ORIGINAL RESEARCH

Red Cell Distribution Width-to-High-Density Lipoprotein Cholesterol Ratio (RHR): A Promising Novel Predictor for Preoperative Deep Vein Thrombosis in Geriatric Patients with Hip Fracture

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Background: Deep vein thrombosis (DVT) is a devastating complication in geriatric patients before hip fracture surgery, and the predictive value of red cell distribution width (RDW) and high-density lipoprotein cholesterol (HDL-C) for DVTs after hip fracture remains to be established. This study aimed to assess the predictive value of RDW, HDL-C, and RDW-to-HDL-C ratio (RHR) in preoperative DVTs screening.

Methods: We retrospectively analyzed the data of geriatric patients (≥65 years old) admitted for hip fracture surgery between 2015 and 2020. The receiver operating characteristic (ROC) curve and related parameters were used to evaluate the predictive value of the biomarkers. Patients were divided into two groups according to the cutoff value of RHR, and propensity score matching (PSM) and subgroup analyses were performed to assess the true correlations between RHR and DVT.

Results: Among 2566 eligible patients included, we identified RDW with the area under ROC curve (AUC) of 0.532, cut-off value of 15.89, specificity of 88.2%, sensitivity of 18.2%, HDL-C with AUC of 0.574, cut-off value of 1.20, specificity of 55.6%, sensitivity of 59.3%, and RHR with AUC of 0.578, cut-off value of 13.45, specificity of 71.3%, sensitivity of 43.4%. RHR (>13.45) was independently associated with 1.54-fold risk (95% CI: 1.11–2.14, P=0.011) of DVTs among the post-PSM cohort. And compared with the counterparts, the relative risk of RHR associated with DVT was higher in the subgroups of aged 65–79 years (1.61 vs 1.45), non-hypoproteinemia (2.70 vs 1.29), non-diabetic (1.58 vs 1.41), non-hypertension (2.40 vs 1.06), ASA score I-II (2.38 vs 1.04), and femoral neck fracture (1.70 vs 1.50).

Conclusion: RDW, HDL-C and RHR were valuable biomarkers in predicting preoperative DVTs in geriatric patients with hip fracture, and RHR would be more efficient in the subgroups of younger age, better medical condition or femoral neck fracture.

Keywords: geriatric patients, hip fracture, deep vein thrombosis, red cell distribution width, high-density lipoprotein cholesterol

Introduction

Deep vein thrombosis (DVT) is a prevalent (11.1–35.0%) in geriatric patients with hip fracture before surgery,[1–3] which potentially causes pulmonary embolism (PE) and even leads to mortality.[4] However, the vast majority (75.2–100%) of the DVTs are asymptomatic, which thus pose clinical challenges for early diagnosis and timely targeted intervention.[5–7] Given that the incidence of hip fracture in geriatric patients would increase dramatically with the exponential increase of

the aging population,[8] improving the ability in predicting or diagnosing DVTs in newly admitted patients becomes increasingly significant and urgent.

In addition to rotational thromboelastometry,[9–11] the hematologic parameters, used alone or in combination with other baseline characteristics to establish prediction models, were cost-effective ways to address this issue.[12–14] D-dimer, as a reliable biomarker for coagulation and fibrinolysis, is generally used in clinical practice for primary screening of DVT due to its high sensitivity and convenience.[15] However, low specificity limited its further application in the DVT diagnostic algorithm. Therefore, it remains a hot spot to find reliable biomarkers with high specificity for the development of DVT prediction models currently, and more emerging evidences have shown red cell distribution width (RDW) and high-density lipoprotein cholesterol (HDL-C) had potential as such. For example, for emergency admissions, high RDW (>18.9%) had a specificity of 93.4% for acute PE prediction.[16] HDL can inhibit VTE through a variety of antithrombotic mechanisms,[17] and low HDL-C (<1.1 mmol/L) has been identified as an independent risk factor for preoperative DVT in patients with spinal or foot fractures.[18,19] Nevertheless, to our best knowledge, no studies have evaluated the role of either biomarker in predicting the incident DVTs after hip fracture; and indeed, extrapolation of the above finding available from non-hip fracture or even non-trauma patients to the geriatric hip fracture patients (characterized by elderly age, hemodynamical instability, and post-traumatic hypercoagulability, etc) might be inappropriate. Furthermore, no studies attempt to explore the predictive value of RDW-to-HDL-C ratio (RHR) in DVTs screening.

Hence, for geriatric patients with hip fracture, this study aims to assess the predictive value of RDW and HDL-C for preoperative DVTs and to further explore whether RHR could be a promising novel predictor.

Materials and Methods

Patients

All data were retrospectively collected from the database of Surgical Site Infection in Orthopaedic Surgery (SSIOS), and clinical data of 2566 geriatric patients admitted to The Third Hospital of Hebei Medical University for hip fracture surgery between October 2015 and December 2020 were included in this study. The inclusion criteria were 1) elderly (≥65 years old) patients; 2) acute hip fracture (femoral neck or intertrochanteric fracture); 3) experiencing both hematological test and duplex ultrasonography (DUS) examination preoperatively. The exclusion criteria were 1) incomplete data; 2) multiple fractures; 3) periprosthetic, pathological or open fracture; 4) old fracture (>21 days from injury to DUS); 5) history of DVT and/or PE events; 6) use of antithrombotic thromboembolism therapy (eg, aspirin, low-molecular-weight heparin) within 3 months. The retrospective study was approved by the ethics committee of The Third Hospital of Hebei Medical University, and all procedures were performed under the principles outlined in the Helsinki Declaration and complied with the guideline of Strengthening the Reporting of Cohort Studies in Surgery (STROCSS). Informed consent for the possible use of the clinical data was obtained from all participants.

Diagnosis and Management of DVT

The diagnostic criteria for DVT were incompletely compressible vein, insufficient flow augmentation to veins of foot and calf after compression, lack of respiratory vibration in the superior knee vein segment, and filling defect or obstruction of the lumen. The scanning range included common femoral vein, popliteal vein, superficial femoral vein, deep femoral vein, posterior tibial vein, anterior tibial vein, and peroneal vein. DUS examination was performed by skilled technicians to identify the presence of DVT within 24 hours of patient admission and got reviewed every 4–6 days during the preoperative waiting period. Depending on the DUS results, patients would be given prophylactic or therapeutic doses of anticoagulant agents (eg, enoxaparin sodium injection). For patients needing long-term bed rest, we usually instruct them to actively move the healthy limb, drink more water, and use the intermittent pneumatic pressure pumps to assist venous blood return for DVT prevention.

Data Collection

The clinical data of interest were collected from four aspects: demographics, injury-concerned data, chronic comorbidities, and laboratory biomarkers. The demographics included age, living place, gender, and the calculated

body mass index (BMI). Injury-concerned data included fracture type, time from injury to DUS, and the American Society of Anesthesiologists (ASA) score. The comorbidities comprised diabetes mellitus, hypertension, heart disease, cerebrovascular disease, hepatopathy, nephropathy, tumors, smoking, alcohol drinking, and history of allergy or operation. The laboratory biomarkers comprised prothrombin time (PT), activated partial thromboplastin time (APTT), the count of platelet (PLT), and the levels of D-dimer, sodium, hemoglobin (HGB), albumin (ALB), fasting blood glucose (FBG), antithrombin III (AT III), fibrinogen (FIB), high-sensitivity C-reactive protein (HCRP), red cell distribution width (RDW), high-density lipoprotein cholesterol (HDL-C) and RDW-to-HDL-C ratio (RHR). These biomarkers were measured using manufacturer recommended methods, where complete blood count test was performed using a hematology analyzer (UniCel DxH 800; Beckman Coulter, Brea, CA, USA), coagulation studies were conducted using an ACL TOP 750 coagulometer (Instrumentation Laboratory, Bedford, MA, USA), and biochemical tests were performed using an autoanalyzer AU5800 (Beckman Coulter). If a patient had undergone multiple hematology tests prior to DUS examination, we analyzed only the initial results. In addition to age and time to DUS, all variables were expressed as categorical variables, and the optimal cutoff values of HCRP, RDW, HDL-C, RHR, and D-dimer were determined by using the Youden's index.

Statistical Analysis

The Kolmogorov–Smirnov test was first used to evaluate the normality of continuous variables. When normally distributed, the variables were expressed as mean ± standard deviation (SD) and analyzed by using Student's t-test, otherwise, were presented as median [interquartile range (IQR)] and analyzed by performing the Mann–Whitney test. Categorical variables were presented as numbers and percentages (%) and tested by the chi-square test or Fisher's exact test as appropriate. The receiver operating characteristic (ROC) curve was performed to evaluate the diagnostic yield of four indicators, including RHR, RDW, HDL-C, and D-dimer, and the diagnostic ability of which was compared via the area under the ROC curve (AUC). Comparison of AUC was performed using the test of DeLong et al[20] by MedCalc software version 18.10 (MedCalc Software, Ostend, Belgium). The optimal cutoff values of these indicators were determined based on the maximum Youden's index. Their accuracy, negative predictive value (NPV), positive predictive value (PPV), sensitivity and specificity for DVT diagnosis, and the 95% confidence interval (95% CI) were also measured.

According to the optimal cutoff value of RHR, patients were divided into two groups of "low RHR" and "high RHR". To minimize the interference of potential confounders between groups, propensity score matching (PSM) was performed to adjust covariates (excluding RDW and HDL-C). The propensity scores for each patient were calculated by using a multivariate logistic regression model and a 1:1 nearest neighbor matching algorithm with a caliper width of 0.02 was used to determine the post-PSM datasets. Standardized mean difference (SMD) was used to measure the balance of covariates before and after PSM, in which SMD>0.1 indicates imbalance. Univariate logistic regression analysis was performed to assess the association between RHR and DVT and acquire the association magnitude.

Subgroup analysis was performed for further exploration of the diagnostic value of RHR in the post-PSM cohort. Hypoproteinemia, diabetes mellitus, and hypertension are common modifiable complications in geriatric traumatic patients on admission. Thus, we divided the post-PSM cohort into several subgroups based on age, albumin level, diabetes mellitus, hypertension, ASA score, and fracture type. Univariate Logistic regression analysis was performed to calculate the relative risk (RR) and 95% CI for incident DVT events associated with high RHR and to assess the interaction between high RHR and grouping covariates. The differences were considered statistically significant when P value was less than 0.05. All the analyses were performed by using R software 3.6.5 (R Foundation for Statistical Computing, Vienna, Austria) and the software SPSS 26.0 (IBM Corp, Armonk, New York, USA).

Results

As is shown in Figure 1, there were totally 3367 geriatric patients with surgically treated hip fracture during the study window. According to exclusion criteria, 2566 patients were finally retained for analysis, and 258 (10.1%) were diagnosed with preoperative DVT after DUS examination.

As is shown in Table 1 and Figure 2, the AUC, PPV, NPV, accuracy, sensitivity, specificity, and their respective 95% CI were calculated for RDW, HDL-C, RHR, and D-dimer. Comparing the parameters of the four predictors, we identified
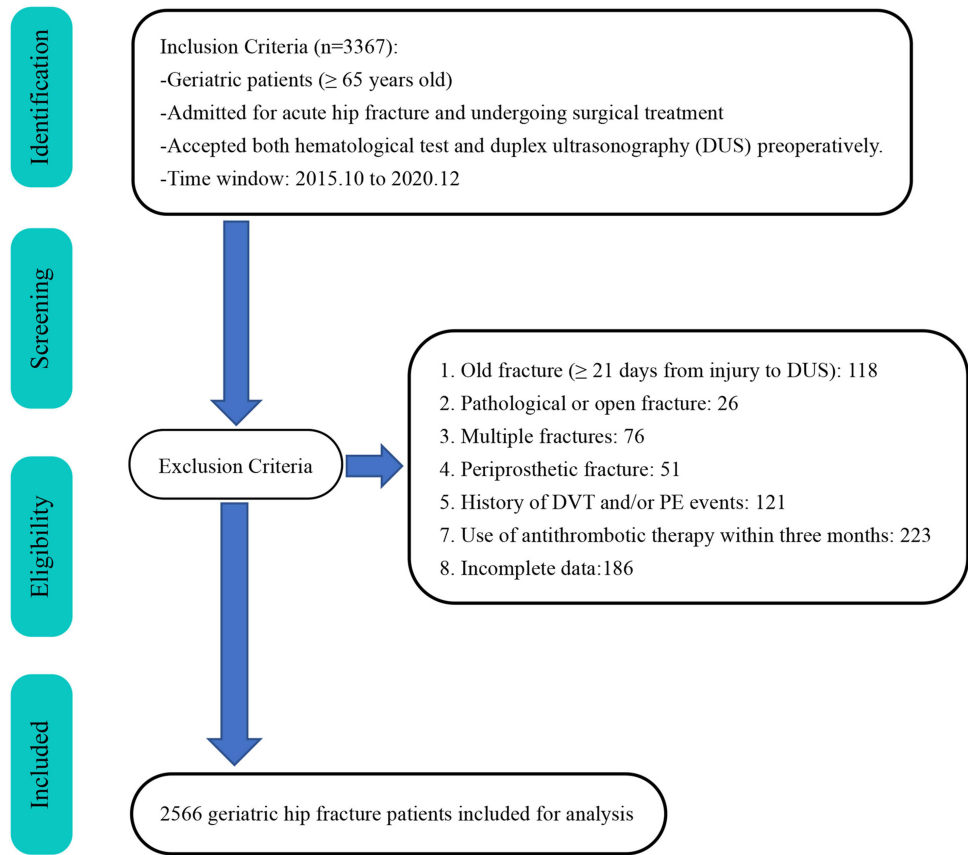
Figure 1 Flowchart of patient eligibility screening.

that RHR has the highest AUC (0.578), RDW has the highest specificity (88.2%), accuracy (81.2%), and PPV (14.7%), and HDL-C has the highest sensitivity (59.3%) and NPV (92.4%). We noted that RDW is characterized by high specificity and low sensitivity. In the comparison with RDW, RHR got significantly improved sensitivity (%, 43.4 vs 18.2) at the cost of slightly decreased specificity (%, 71.3 vs 88.2). The AUC of RHR was higher than that of RDW (0.578 vs 0.532, P=0.024), HDL-C (0.578 vs 0.574, P=0.506), and D-dimer (0.578 vs 0.569, P=0.773). In addition, compared with D-dimer, RHR has higher specificity (%, 71.3 vs 59.6), accuracy (%, 68.5 vs 59.2), and PPV (%, 14.5 vs 13.2).

The optimal cutoff value of RHR was 13.45 and based on which, patients were divided into two groups of "low RHR" and "high RHR". As is shown in Table 2, for patients in the before-PSM dataset, 1790 (69.8%) were included in

Table 1 Evaluation of Characteristic Parameters in Four Biomarkers

Variables	Cut-off value	AUC (95% CI)	Accuracy (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	PPV (%, 95% CI)	NPV (%, 95% CI)
RHR	13.45	0.578 (0.540–0.616)	68.5 (68.5–68.5)	43.4 (37.4–49.5)	71.3 (69.4–73.1)	14.5 (12.0–16.9)	91.8 (90.6–93.1)
RDW	15.89	0.532 (0.494–0.570)	81.2 (81.2–81.2)	18.2 (13.5–22.9)	88.2 (86.9–89.5)	14.7 (10.8–18.6)	90.6 (89.4–91.8)
HDL-C	1.20	0.574 (0.537–0.611)	56.0 (56.0–56.0)	59.3 (53.3–65.3)	55.6 (53.6–57.7)	13.0 (11.1–14.9)	92.4 (91.1–93.8)
D-dimer	1.57	0.569 (0.533–0.606)	59.2 (59.1–59.2)	55.0 (49.0–61.1)	59.6 (57.6–61.6)	13.2 (11.2–15.2)	92.2 (90.9–93.6)

Abbreviations: CI, confidence interval; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; RDW, red cell distribution width; HDL-C, high-density lipoprotein cholesterol; RHR, red cell distribution width-to-high-density lipoprotein cholesterol ratio.
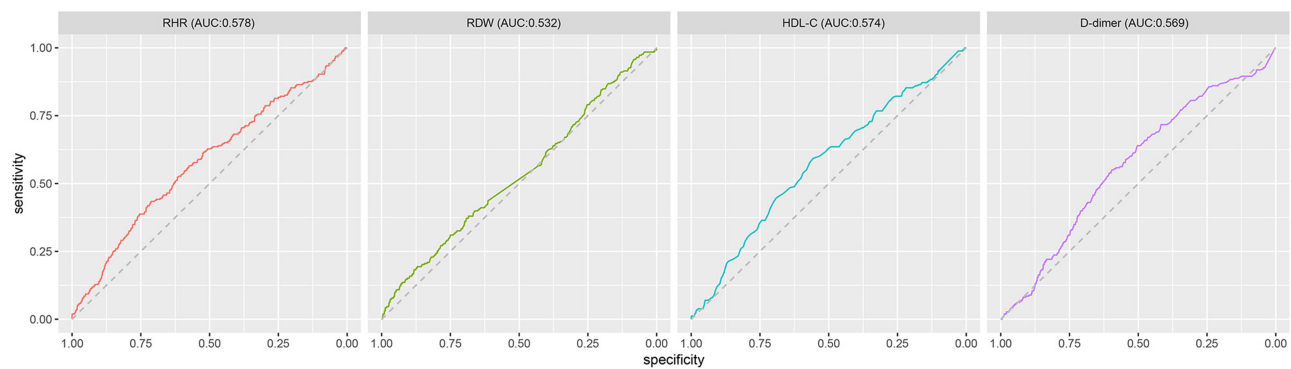
Figure 2 ROC curves for comparisons RDW, HDL-C, RHR, and D-dimer in geriatric patients with hip fracture.

the low RHR group and 776 (30.2%) in the high RHR group. After univariate analyses, we found the between-group differences were statistically significant in the following covariates: age, time to DUS, BMI, fracture type, gender, living place, allergic history, HGB, PLT, ALB, PT, AT III, FIB, D-dimer and HCRP. Thirteen covariates were calculated with SMD>0.1 before PSM, including gender, time to DUS, fracture type, living place, allergic history, BMI, FIB, AT III, PT, PLT, HGB, ALB, and HCRP. After PSM, 1386 were retained with 1:1 between-group matching. The univariate logistic analyses showed no covariate statistically significant between the two groups and all covariates were calculated with

Table 2 Comparison of the Baseline Characteristics of Patients Before and After PSM According to the Propensity Score

Variables	Unmatched		P value	After PSM		P value
	Low RHR (n=1790)	High RHR (n=776)		Low RHR (n=693)	High RHR (n=693)	
Age (years)	78.0 [71.0, 83.0]	78.0 [72.0, 84.0]	0.021*	79.0 [72.0, 84.0]	78.0 [72.0, 84.0]	0.557
Time to DUS (days)	4.0 [3.0, 6.0]	5.0 [3.0, 7.0]	<0.001*	5.0 [3.0, 7.0]	5.0 [3.0, 7.0]	0.216
BMI (kg/m^2)			0.037*			0.859
18.5–23.9	1055 (58.9%)	411 (53.0%)		391 (56.4%)	382 (55.1%)	
<18.5	119 (6.6%)	53 (6.8%)		39 (5.6%)	46 (6.6%)	
24.0–27.9	497 (27.8%)	253 (32.6%)		211 (30.4%)	215 (31.0%)	
≥28.0	119 (6.6%)	59 (7.6%)		52 (7.5%)	50 (7.2%)	
Fracture type			0.002*			0.746
Femoral neck fracture	910 (50.8%)	342 (44.1%)		304 (43.9%)	311 (44.9%)	
Intertrochantericfracture	880 (49.2%)	434 (55.9%)		389 (56.1%)	382 (55.1%)	
Gender			<0.001*			0.955
Males	520 (29.1%)	299 (38.5%)		247 (35.6%)	249 (35.9%)	
Females	1270 (70.9%)	477 (61.5%)		446 (64.4%)	444 (64.1%)	
Living place			0.002*			0.233
Rural	891 (49.8%)	439 (56.6%)		0.83	0.83	
City	899 (50.2%)	337 (43.4%)		0.83	0.83	
ASA score			0.060			0.830
I-II	902 (50.4%)	359 (46.3%)		336 (48.5%)	331 (47.8%)	
III-IV	888 (49.6%)	417 (53.7%)		357 (51.5%)	362 (52.2%)	
Hypertension	986 (55.1%)	428 (55.2%)	1.000	383 (55.3%)	382 (55.1%)	1.000
Diabetes mellitus	433 (24.2%)	206 (26.5%)	0.223	192 (27.7%)	183 (26.4%)	0.629
Cerebrovascular disease	657 (36.7%)	294 (37.9%)	0.599	246 (35.5%)	257 (37.1%)	0.576
Heart disease	646 (36.1%)	249 (32.1%)	0.056	229 (33.0%)	229 (33.0%)	1.000
Tumors	48 (2.7%)	23 (3.0%)	0.788	20 (2.9%)	20 (2.9%)	1.000
Hepatopathy	47 (2.6%)	28 (3.6%)	0.219	23 (3.3%)	25 (3.6%)	0.883

(Continued)

Table 2 (Continued).

Variables	Unmatched		P value	After PSM		P value
	Low RHR (n=1790)	High RHR (n=776)		Low RHR (n=693)	High RHR (n=693)	
Nephropathy	85 (4.7%)	52 (6.7%)	0.054	42 (6.1%)	40 (5.8%)	0.909
Operation history	551 (30.8%)	250 (32.2%)	0.500	218 (31.5%)	221 (31.9%)	0.908
Allergic history	279 (15.6%)	169 (21.8%)	<0.001*	133 (19.2%)	133 (19.2%)	1.000
Current smoking	79 (4.4%)	46 (5.9%)	0.124	33 (4.8%)	37 (5.3%)	0.713
Alcohol consumption	38 (2.1%)	14 (1.8%)	0.709	9 (1.3%)	13 (1.9%)	0.519
HGB (< lower limit)	963 (53.8%)	526 (67.8%)	<0.001*	455 (65.7%)	454 (65.5%)	1.000
PLT (> 300×10^9/L)	199 (11.1%)	131 (16.9%)	<0.001*	506 (73.0%)	514 (74.2%)	0.670
ALB (<35g/L)	1037 (57.9%)	595 (76.7%)	<0.001*	185 (26.7%)	180 (26.0%)	0.807
Sodium (<135mmol/L)	462 (25.8%)	195 (25.1%)	0.754	399 (57.6%)	388 (56.0%)	0.588
FBG (>6.1mmol/L)	980 (54.7%)	436 (56.2%)	0.529	181 (26.1%)	177 (25.5%)	0.854
PT (> 12.5s)	370 (20.7%)	215 (27.7%)	<0.001*	166 (24.0%)	156 (22.5%)	0.567
AT III (<80%)	325 (18.2%)	186 (24.0%)	0.001*	218 (31.5%)	223 (32.2%)	0.818
APTT (<28s)	577 (32.2%)	251 (32.3%)	0.993	218 (31.5%)	210 (30.3%)	0.684
FIB (4.4 g/L)	466 (26.0%)	246 (31.7%)	0.004*	274 (39.5%)	264 (38.1%)	0.620
D-dimer (>1.565mg/L)	775 (43.3%)	299 (38.5%)	0.028*	418 (60.3%)	425 (61.3%)	0.741
HCRP (>37.39mg/L)	797 (44.5%)	500 (64.4%)	<0.001*	383 (55.3%)	382 (55.1%)	1.000

Notes: *Statistical significance.
Abbreviations: PSM, propensity score matching; RHR, red cell distribution width-to- high-density lipoprotein cholesterol ratio; IQR, interquartile range; DUS, duplex ultrasonography; BMI, body mass index; ASA, American Society of Anesthesiologists; HGB, hemoglobin, reference range: Females, 110–150g/L; males, 120–160g/L; PLT, platelet; ALB, albumin; FBG, fasting blood glucose; AT III, antithrombin III; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen; HCRP, high-sensitivity C-reactive protein.

SMD<0.1, indicating that all covariates got well balanced in the post-PSM cohort (Figure 3). Univariate logistic regression analysis showed that high RHR was associated with a 1.54-fold increased risk of DVT and the difference was statistically significant (OR: 1.54, 95% CI: 1.11–2.14, P=0.011).

As is shown in Figure 4, high RHR was positively associated with the risk of developing DVT among all of the subgroups (all RR>1), and the interaction between high RHR and intertrochanteric fracture was statistically significant (P<0.001). Compared with the counterparts, the relative risk of DVT associated with high RHR was higher in the subgroups of aged 65–79 years (1.61 vs 1.45, P=0.028), non-hypoproteinemia (2.70 vs 1.29, P=0.006), non-diabetic (1.58 vs 1.41, P=0.019), non-hypertension (2.40 vs 1.06, P=0.001), ASA score I-II (2.38 vs 1.04, P=0.001), and femoral neck fracture (1.70 vs 1.50, P=0.088).

Discussion

To our knowledge, this is the first study to explore the diagnostic capacities of RDW, HDL-C, and RHR in incident DVTs among geriatric patients before hip fracture surgery. When comparing the predictive performances of RDW, HDL-C, and D-dimer, we identified RDW with the highest specificity and PPV, and HDL-C with the highest sensitivity and NPV. RHR has complementary strengths of the above two biomarkers. Compared with D-dimer, RHR, a novel biomarker, has higher AUC and specificity in predicting DVTs. We identified that high RHR (>13.45) was independently associated with 1.54-fold risks of incident DVT in the post-PSM cohort. Compared with the counterparts, the relative risk of DVT associated with high RHR was higher in the subgroups of aged 65–79 years, non-diabetic, non-hypertension, non-hypoproteinemia, ASA score I-II, and femoral neck fracture.

RDW reflects the heterogeneity of circulating red blood cell volume, which is a convenient and cost-effective measurement of the variation in size of red blood cells (RBCs).[21] Zöller et al[22] studied 27,042 subjects (60.6% women, aged 45–73 years) and found that those with the top 5% RDW values had a 2.51-fold higher risk of developing venous thrombus embolism (VTE) than those of the bottom quartile. Increased RDW indicates significant deregulation of
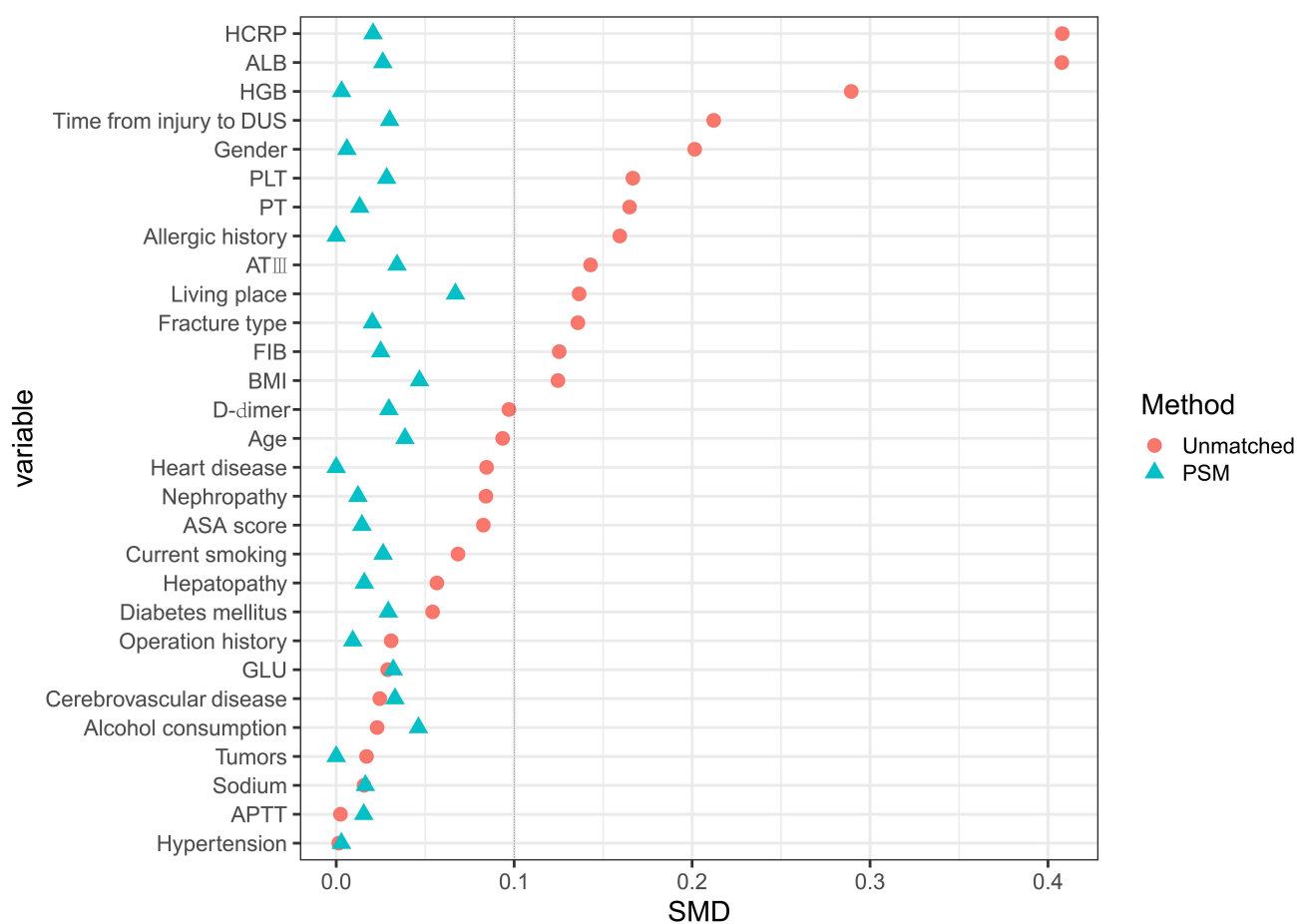
Figure 3 Standardized mean differences (SMD) between the groups of high RHR and low RHR across baseline clinical data.

erythrocyte homeostasis, including both abnormal RBC survival and impaired erythropoiesis, and was strongly associated with a higher risk of DVT, which can be explained by the following underlying mechanisms. For one thing, increased RDW is significantly associated with reduced RBC deformability, which can cause elevated blood viscosity and impair microcirculatory blood flow; furthermore, enhanced RBC aggregation promotes greater margination of leukocytes and platelets.[23–25] For another, high RDW is closely related to oxidative stress. Increased reactive oxygen species (ROS) can stimulate coagulation by inhibiting tissue factor pathway inhibitor (TFPI) and upregulating the tissue factor (TF) expression; in addition, ROS can make fibrinogen more readily translatable to fibrin, and decrease the interaction between thrombin and anticoagulants, such as the antithrombin III-heparin complex.[26]

Low HDL-C is a common feature of dyslipidemia, and its predictive role in thrombus formation has been verified by numerous studies. HDL-C has been identified as an independent predictor of DVT in both the trauma and oncology fields,[18,19,27] and HDL-C levels were found lower in thromboembolic patients among researches providing evidence of the direct link between dyslipidemia and VTE.[28,29] The inverse relationship between HDL-C levels and DVT risks could be attributed to the antithrombotic effect of HDL. Firstly, HDL has antiplatelet actions, which not only can decrease platelet aggregation by downregulating the production of thromboxane A2 but also inhibit platelet activation by upregulating biosynthesis and release of nitric oxide (NO).[17,30] Secondly, HDL can help maintain the integrity of endothelial cells.[31] Dysfunctional and apoptotic endothelial cells can promote thrombosis by releasing membrane microparticles and promoting the platelets–leukocytes adhesion reaction.[32] Thirdly, the selectins interaction promotes platelet–leukocyte adherence and aggregation to vessel walls in the post-traumatic inflammatory response period, and thus the anti-inflammatory effects of HDL could contribute to the inhibition of thrombosis.[33]
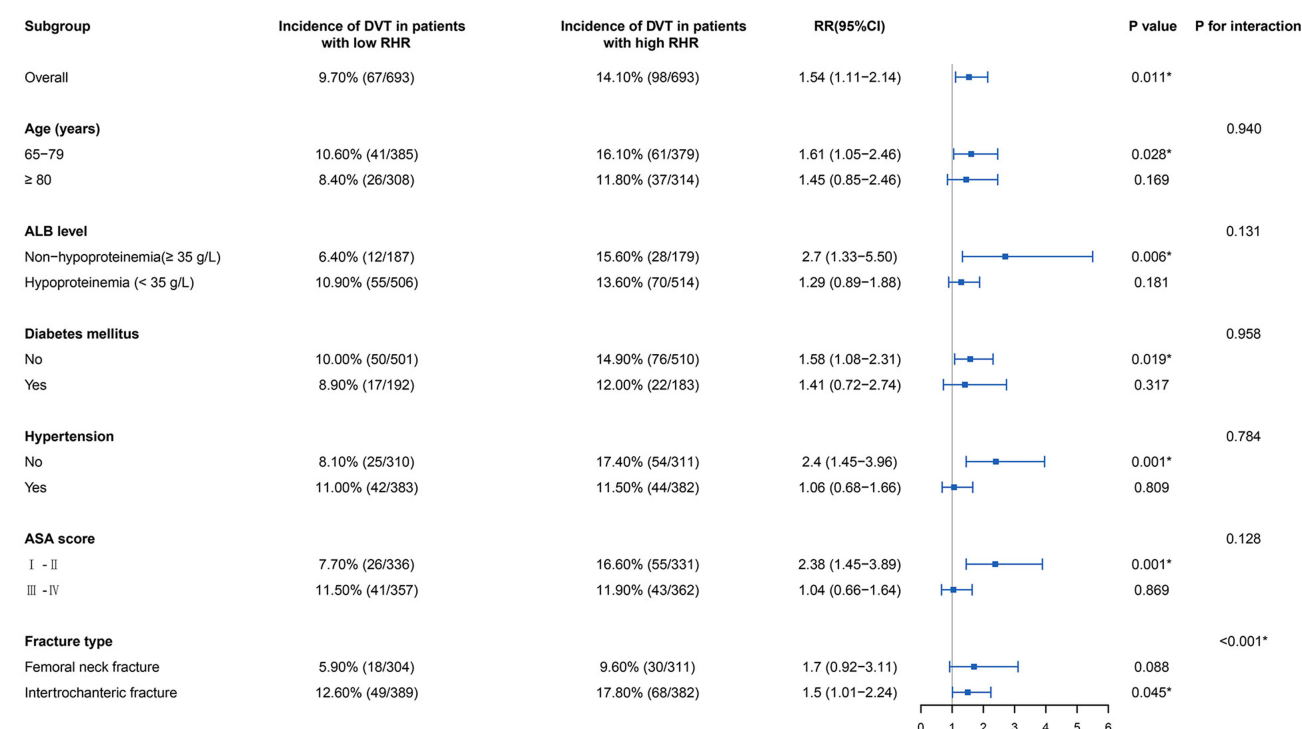
Subgroup	Incidence of DVT in patients with low RHR	Incidence of DVT in patients with high RHR	RR(95%CI)		P value	P for interaction
Overall	9.70% (67/693)	14.10% (98/693)	1.54 (1.11–2.14)		0.011*	
Age (years)						0.940
65–79	10.60% (41/385)	16.10% (61/379)	1.61 (1.05–2.46)		0.028*	
≥ 80	8.40% (26/308)	11.80% (37/314)	1.45 (0.85–2.46)		0.169	
ALB level						0.131
Non–hypoproteinemia(≥ 35 g/L)	6.40% (12/187)	15.60% (28/179)	2.7 (1.33–5.50)		0.006*	
Hypoproteinemia (< 35 g/L)	10.90% (55/506)	13.60% (70/514)	1.29 (0.89–1.88)		0.181	
Diabetes mellitus						0.958
No	10.00% (50/501)	14.90% (76/510)	1.58 (1.08–2.31)		0.019*	
Yes	8.90% (17/192)	12.00% (22/183)	1.41 (0.72–2.74)		0.317	
Hypertension						0.784
No	8.10% (25/310)	17.40% (54/311)	2.4 (1.45–3.96)		0.001*	
Yes	11.00% (42/383)	11.50% (44/382)	1.06 (0.68–1.66)		0.809	
ASA score						0.128
Ⅰ –Ⅱ	7.70% (26/336)	16.60% (55/331)	2.38 (1.45–3.89)		0.001*	
Ⅲ –Ⅳ	11.50% (41/357)	11.90% (43/362)	1.04 (0.66–1.64)		0.869	
Fracture type						<0.001*
Femoral neck fracture	5.90% (18/304)	9.60% (30/311)	1.7 (0.92–3.11)		0.088	
Intertrochanteric fracture	12.60% (49/389)	17.80% (68/382)	1.5 (1.01–2.24)		0.045*	

Figure 4 Forest plot for subgroup analysis, representing the relative risk (RR) and 95% confidence interval (CI) of DVT associated with high RHR. *Statistical significance.
Abbreviations: DVT, deep vein thrombosis; RR, relative risk; CI, confidence interval; RHR, red cell distribution width to high-density lipoprotein cholesterol ratio; ALB, albumin; ASA, American Society of Anesthesiologists.

RDW and HDL-C in combination with other biomarkers had been consistently the hot topic in risk factor analyses of clinical diseases in recent years. For RDW, RDW-to-lymphocyte ratio was confirmed to be independently associated with the prognosis of cutaneous malignant melanoma, and RDW-to-platelet ratio can be used for the early prediction of cirrhosis and hepatic fibrosis in patients with chronic hepatitis B.[34,35] For HDL-C, neutrophils-to-HDL-C ratio had been confirmed as a significant predictor of severe coronary artery stenosis, and triglyceride-to-HDL-C ratio was employed to identify insulin resistance and cardiometabolic risk among children with obesity.[36,37] Different from previous studies, the current one was the first attempt to use RDW-to-HDL-C ratio and fully demonstrate its excellent thrombotic predictive value in the field of trauma.

The different distribution of characteristics in geriatric hip fracture patients increased the heterogeneity and may lead to differences in the predictive efficacy of RHR for DVTs. Based on the subgroup analyses, we found that the predictive value of RHR was efficient in most subgroups, especially in those of younger age, better medical conditions, or femoral neck fracture. The underlying mechanism is presumably that high RHR and pathological conditions, including advanced age, poor medical conditions and intertrochanteric fracture, collectively contributed to the development of DVT, and the correlation between high RHR and DVT got highlighted after excluding the influential effects of these pathological conditions.[38] Thus, it is rational to speculate that RHR would be more effective in predicting DVT in traumatic patients of middle age and relatively good health status, which warrants further investigation. In addition, we noted that albumin is a potentially modifiable nutritional indicator in the subgroup analyses, and recent studies have confirmed that hypoproteinemia is closely associated with the development of pneumonia in geriatric patients before or after hip fracture surgery.[39,40] Therefore, it is worth emphasizing that targeting correction of hypoproteinemia is a feasible and cost-effective way to prevent or reduce preoperative DVTs and improve prognosis in geriatric patients with hip fracture.

The advantages of the current study included identification of RHR as a high specificity novel predictor for preoperative DVT and also confirmation and validation of their true association and association magnitude by using large size samples. However, several limitations ought to be mentioned. First, some variables that might have caused

differences between groups were not collected, such as the mechanism of injury. Second, recall bias is unavoidable for that some variables, especially the potential complications, were self-reported by patients at admission. Third, although the clinical data were drawn from a prospectively collected database, the potential selection bias of this single-center study would limit the generalizability of the findings. Fourth, we did not further follow up the influence of RHR on the recurrence of DVT and occurrence of postoperative DVT, which would be valuable for improving patient prognosis.

Conclusion

In this study, we identified that RDW, HDL-C and RHR are valuable biomarkers in predicting preoperative DVTs in geriatric patients with hip fracture. In the post-PSM cohort, RHR, as a novel predictor with high specificity (71.3%), was independently associated with 1.54-fold risk of DVT before hip fracture surgery, and would be more efficient in the subgroups of younger age, better medical condition and femoral neck fracture.

Abbreviations

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thrombus embolism; SSIOS, Surgical Site Infection in Orthopaedic Surgery; STROCSS, Strengthening the Reporting of Cohort Studies in Surgery; DUS, duplex ultrasonography; ROC, receiver operating characteristic; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; PSM, propensity score matching; IQR, interquartile range; RR, relative risk; CI, confidence interval; RDW, red cell distribution width; HDL-C, high-density lipoprotein cholesterol; RHR, red cell distribution width-to-high-density lipoprotein cholesterol ratio; BMI, body mass index; ASA, American Society of Anesthesiologists; HGB, hemoglobin, reference range: Females, 110–150g/L; males, 120–160g/L; PLT, platelet; ALB, albumin; FBG, fasting blood glucose; AT III, antithrombin III; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen; HCRP, high-sensitivity C-reactive protein; RBCs, red blood cells; TFPI, tissue factor pathway inhibitor; ROS, reactive oxygen species; TF, tissue factor; NO, nitric oxide.

Data Sharing Statement

All the data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of The Third Hospital of Hebei Medical University, and the informed consent was waived for its retrospective nature. All the data were analyzed anonymously to safeguard patient privacy.

Consent for Publication

We have obtained the consent for publication from all participants.

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Author Contributions

Xinqun Cheng and Lingjia Fan are considered first co-authors. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

All the authors declare that they do not have a conflict of interest

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