.5% and ≤14.5% (p<0.001 for both) (Table V).

The sensitivity and specificity values of NHFS >4 in predicting mortality were determined as 87.7% and 84.0%, respectively (AUC=0.910, 95% CI: 0.860-0.947, p<0.001). Estimation of mortality using an RDW cut-off value of >13.7 showed 87.7% sensitivity and 80.0% specificity (95% CI: 0.789-0.904, p<0.001). The AUC of the NLR-D5 using a cut-off value of >6.8 for predicting mortality was determined as 0.953 (95%

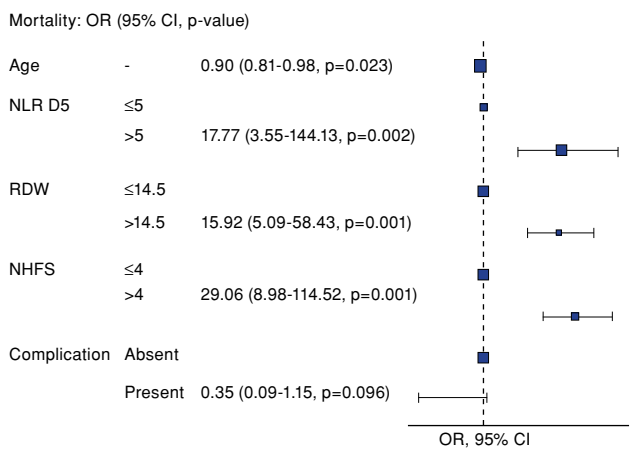

FIGURE 1. Graphical representation of logistic regression analysis showing the independent risk factors for mortality.
OR: Odds ratio; CI: Confidence interval; NLR D5: Neutrophil-to-lymphocyte ratio on Day 5, RDW: Red cell distribution width; NHFS: Nottingham Hip Fracture Score.

CI: 0.912-0.978, p<0.001) (Table IV).

Univariate and multivariate logistic regression analyses were used to estimate mortality. Accordingly, age, NLR-D5, RDW, NHFS, and the presence of at least one complication were identified as independent risk factors for mortality in the univariate analysis. Further analysis of these factors in the multivariate analysis revealed that age, NLR-D5 (>5), RDW (>14.5%), and NHFS (>4) were independent risk factors for mortality (Figure 1).

DISCUSSION

In the present study, we investigated the prognostic powers of three independent parameters in predicting the one-year mortality in elderly patients who underwent hip fracture surgery. As a result, the median NLR and RDW values and the rate of patients with NHFS ≥4 were significantly higher in the deceased patient group compared to the survived patients. A significant and positive correlation was also found between having a complication and one-year mortality, regardless of the type of complication. In addition, based on the cut-off values, high NLR, NHFS, and RDW values and age were found to be positively and significantly correlated with mortality.

Postoperative complications increase with advanced age and comorbidities. It is crucial to identify the patients at risk for developing complications and the diseases that may lead to complications. Of 190 patients included in the study, 46 (24.2%) patients had at least one type of complication. Cardiovascular complications and infections, which were seen in 23 (50%) of the 46 patients with complications, were the most common types of complications. These findings are in line with the risk factors identified for mortality after femoral neck fracture surgery, as well as the risk factors identified for one-year mortality after hip fracture, reported in the literature.[15] There are also studies in which NLR, RDW, or NHFS are emphasized for their prognostic value in predicting mortality.[5,6,13,14,24]

In previous studies, NLR was significantly correlated with the one-year mortality rate following hip fractures.[27,28] In one of these studies, Forget et al.[27] reported that NLR-D5 >5 was a risk factor for postoperative mortality in patients with hip fractures. In another study, Temiz and Ersözlü[28] found that high NLR-D0 values (based on a cut-off value of 4.7) predicted mortality in elderly patients with hip fracture. Similarly, Fisher et al.[29] reported that high NLR-D0 values (based on a cut-off value of 8.5) predicted hospital mortality in patients. Bingol et al.[5] also showed that NLR was a useful predictor in predicting the one-year mortality in elderly patients with hip fractures. In this study, the median NLR-D5 and the rate of patients with NLR >5 were significantly higher in deceased patients than in the survived patients. Additionally, NLR-D5 values of >6.8 predicted one-year mortality with 86.2% sensitivity and 94.4% specificity.

Several studies have shown that RDW is associated with the increased mortality risk in middle-aged and elderly patients.[7,30] Recent studies have demonstrated that RDW is an independent predictor factor of mortality in patients with hip fractures.[12,31] Zehir et al.[12] found a significant relationship between mortality, advanced age, and high RDW level treatment with partial prosthesis. The mortality rate in patients with high RDW levels (>14.5%) was 2.8 times higher than in patients with low RDW levels.[12] Lv et al.[32] reported that elevated RDW values were significantly associated with the increased long-term mortality following hip fractures in non-anemic elderly patients. Garbharran et al.[31] also found that high RDW values were associated with four-month and one-year mortality rates in patients with hip fractures. Yin et al.[26] showed that RDW and ASA scores were independent factors for two-year mortality in orthogeriatric patients treated with surgery. In the present study, there were significantly more patients with high RDW levels (>14.5%) in the deceased patient group than in the survived patient group. In addition, the sensitivity and specificity values of the RDW using a cut-off value of >13.7 were determined as 87.7% and 80.0%, respectively (95% CI: 0.789-0.904, p<0.001).

The NHFS can reportedly predict 30-day and one-year mortality rates in patients with hip fractures.[33] In a study, patients with NHFS of ≤4 were considered low-risk, and patients with NHFS of ≥5 were considered high-risk patients.[33] Wiles et al.[23] investigated the correlations between low (≤4) and high NHFS (≥5) values and one-year mortality in patients with hip fractures. They divided the patients into two groups: patients that underwent hip fracture surgery within 48 h of the fracture and patients that underwent hip fracture surgery any time after 48 h of the fracture. The authors found that the mortality rate in the patient group with high NHFS values was 30% higher than in the patient group with low NHFS values, indicating a significant difference between the groups. In our study, the median NHFS and the rate of patients with NHFS >4 were significantly higher in the deceased group than in the survived group.

Additionally, NHFS values of >4 predicted one-year mortality with 87.7% sensitivity and 84.0% specificity.

To the best of our knowledge, the use of NLR, RDW, and NHFS values in combination to predict the mortality in elderly patients diagnosed with hip fractures has not been investigated previously. Statistical analyses revealed significant correlations between age, NLR-D0 and NLR-D5, and NHFS in our study. Additionally, the mortality rate was significantly higher in the patient group with complications than in the patient group without complications. When the NLR, RDW, and NFHS values were evaluated in terms of sensitivity and specificity, the highest sensitivity was seen in NFHS (87.7%) and RDW (87.7%), while the highest specificity was in NLR-D5 (94.4%).

Apart from its strengths, the fact that the study was carried out in a single-center, retrospective design is the main limitation. Therefore, further large-scale, multi-center studies are needed to confirm these findings. Nonetheless, this study is remarkable, as it is the first study in the literature to examine these findings together.

In conclusion, our study results revealed that high NLR, RDW, and NHFS values were the risk factors for one-year mortality in elderly patients operated for hip fractures. In addition, advanced age, NLR-D5 (>5), RDW (>14.5%), and NHFS (>4) had prognostic values in predicting one-year mortality rate in this patient group. The NHSF and RDW values have the highest and similar sensitivity merit, while the highest specificity was in the NLR-D5. Based on these findings, we conclude that all three parameters, that is, NLR, RDW, and NHFS, can be used for stratification of patients with hip fractures according to the one-year mortality risk, using the respective cut-off values established in this study. However, a multidisciplinary approach is needed to standardize the risk factors related to hip fracture to plan for appropriate treatments in this patient population.

Ethics Committee Approval: The study protocol was approved by the Amasya University Non-Interventional Clinical Research Ethics Committee (date: 06.05.2021, no: 66). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: The first draft of the manuscript was written by: A.Y.; Material preparation, data collection and analysis were performed: S.K., A.Y.; All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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