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Clinical importance of red cell distribution width and red cell index in pulmonary embolism

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Abstract. – OBJECTIVE: Discrimination of high mortality risk pulmonary embolism (PE) patients at the first admission to the hospital is important for the follow-up and the clinical progress of patients. Additional biomarkers are needed for the initial assessment. The aim of this study was to investigate whether red cell distribution width (RDW) and red cell index (RCI) were associated with 30-day mortality risk and mortality rate in PE patients.

PATIENTS AND METHODS: 101 PE patients and 92 non-PE patients were included in the study. PE patients were divided into three groups according to 30-day mortality risk. The correlations of RDW and RCI with PE, 30-day mortality risk and mortality rates were determined.

RESULTS: RDW value was significantly higher in the PE group than in the non-PE group (15.0% *vs.* 14.3%, respectively, p=0.016). The cut-off value of RDW to discriminate PE from the non-PE group was 14.55% (sensitivity: 45.7%; specificity: 55.5%, p=0.016). There was a significant correlation between RDW values and mortality rates (R^2= 0.11, p=0.001). The cut-off value of RDW in mortality of PE was 15.05% (sensitivity: 40.6%, specificity: 31.2%, p=0.001). On the other hand, simultaneously measured RCI values were similar between PE and non-PE groups. There wasn't any significant difference in RCI values between 30 day-mortality risk groups. No correlation was found between RCI and the mortality due to PE.

CONCLUSIONS: To the best of our knowledge, this is the first report in the literature to simultaneously investigate RDW and RCI values for their association with 30-day mortality risk and mortality rates in pulmonary embolism (PE) patients. Our findings suggest that RDW values may serve as a new early predictor, while RCI values were not predictive.

Key Words:
Red cell distribution width, Red cell index, Pulmonary embolism.

Introduction

Venous thromboembolism (VTE), generally presenting as deep venous thrombosis (DVT) or pulmonary embolism (PE), is the third most frequent cardiovascular disorder[1]. The annual incidence of PE is 39-115/100,000 and it causes approximately 300,000 deaths per year in US[2,3]. Its 30-day mortality is 1.8%, and its seven-day mortality is 1.1%[4]. It has been reported that about 34% of deaths generally occur within a few hours[5]. The most important factor affecting the success of the treatment is the early prediction of the mortality risk on admission. Pulmonary embolism severity index (PESI) and its simplified version Simple PESI (sPESI) scores have been frequently used to evaluate the severity of the disease. According to the European Society of Cardiology-2019 (ESC-2019) pulmonary thromboembolism treatment guideline, the patient's hemodynamic status, echocardiographic findings, and troponin values, in addition to PESI or sPESI, should be taken into account in the assessment of 30-day mortality risk. The patients are classified for their risk of 30-day mortality in three groups as high, medium and low-risk subjects[6]. However, a patient with a low or medium mortality risk may quickly become a high-risk patient because the risk determined at the beginning may not remain constant and the hemodynamic status may quickly change within hours. Therefore, additional biomarkers that can be measured at the first admission to reflect the mortality risk of the patient are needed.

Red cell distribution width (RDW) is a parameter calculated among routine complete blood count (CBC) parameters. It reflects the heterogeneity and distribution of red sphere sizes. In previous studies[7-10], it has been shown that high RDW values might be associated with increased mortality in patients with pulmonary thromboembolism.

Red cell index (RCI) is another recently defined biomarker that reflects the pulmonary functions of patients[11]. RCI is calculated by using hemoglobin levels and red blood cell, lymphocyte and platelet counts obtained from complete blood count measurements. RCI has been previously evaluated in chronic obstructive pulmonary

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disease and was shown to be associated with decreased pulmonary functions[12]. This new biomarker has not been studied previously in the literature for its predictive value for mortality in patients with PE.

The aim of this study was to investigate RDW and RCI simultaneously in a cohort of Turkish patients for their association with 30-day mortality risk, and also with overall mortality rates due to PE.

Patients and Methods

Between October 2015 and May 2022, 101 PE patients who were diagnosed in Hacettepe University Hospital, Department of Chest Diseases, were included in the study group retrospectively. Non-PE or healthy subjects (n=92) were included as the control group.

This study was approved by the Ethics Committee of Hacettepe University (19.04.2022 - 2022/07-33) and conducted in accordance with the principles in Declaration of Helsinki.

Patients diagnosed as PE by computed tomography pulmonary angiography (CTPA) were included in the study. Exclusion criteria were: Presence of 1) chronic liver disease or cirrhosis, 2) renal failure, 3) cancer, 4) pregnancy, 5) hematological diseases or history of blood transfusion within 2 weeks, or 6) patients younger than 18 years old of age. Demographic information, co-morbidities, and blood test values of the patients at the time of PE diagnosis were obtained from the hospital database. CTPA was performed using pulmonary embolism protocol.

The normal reference range for RDW is from 11.8% to 14.3% in the hospital laboratory. RCI values were calculated by using hemoglobin, red blood cell, lymphocyte and platelet counts. It is calculated by the following equation:

RCI = [Red blood cell count x Hemoglobin (gr/L)]/(Lymphocyte count x Platelet count).

The 30-day mortality risks were assessed according to the recent ESC 2019 guideline[13]. Information for mortality was obtained from the electronic mortality declaration system, retrospectively.

Statistical Analysis

SPSS software version 25 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Statistical significance was assumed when the *p*-value is lower than 0.05. Distribution of variables was investigated using visual, analytical methods and Kolmogorov-Smirnov test. Data were presented as means±standard deviations, medians (min-max) or percentages.

Mann-Whitney U test or *t*-test was used to compare variables between non-PE and PE groups, where applicable according to the data distribution. Variables in the PE group were compared among 30-day mortality risk groups (low, medium and high mortality risk groups) with ANOVA or Kruskal-Wallis tests, where applicable according to the data distribution. Frequencies were compared by using the Chi-square test. The associations between non-normally distributed variables were analyzed with Spearman test. A 5% types-I error level was used to infer statistical significance.

The capacity of RDW in predicting PE diagnosis and mortality was investigated using receiver operating characteristics curve (ROC) analysis. When a significant cut-off value was observed, sensitivity and specificity values were presented. While evaluating the area under the curve, a 5% type-I error level was used to accept a statistically significant predictive value.

Results

Demographics, co-morbidities, and blood test parameters of 101 PE and 92 non-PE patients are summarized in Table I. In comparison of the clinical characteristics of subjects in the PE group and the non-PE group, the mean age in the patient group was higher but comparable with that of the control group. While female-to-male ratios and smoking status were similar between the two groups. Furthermore, the occurrence of co-morbidities such as diabetes mellitus type-2 (DM), chronic obstructive lung disease (COPD), coronary artery disease (CAD), cerebrovascular disease or asthma were similar. Among the reported co-morbidities, only hypertension was significantly more commonly observed (26.4% *vs*. 15.0%) in the PE group. The number of deceased patients was also significantly higher in the PE group (31.6% *vs*. 9.7%) than in the non-PE group.

For the laboratory measurements, it was found that D-dimer levels, white blood cell (WBC) and neutrophil counts were significantly higher in the PE group than in the non-PE group. Hemoglobin, troponin, brain-type natriuretic peptide (BNP), C-reactive protein (CRP), platelet count, and RCI were similar between the study and control groups ($p>0.05$).

Table I. Demographics, co-morbidities and blood test parameters of patients.

	Non-PE group n=92	PE Group n=101	*p*-value
Age* (years)	57.1±18.1	62.21±15.36	0.036
Female/Male (n)	44/48	46/55	0.75
Smoker/Ex smoker/Nonsmoker (n)	7/25/60	14/34/53	0.15
Number of cigarettes (package per year)	0 (0-100)	0 (0-70)	0.09
Diabetes mellitus type-2 (DM)	18 (9.3%)	27 (14%)	0.24
Hypertension (HT)	29 (15%)	51 (26.4%)	0.008
COPD	10 (5.2%)	4 (2.1%)	0.065
Coronary artery disease (CAD)	13 (6.7%)	14 (7.3%)	0.95
Asthma	5 (2.6%)	7 (3.6%)	0.66
Cerebrovascular disease	3 (1.6%)	8 (4.1%)	0.163
Dementia	4 (2.1%)	2 (1%)	0.34
Number of deceased patients	9 (9.7%)	32 (31.6%)	0.007
Haemoglobin* (gr/dL)	12.8±2.3	13.25±14.12	0.80
D-Dimer (mg/L)	1.89 (0.22-16.3)	7.05 (1.14-69.2)	<0.0001
Troponin (ng/L)	7.25 (2.3-3,332)	11.2 (2.3-662)	0.085
BNP (pg/mL)	68.1 (10-6,616)	83.5 (10-2,717)	0.405
CRP (mg/dL)	4.29 (0.23-45.2)	6.7 (0.07-29.3)	0.254
Neutrophil count (K/µL)	5,245 (710-43,740)	6,610 (700-37,700)	0.009
WBC (K/µL)	8,000 (1,500-196,900)	9,200 (1,600-28,700)	0.035
Platelet count* (K/µL)	233,336±99,922	224,613±152,262	0.64
RCI	1.57 (0.01-3.9)	1.47 (0.02-23.6)	0.40
RDW (%)	14.35 (12.5-20)	15 (12.6-27)	0.016

Data were represented by median (min-max) or (*) mean±standard deviation. BNP: Brain type natriuretic peptide; CRP: C-reactive protein; WBC: White-blood count; RCI: Red-cell index; RDW: Red cell distribution width; DM: Diabetes mellitus; HT: Hypertension; COPD: Chronic obstructive pulmonary disease.

We found that RDW measurements were significantly higher in the PE group than in the non-PE group (15.0% *vs.* 14.35%, p=0.02). In the ROC analysis, the cut-off value of RDW to discriminate PE from non-PE subjects was calculated as 14.55% (Figure 1, AUC: 0.400, sensitivity: 45.7%; specificity: 55.5%, p=0.016).

In the correlation analysis for overall mortality rates between PE-group and the control group, a significant correlation between RDW and the number of deceased patients (R^2= 0.11, p=0.001) (Figure 2) was observed; while a correlation for RCI values between the two groups was not observed (R^2=0.012, p=0.26).

In the ROC curve analysis, the cut-off value of RDW for the mortality due to PE was 15.05% (Figure 3, AUC: 0.325, sensitivity: 40.6%, specificity: 31.2%, p=0.001).

Mortality risk groups for PE patients are summarized in Table II. In the comparison of the clinical characteristics of PE subjects between 30-day mortality risk groups, the youngest PE patients were in the low-mortality risk group and the oldest ones were in the medium-mortality risk group. Female/male ratio was higher in the high mortality risk group than in the other groups and the number of smokers was higher in the low mortality risk group than in the other groups (Table II). In terms of comorbidities, the number of DM patients was higher in the high-mortality risk group and the number of HT patients was higher in the medium-mortality risk group. Pulmonary artery pressures and the number of patients with tricuspid regurgitation were significantly higher in the high-mortality risk group. Other co-morbidities and ejection fraction values were similar in all groups.

For the laboratory measurements, D-dimer, troponin, BNP and neutrophil counts were found significantly higher in the high mortality risk group than in other groups. The highest WBC and RDW values were in the medium mortality risk group. CRP, platelet count and RCI values were similar in all groups (Table II).

RDW was correlated with BNP levels (R^2=0.078, p=0.006) but not with troponin, D-Dimer or CRP values (p>0.05). The median duration of hospital stay in the PE group was 6 days (range: 0-80 days) while 0 days in the non-PE group. Median duration of ICU (Intensive Care Unit) stays both in the PE group and the non-PE group was 0 days. The average duration of hospital stay was significantly higher in the high-risk group than in other groups (medians, 11 days *vs.* 7 and 0 days, respectively), while the average durations for ICU stay were

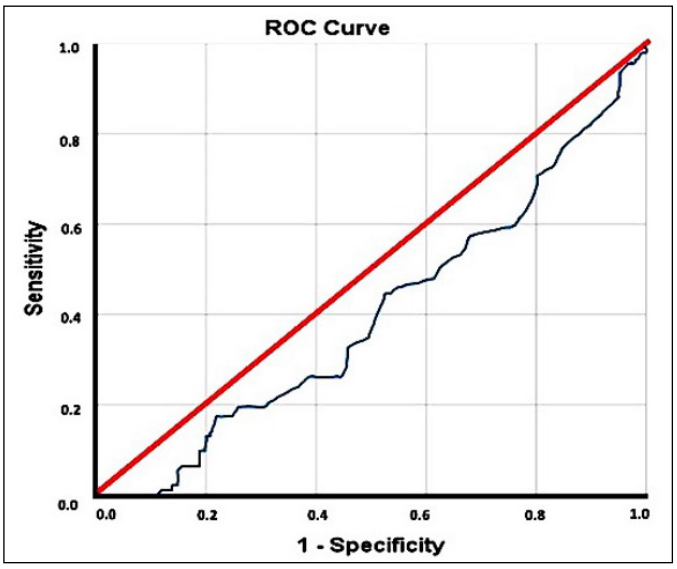

Figure 1. The ROC curve of RDW at the diagnosis of PE.

statistically similar (medians, 4 days *vs.* 2 and 0 days, respectively) (Table II).

In the clinical follow-up for mortality, the number of deceased patients was significantly different among risk groups (Table II, p=0.009). The highest number of deceased patients was in the medium-mortality risk group (22 patients, mortality rate of 44.8%). In line with this finding, the mean RDW value in the medium-risk group was significantly higher than the other two groups (15.6 *vs.* 14.3 and 15.1, respectively, p=0.038). Other parameters that were found significantly higher in the medium-risk group patients were age, female-to-male ratio, neutrophil counts, and the number of hypertensive subjects. When the same parameters above (RDW, age, female/male ratio, neutrophil count, and the number of hypertensive subjects) were compared between medium and high mortality risk groups, no statistically significant differences were observed (all p-values >0.05). Significant correlations with the number of deceased patients were only detected for RDW and neutrophil counts (R^2=0.07, p=0.01 and R^2=0.05, p=0.04, respectively).

Discussion

In this study, we investigated whether concurrent measurements of RDW and RCI were asso-

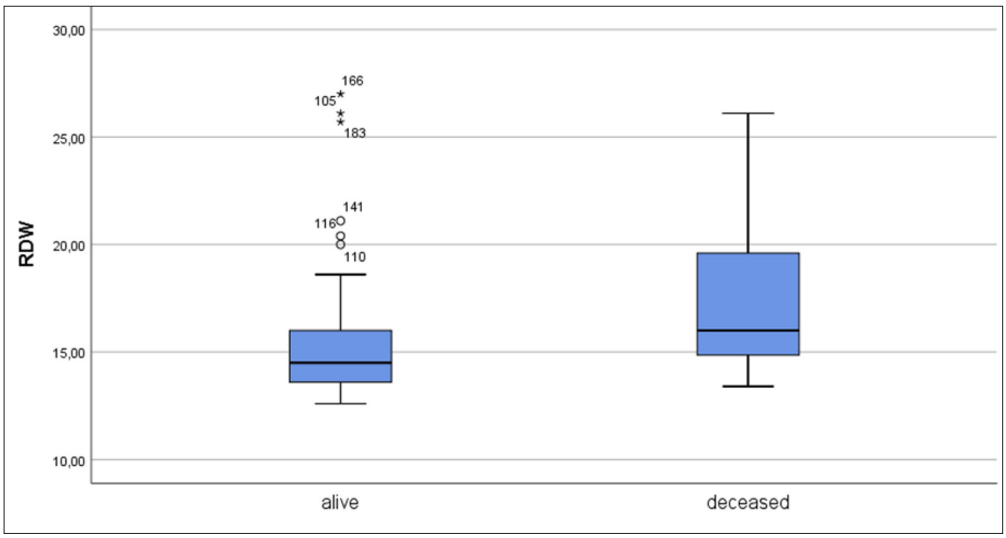

Figure 2. The correlation between RDW and the numbers of deceased patients

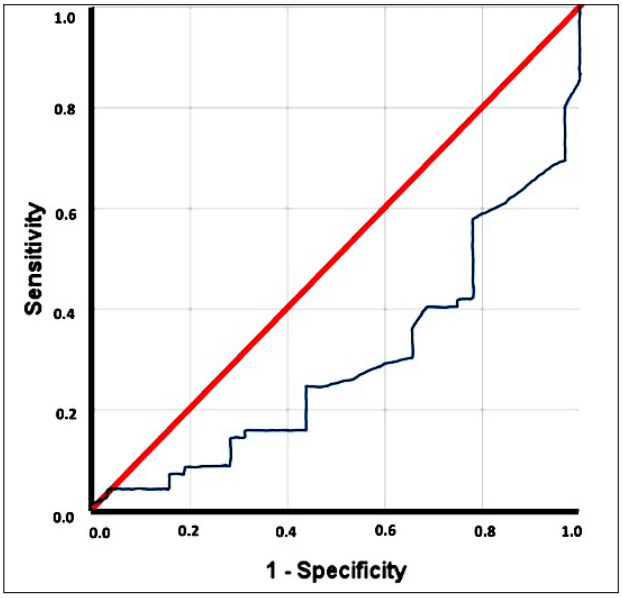

Figure 3. The ROC curve of RDW for mortality in PE patients.

ciated with the 30-day mortality risk and mortality rates in patients with pulmonary embolism. To our knowledge, this is the first report in the literature to simultaneously investigate RDW and RCI for their association with 30-day mortality risk and mortality rates in PE patients. Our findings suggest that RDW values may serve as a new early predictor, while RCI values were not predictive in the assessment of the mortality risk in PE patients.

In the literature, while the relationship between RDW and PE has been little investigated, the association between PE and RCI have not been investigated before. In a study by Guang et al[11], a relationship between RCI values and PCO_2 and FEV1/FVC values has been shown. In a more recent study, Huang et al[12] reported RCI as a novel biomarker to better assess pulmonary function and severity of COPD as compared to the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR).

In our study, although we found that RDW was correlated with 30-day mortality risk and mortality rates in PE, a correlation between RCI and mortality risk or mortality rates in PE was not evident. There was a correlation between RDW and the number of deceased patients (Figure 2, R^2=0.11, p=0.001). The highest RDW values and the highest mortality rate were observed in the medium-mortality risk group. This finding is of clinical importance since it supports the previous findings that RDW may be used as an early predictor for mortality. The mortality rate was lower in the high-risk group as compared to the medium-risk group in our patient group. One reason that may explain this finding is that troponin, BNP and pulmonary artery pressure were detected higher in the high-risk group than the other two groups, thereby the patients were treated with thrombolytic agents in this group. In the medium-risk group, there were possibly some patients with high-mortality risk but their troponin, BNP and pulmonary artery pressures were not elevated at the first admission. Since such patients were not included in the high-risk group, they were not administered thrombolytic agents.

The relationship between RDW and mortality in PE was investigated in a few other studies[14,15]. Jurin et al[14] reported that the calculation of on-admission RDW improves the stratification of 30-day mortality risk based on PESI scores in acute PE. Slajus et al[15] found out that sPESI including RDW, hematocrit and neutrophil-lymphocyte ratio parameters had a better predictive ability as compared to sPESI alone. In a systematic review and meta-analysis about RDW in acute PE, RDW was found relatively efficient as a metric predictor[16]. In a study by Yazıcı et al[10], increasing RDW levels after admission to the hospital was found to be associated with higher mortality rates. Our findings further support the view that RDW may be used as an early predictor of mortality, particularly in the medium-risk group of patients with PE.

It is still not known whether higher RDW levels are the cause or the consequence of the pathological processes. RDW was associated with mortality in disorders other than PE, such as

Table II. Patients' characteristics in PE 30-day mortality risk groups in PE.

	Low-mortality risk group (n=27)	Medium-mortality risk group (n=49)	High-mortality risk group (n=25)	*p*-value
Age* (years)	55.19±12.97	66.49±13.6	61.40±18.36	0.007
Female/Male	8/19	22/27	16/9	0.045
Smoker/Ex-smoker/Non-smoker	9/7/11	5/19/25	0/8/17	0.007
Number of cigarettes (package per year)	0 (0-20)	0 (0-65)	10 (0-25)	0.178
DM	5	9	13	0.004
HT	8	29	14	0.039
COPD	0	3	1	0.42
Coronary artery disease	5	5	4	0.56
Asthma	2	5	0	0.26
Cerebrovascular disease	3	3	2	0.74
Dementia	1	1	0	0.63
Pulmonary artery pressure (mmHg)	27.5 (20-35)	35 (30-55)	45 (35-60)	<0.0001
Ejection fraction	60 (60-60)	60 (45-65)	57.5 (50-60)	0.268
Tricuspid regurgitation	1 (0-2)	2 (1-3)	2.5 (1-3)	0.003
Haemoglobin (gr/dL)	12.8 (7.8-16.8)	11.61±2.19	11.53±2.39	0.068
D-dimer (mg/L)	2.92 (1.30-4.77)	6.79 (1.14-25.14)	17.15 (5.25-41.97)	0.0098
Troponin (mg/L)	5.15 (2.30-11.20)	14.30 (2.30-662)	386 (99.80-645)	<0.0001
BNP (pg/mL	17.75 (10-101.70)	133.5 (10-1,014)	182 (17.70-463.8)	<0.0001
CRP (mg/dL)	4.47 (0.52-14)	2.62 (0.07-20.39)	1.71 (0.64-6.66)	0.74
Neutrophil count (K/µL)	4,500 (1,650-5,740)	8,250 (1,000-37,700)	7,530 (3,860-25,500)	0.032
WBC (K/µL)	7,550 (4,400-9,000)	10,800 (2,000-21,200)	8,800 (4,800-28,500)	0.22
Platelet count (K/µL)	207,000 (117,000-470,000)	204,000 (21,000-424,000)	191,000 (9,000-384,000)	0.11
RCI	1.27 (0.54-3.67)	1.59 (0.23-23.6)	0.83 (0.19-3.5)	0.31
RDW (%)	14.3 (14-16.3)	15.6 (12.8-23.1)	15.1 (13.6-21.1)	0.038
Hospital Stay (days)	0 (0-80)	7 (0-54)	11 (0-75)	0.001
ICU Stay (days)	0 (0-80)	2 (0-36)	4 (0-66)	0.068
Number of deceased patients	3 (11.1%)	22 (44.8%)	7 (28%)	0.009

Data were represented by median (min-max) or (*) mean±standard deviation. BNP: Brain type natriuretic peptide; CRP: C-reactive protein; WBC: White-blood count; RCI: Red-cell index; RDW: Red cell distribution width; DM: Diabetes mellitus; HT: Hypertension; COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit.

sepsis or pulmonary fibrosis[17-19]. It is well-known that elevated levels of cytokines in inflammation may decrease sensitivity and production of erythropoietin in the bone marrow, slowing down the maturation of erythrocytes[20,21]. On contrary, there are some reports claiming that the association between RDW and mortality was independent of inflammation[22,23]. In support of the latter view, RDW values were not correlated with CRP values in our patient group.

In our study, the cut-off value of RDW was 14.55% for discrimination of PE from the non-PE group and 15.05% for mortality. Similarly, Bucciarelli et al[24] reported that the risk of VTE was increased by 2.5-fold in patients with RDW>14.624. In a study by Martínez-Quintana et al[25], a RDW value over 15.0 % was reported as a predictive factor for major adverse cardiac events. Also, Pehlivanlar-Kucuk et al[26] reported that a RDW values over 15.2% might serve as an independent risk factor for predicting mortality from PE.

Conclusions

In conclusion, RDW may be used as an early predictor of PE and its mortality risk, while RCI was not found useful in PE diagnosis or prediction of mortality. Further studies are required and should be encouraged in various ethnic groups to investigate the association of RCI and RDW simultaneously in cardiovascular diseases and VTE, particularly in the current days, in which these disorders have increased due to factors such as COVID-19 epidemic that are known to severely affect cardiovascular and pulmonary health status in general population.

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Ethics Approval
This study was approved by the Ethics Committee of Hacettepe University (19.04.2022 - 2022/07-33) and conducted in accordance with the principles in Declaration of Helsinki.

Informed Consent
Not applicable due to the retrospective nature of the study.

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Authors' Contributions
Babaoglu and Sarinc-Ulasli, have substantial contributions to the conception and design of the study, acquisition of data, or analysis and interpretation of data; drafting the article or making critical revisions related to relevant intellectual content of the manuscript; supervision; validation and final approval of the version of the article to be published.

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Conflict of Interest
The authors declare no conflicts of interest.

Availability of Data and Materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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