Role of a New Age-adjusted D-dimer Cutoff Value for Preoperative Deep Venous Thrombosis Exclusion in Elderly Patients With Hip Fractures

Kexin Zhang
Hebei Medical University
Yanbin Zhu
Hebei Medical University Third Affiliated Hospital
Yunxu Tian
Hebei Medical University
Miao Tian
Hebei Medical University
Xiuting Li (lixiuting2021@126.com)
Hebei Medical University Third Affiliated Hospital
Yingze Zhang
Hebei Medical University Third Affiliated Hospital https://orcid.org/0000-0002-5419-7078

Research Article

Keywords: Deep venous thrombosis, Age-adjusted D-dimer cutoff value, Hip fracture, Aged people

Posted Date: August 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-829562/v1

Abstract

Objective: This study aimed to describe the characteristics of plasma D-dimer level with increasing age and establish a new age-adjusted D-dimer cutoff value for excluding preoperative lower limb deep vein thrombosis (DVT) in elderly patients with hip fractures.

Methods: This was a retrospective study of elderly patients who presented with acute hip fracture in our institution between June 2014 and May 2020. All patients underwent D-dimer test and duplex ultrasound. Patients were divided into six 5-year-apart age groups. The optimal cutoff value for each group was calculated by using receiver operating characteristic (ROC) curves, whereby the new age-adjusted D-dimer cutoff value was determined. The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were calculated and compared when different D-dimer cutoff values were applied, i.e. conventional 0.5mg/L, previously well-established age-adjusted cutoff value (age*0.01 mg/L) and the new age-adjusted D-dimer cutoff value herein.

Results: There were 2759 included, 887 males and 1872 females, with an average age of 77.8 years. 280 patients were diagnosed with preoperative DVT. The optimal cutoff values for the six age groups were 0.715 mg/L, 1.170 mg/L, 1.620 mg/L, 1.665 mg/L, 1.690 mg/L and 1.985 mg/L, respectively and the calculated age-adjusted coefficient was 0.02 mg/L. With this new coefficient applied, the specificity was 61.3%, clearly higher than those for conventional threshold (0.5mg/L, 36.9%) or previously established age-adjusted D-dimer threshold (age*0.01 mg/L, 22.2%). In contrast, the sensitivity was lower than that (58.9% vs 85.0% or 77.1%) when D-dimer threshold of 0.5 mg/L or age-adjusted cutoff value (age*0.01 mg/L) was used. The other indexes as PPV (14.7%, 11.0% and 12.1%) and NPV (93.0%, 92.9% and 93.5%) were comparable when three different D-dimer thresholds were applied.

Conclusions: The use of the new age-adjusted D-dimer threshold increased the proportion of elderly hip fracture patients in whom preoperative lower limb deep vein thrombosis could be safely excluded.

Introduction

Deep vein thrombosis (DVT) is a common disease, with a variable prevalence of 4.2–51.6% [1–5]. Prompt diagnosis and targeted treatment are the most major methods to avoid proximal DVT migration or pulmonary embolism (PE), and even death[6]. The D-dimer test, as an important link of the DVT diagnostic algorithm, is generally used as an initial screening tool in large population with a low medical costs and high sensitivity, but a low specificity[7]. In order to improve the specificity and reduce unnecessary expenditure on medical resources, the age-adjustment and combination diagnosis trials including D-dimer have been consistently the research focuses in recent years [8, 9]. D-dimer as a diagnostic biological marker of DVT, is affected not only by age but also by trauma from fracture or surgery [10]. Fractures associated with hypercoagulability of blood, trauma, immobility, hospitalization, and inflammatory immune response of the body put patients at a high risk of DVT.[11, 12]. The prevalence rates of DVT in disparate fracture sites are different in previously published literature. Hip fractures presented with a substantially higher incidence rate of 17%-58% for preoperative DVT than that in distal limb fractures, such as tibiofibular or plateau fractures

(11.9%), and ankle fractures (6.40%), calcaneal fractures (12.0%), and further had the significantly increased risk of proximal thrombosis, PE, and mortality[10, 13–16].

A considerable number of studies have re-adjusted D-dimer level associated with age in patients with venous thromboembolism (VTE)[17–19]. Douma et al [20] proposed and established the typical age-adjusted D-dimer threshold (age*0.01mg/L) to improve specificity. In the past decade, the use of age-adjusted D-dimer threshold (age*0.01mg/L) has demonstrated the improved specificity in diagnosis of DVTs, aiding in exclusion of those with no thromboembolism in most cases[21–24]. For example, Dutton et al [25] used the age-adjusted D-dimer threshold (age*0.01mg/L) for the diagnosis of PE, with specificity increasing from 7–32%. However, as a high-risk and large group for DVT, hip fracture elderly patients have not obtained adequate attention on investigation of the age-adjusted D-dimer level to improve the diagnosis of DVT, especially the specificity.

Therefore, the study aims to investigate the age-dependent characteristics of D-dimer in aged (≥ 65 years) patients who had hip fractures, and second to establish a new age-adjusted D-dimer cutoff value and evaluate its ability to safely exclude elderly hip fractures patients without DVT.

Methods

Study population

In this study, data on 2759 patients with the diagnosis of acute hip fractures who were surgically treated at the 3rd Hospital of Hebei Medical University between June 2014 and May 2020, were retrospectively collected. All patients who adhered to the following criteria were included: age ≥ 65 years and experiencing both D-dimer test and duplex ultrasound (DUS) preoperatively. Patients were excluded if they had suffered a VTE within the three months before the index hip fracture, concomitant suspicion of PE, ongoing anticoagulant treatment, multiple fractures, acute episode (acute infection, acute heart failure, etc.), malignancy, incomplete data. The demographic data (age and sex) were collected from clinical medical records. The D-dimer test results and DUS results were extracted from the laboratory department and the imaging department respectively. If there were multiple preoperative examinations for one patient, we only selected the initial result to analyze. The flow diagram for the patient selection was shown in Fig. 1.

Study design

Following the strategy of Douma et al [20] to establish an age-adjusted D-dimer cutoff value, we attempted to explore a new age-adjusted D-dimer cutoff value to increase the proportion of elderly hip fracture patients in whom a preoperative DVT could be safely excluded. We divided all patients into six 5-year-apart age groups (65–69 years; 70–74 years; 75–79 years; 80–84 years; 85–89 years; more than or equal to 90 years). The receiver operating characteristic (ROC) curves were subsequently constructed to determine the optimal cutoff value (defined as the value at which the Youden index is at its maximum) for each group. The simple linear regression model was used to calculate regression coefficients based on the six optimal cutoff values in age groups. The calculated coefficient corresponded to an increase in the D-dimer cutoff value per five years. To calculate the annual increase in the D-dimer cutoff value, the regression coefficient was divided by

5 (the number of years per five years). This coefficient was used as a multiplier of the patient's age when determining the new age-adjusted D-dimer cutoff value.

Diagnostic procedure

D-dimer detection was carried out in all patients on the morning following admission. Blood samples were collected on an empty stomach and in a quiet state and sent to the central laboratory for testing on the Wondfo FS-301 Auto-Immunofluorescence Quantitative Analyzer (Xiamen, China) within 60 minutes. D-dimer results were categorized into negative or positive based on the manufacturers' cut-off value (0.5 mg/L).

A complete DUS examination was performed with Philips Affiniti 50 ultrasonographic machine (Royal Phillips Electronics, Amsterdam, The Netherlands) in all patients before surgery. Detection areas consisted of femoral vein, popliteal vein, calf vein, peroneal and tibial veins. DUS examination was performed by technicians with professional qualification certificates and without knowledge of the patients' D-dimer test results. The DVT diagnosis was based on the Robinov group's criteria [26]. As follows, there were not completely compressible vein, intraluminal thrombus or filling defect and poor in phasic vibration with respiratory movements of calf compression. Thrombosis can be diagnosed if any of the above two or more ultrasound criteria were confirmed. All lower limb veins were scanned as many as possible by registered technicians.

Outcomes

The primary outcome was the establishment of the new age-adjusted cutoff value and the diagnostic parameters of three different thresholds including specificity, sensitivity, negative predictive value (NPV) and positive predictive value (PPV), negatives number, false negatives number, number needed to test (NNT). The secondary outcome was the average value of D-dimer and the incidence of DVT for each age group to verify the increasing trend of D-dimer with age.

Statistical analysis

Continuous variables were described as mean ± standard deviation, categorical variables were expressed by the number and percentages (%). Kruskal-Wallis test was used for the comparison of multiple groups of non-normally distributed data. Chi-square test was used to compare the specificity and sensitivity among three different groups. $P < 0.05$ was considered significant. The ROC analysis was subsequently constructed to determine the optimal cutoff value. The simple linear regression analysis was used to calculate regression coefficients SPSS 26.0 was used for analysis and Graph Pad Prism 9 software was used to draw figures.

Ethics approval

The study was carried out adhering to the Helsinki Declaration consensus and was approved by the institutional review board. Informed consent was waived for this retrospective review as no identifying information was recorded.

Result

Characteristics of study subjects and D-dimer blood level

Our study included 2759 elderly patients who had a hip fracture. Of these, 887 were male and 1872 were female, with a mean age of 77.8 years. 280 (10.15%) patients were diagnosed with DVT by DUS. The level of D-dimer increased consecutively with age from 2.00 mg/L in the 65–69 years group to 2.36 mg/L in the ≥ 90 years group. The difference was statistically significant ($P < 0.05$). D-dimer level was 2.36 mg/L in DVT group higher than 2.11 mg/L in non-DVT group. The variation of D-dimer levels with age, specific gender distribution, mean age, D-dimer level mean, and prevalence of DVT in each age group were presented in Table 1 and Fig. 2.

Table 1
Baseline characteristics

	65–69	**70–74**	**75–79**	**80–84**	**85–89**	**≥ 90**	**All ages**
Number **n (%)**	495 (17.94)	518 (18.77)	555 (20.12)	611 (22.15)	407 (14.75)	173 (6.27)	2759 (100)
Female sex **n (%)**	325 (65.66)	356 (68.73)	371 (66.85)	411 (67.27)	287 (70.52)	122 (70.52)	1872 (67.85)
Age **(mean ± SD)**	67.12 ± 1.39	72.00 ± 1.41	77.14 ± 1.40	81.88 ± 1.40	86.72 ± 1.39	92.19 ± 2.55	77.78 ± 7.59
D-dimer mean in patients with DVT (mg/L)	2.14	2.20	2.31	2.37	2.52	3.35	2.36
D-dimer mean in patients without DVT (mg/L)	1.98	2.09	2.10	2.11	2.26	2.27	2.11
D-dimer mean in all patients (mg/L)	2.00	2.10	2.12	2.13	2.28	2.36	2.14
DVT **N (%)**	55 (11.11)	45 (8.69)	70 (12.61)	57 (9.33)	38 (9.34)	15 (8.67)	280 (10.15)

Notes: SD, standard deviation; DVT, Deep venous thromboembolism.

Establishment of a new age-adjusted D-dimer cutoff value

According to the ROC curves, the optimal thresholds of the six 5-year-apart age groups were 0.715 mg/L, 1.170 mg/L, 1.620 mg/L, 1. 665 mg/L, 1.690 mg/L and 1.985 mg/L in turn, as they were shown in Fig. 3. The optimal D-dimer cutoff values of each age group were plotted by simple linear regression analysis. Thereby, the regression coefficient (r) corresponding to the slope of the regression line was calculated as 0.23 mg/L (95% confidence interval 0.11 to 0.35), as it was shown in Fig. 4. To ensure maximum sensitivity, we chose the lower limit 0.11 mg/L (5% CL value) instead of 0.23 mg/L as regression coefficient. This coefficient represented the increase in the D-dimer cutoff value per five years. The annual increase in the D-dimer cutoff value was obtained by dividing the regression coefficient (0.11 mg/L) by 5. 0.02 mg/L was used as a multiplier of the patient's age when determining the new age-adjusted D-dimer cutoff value. All procedures were summarized in Fig. 3. and Fig. 4.

Comparison of different D-dimer cutoff value

Among 2759 patients, 594 (21.53%) had a D-dimer level of < 0.5 mg/L (traditional threshold), 979 (35.48%) and 1293 (59.22%) patients had a lower dichotomized D-dimer level, based on previously established age-adjusted cutoff values of age*0.01 mg/L and the new age-adjusted cutoff value of age*0.02 mg/L. At the threshold of 0.5 mg/L, sensitivity was 85.0% (95% confidence interval [CI], 80.1–88.9) with a specificity of 22.2% (95% CI, 20.7–24.0), PPV of 11.0% (95% CI, 9.7–12.4) and NPV of 92.9% (95% CI, 90.5–94.8) in all ages. At the age-adjusted cutoff value (age*0.01 mg/L), sensitivity was 77.1% (95% confidence interval [CI], 71.7–81.8) with a specificity of 36.9% (95% CI, 35.0-38.8), PPV of 12.1% (95% CI, 10.7–13.8) and NPV of 93.5% (95% CI, 91.7–94.9) in all ages. At the new age-adjusted cutoff value (age*0.02 mg/L), sensitivity was 58.9% (95% confidence interval [CI], 52.9–64.7) with a specificity of 61.3% (95% CI, 59.3–63.2), PPV of 14.7% (95% CI, 12.7–16.9) and NPV of 93.0 % (95% CI, 91.6–94.1) in all ages. The number of patients needed to test to find one normal D-dimer test result was 4.2 at the threshold of 0.5 mg/L and 2.5 at the age-adjusted cutoff value (age*0.01 mg/L) and 1.5 at the new age-adjusted cutoff value (age*0.02 mg/L). In contrast, the sensitivity was lower than that (58.9% vs 85.0% or 77.1%) when D-dimer threshold of 0.5 mg/L or age-adjusted cutoff value (age*0.01 mg/L) was used. All results were reported in Table 2.

Table 2

Evaluation parameters in three different strategies

	Negative number (%)	Number needed to test	False negatives number (%)	Positive predictive value (%,95% CI)	Negative predictive value (%,95% CI)	Sensitivity (%,95% CI)	Specificity (%,95% CI)
All age							
0.5	594 (21.53)	4.2	42 (15.00)	11.0 (9.7,12.4)	92.9 (90.5,94.8)	85.0 (80.1,88.9)	22.2 (20.7,24.0)
0.01*age	979 (35.48)	2.5	64 (22.86)	12.1 (10.7,13.8)	93.5 (91.7,94.9)	77.1 (71.7,81.8)	36.9 (35.0,38.8)
0.02*age	1293 (59.22)	1.5	115 (41.07)	14.7 (12.7,16.9)	93.0 (91.6,94.1)	58.9 (52.9,64.7)	61.3 (59.3,63.2)
P	-	-	-	-	-	□0.05	□0.05
65-69							
0.5	148 (29.90)	3.0	8 (14.55)	13.5 (10.2,17.7)	94.6 (89.3,97.5)	85.5 (72.8,93.1)	31.8 (27.5,36.4)
0.01*age	183 (36.97)	2.4	10 (18.18)	14.4 (10.8,18.9)	94.5 (89.9,97.2)	81.8 (68.6,90.5)	39.3 (34.8,44.1)
0.02*age	291 (58.79)	1.5	26 (42.27)	14.2 (9.9,19.9)	91.1 (87.0,94.0)	52.7 (38.9,66.1)	60.2 (55.5,64.8)
P	-	-	-	-	-	□0.05	□0.05
70-74							
0.5	166 (32.05)	2.8	17 (37.78)	8.0 (5.4,11.4)	89.8 (83.9,93.7)	62.2 (46.5,75.8)	31.5 (27.4,35.9)
0.01*age	221 (42.66)	2.1	19 (42.22)	8.8 (5.9,12.7)	91.4 (86.7,94.6)	57.8 (42.2,72.0)	42.7 (38.2,47.3)
0.02*age	335 (64.67)	1.4	26 (57.78)	10.4 (6.5,16.0)	92.2 (88.7,94.8)	42.2 (28.0,57.8)	65.3 (60.8,69.6)
P	-	-	-	-	-	□0.05	□0.05
75-79							
0.5	121	4.0	13	13.1	89.3	81.4	22.3

	(21.80)		(18.57)	(10.2,16.8)	(82.0,93.9)	(70.0,89.4)	(18.7,26.3)
0.01*age	208 (37.48)	2.3	22 (31.43)	12.8 (10.5,18.0)	89.4 (84.2,93.1)	68.6 (56.2,78.9)	38.4 (34.0,42.9)
0.02*age	340 (61.26)	1.4	36 (51.43)	15.8 (11.3,21.5)	89.4 (85.5,92.4)	48.6 (36.6,60.7)	62.7 (58.2,67.0)
P	-	-	-	-	-	⊠0.05	⊠0.05
80-84							
0.5	97 (15.88)	5.7	2 (3.51)	9.6 (7.4,12.5)	94.1 (82.8,98.5)	94.7 (84.5,98.)	8.7 (6.5,11.4)
0.01*age	189 (30.93)	2.9	7 (12.28)	11.1 (8.1,14.8)	93.3 (89.2,96.0)	71.9 (58.3,82.6)	40.4 (36.3,44.7)
0.02*age	332 (54.34)	1.7	14 (24.56)	15.4 (11.5,20.3)	95.8 (92.9,97.6)	75.4 (62.0,85.5)	57.4 (53.2,61.5)
P	-	-	-	-	-	⊠0.05	⊠0.05
85-89							
0.5	44 (10.81)	8.4	2 (5.26)	9.9 (7.1,13.6)	95.5 (83.3,99.2)	94.7 (80.9,99.1)	11.4 (8.4,15.2)
0.01*age	120 (29.48)	3.1	6 (15.79)	11.1 (7.9,15.5)	95.0 (89.0,98.0)	84.2 (68.1,93.4)	30.9 (26.3,35.9)
0.02*age	240 (58.97)	1.5	13 (34.21)	15.0 (10.1,21.5)	94.6 (90.7,97.0)	65.8 (48.6,79.9)	61.5 (56.3,66.5)
P	-	-	-	-	-	⊠0.05	⊠0.05
≥90							
0.5	18 (10.40)	8.8	0 (0.00)	9.7 (5.7,15.7)	100 (78.1,100.0)	100 (74.7,100.0)	11.4 (7.1,17.7)
0.01*age	58 (33.53)	2.7	(0.00)	13.0 (7.7,20.9)	100 (92.3,100.0)	100 (74.7,100.0)	36.7 (29.3,44.8)
0.02*age	96 (55.49)	1.6	0 (0.00)	19.5 (11.7,30.4)	100 (95.2,100.0)	100 (74.7,100.0)	60.8 (52.7,68.3)
P	-	-	-	-	-	⊠0.05	⊠0.05

Note: Number needed to test to find one normal D-dimer test result

Discussion

Our findings are consistent with published research showing that D-dimer levels increase with age. The new age-adjusted D-dimer cutoff value (age*0.02 mg/L) significantly improved the specificity of the D-dimer assay, from 22.2–61.3% ($P < 0.05$), and reduced the number needed to test to find one normal D-dimer test result to 1.5. When the new threshold was used, the proportion of patients in whom DVT could be safely ruled out among the six 5-year-apart age groups was between 52.0% and 59.7%, increasing by 66% when compared to the typical cutoff value of age*0.01 mg/L.

In the setting of both advanced age and a major trauma, the risk of DVT was higher than general population or other conditions, and investigation of targeted prompt examination method remains a key topic [27–30]. Other scholars tried to use adjustment formulas or other specific thresholds of well-established biomarkers to more accurately diagnose or predict the VTE after fracture. For example, Niikura et al [27] established D-dimer cutoff levels for VTE screening in patients with fractures caused by high-energy injuries and showed moderate or high accuracy (area under curve 0.7-1.0) for predicting a VTE;Wu et al [18] used the typical age-adjusted D-dimer cutoff value (age*0.01 mg/L) in patients with knee fracture or hip fracture, and the results showed it had a better value in predicting DVT than a traditional threshold. In this study, we have got a new coefficient related to age (0.02), demonstrating a significantly improved specificity in diagnosis of a DVT, aiding in safely excluding those without a DVT in a larger proportion.

Compared with previous thresholds, the new age-adjusted D-dimer cutoff value had higher specificity of 61.3%, significantly higher than 36.9% when using the typical age-adjusted D-dimer cutoff value. The number of patients with a negative D-dimer result increased from 594 (21.53%) when the traditional threshold of 0.5 mg/L was used to 1293 (59.22%) when the new age-adjusted formula was used. By definition, the reduction in sensitivity was due to the raising of the threshold for higher specificity, which caused some patients to fall below the new threshold and causes them to change from true positive to false negative[31].

Elderly patients with hip fractures can benefit from this new age-adjusted D-dimer value. A research on cost-effectiveness showed that the cost-effectiveness of applying traditional thresholds in older people over 80 was poor due to excessive DUS[32]. The efficiency of typical age-adjusted D-dimer value was limited, in our study, the typical threshold only increases the specificity from 22.2% (0.05mg/L) to 36.9% while the specificity was 61.3% when the new age-adjusted cutoff value was used. The new age-adjusted D-dimer value increased the DVT excluded proportion of older hip fracture patients to 59.22%, comparing with 21.53% when the age-adjusted cutoff value (age*0.01 mg/L) was used. The increased specificity of the D-dimer test and DVT excluded proportion reduced the number of patients who need further DUS and unnecessary anticoagulant therapy with consequent clinical. The potential benefit would be fewer long waits and frequent mobility, thus decreasing physical impairments.

D-dimer test must be integrated with clinical pre-test probability (PTP) scores (such as the Wells score or the revised Geneva score) and DUS, when it was used to diagnosis DVT in published studies [24]. But when using the new age-adjusted threshold, we believe that there is no need to consider PTP, because PTP is routinely used to screen the patients with low and moderate pretest probability[25, 33], elderly hip fracture patients usually have a moderate, or high pretest probability due to trauma, mobility limitations or other comorbidities. Moreover, the applicant effect of PTP is not good in clinical practice, and the rate of PTP in which clinicians' adherence to standardized diagnostic procedures is as poor as 50–60% in prior studies [34, 35]. Simplified clinical assessment algorithms using the new age-adjusted formula and DUS can save time and energy for medical staff. The new age-adjusted D-dimer cutoff value should be applied to specific D-dimer assays. The wide diversities of D-dimer assays used in the published studies showed the difficulty selecting unified reference ranges and clinical thresholds, because of the multiple combinations of monoclonal antibodies and different assay reagent,and diverse D-dimer assays had the substantial differences in analytical performance[31, 36, 37]. The age-adjustment formula should be established based on different D-dimer assays correspondingly, instead of being widely used without a second thought.

Limitation

There are several limitations of our study. It is a single-center retrospective study with inherent defects. Retrospective data extraction may cause inaccurate information. The study is limited to elderly patients with hip fractures, so the results may not have excellent applicability in the general population. We don't evaluate patients who only undergo the D-dimer test or DUS. Likely, patients with highly reasonable suspicion of DVT go straight to perform DUS, resulting in a lower calculated incidence of DVT than that in nature. The D-dimer assays are heterogeneous in different researches. Our study only adopts one laboratory testing method, and how effective is the new age-adjusted cutoff value when other D-dimer assays are used, is unclear.

A large multi-center prospective study should be conducted before the application of the new age-adjusted cutoff value which comes from our exploration.

Conclusions

Our new age-adjusted D-dimer cutoff value is developed for aged people with hip fractures specifically. Clinicians could greatly increase the proportion of older hip fracture patients in whom DVT can be safely excluded to minimize irrelevant DUS and avoid unnecessary anticoagulant therapy with consequent clinical. It has practical and economic advantages by adopting the new age-adjusted cutoff value.

Abbreviations

DVT: deep vein thrombosis

PE: pulmonary embolism

VTE: venous thromboembolism

ROC: receiver operating characteristic curves

PPV: positive predictive values

NPV: negative predictive values

DUS: duplex ultrasound

PTP: pre-test probability

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Third Hospital of Hebei Medical University. Informed consent was waived for this retrospective review as no identifying information was recorded.

Consent for publication

Not application.

Availability of data and materials

All the data used are available from the corresponding author on motivated request.

Competing interests

None declared.

Funding

None.

Contributions

ZKX and ZYB participated in study design, statistical analysis, interpreted results and drafted the manuscript, ZKX and ZYB contributed equally to this work and should be considered co-first authors. LXT and ZYZ provided the original idea and article revision; TYX and TM participated in data collection. All authors are responsible for its accuracy of the analysis.

Acknowledgments

The Institute of Orthopedics of the Third Hospital of Hebei Medical University provided the site for querying data.

References

1. Broen K, Scholtes B, Vossen R. Predicting the need for further thrombosis diagnostics in suspected DVT is increased by using age adjusted D-dimer values. Thrombosis research. 2016;145:107-8.
2. Hamblin A, Cairns K, Keeling D. The use of age-dependent D-dimer cut-off values to exclude deep vein thrombosis. Reply to "Using an age-dependent D-dimer cut-off value increases the number of older

patients in whom deep vein thrombosis can be safely excluded". Haematologica 2012;97(10):1507-13. Haematologica. 2012;97(11):e43-4.

3. Han C, Zhao Y, Cheng W, Yang J, Yuan J, Zheng Y, et al. The performance of age-adjusted D-dimer cut-off in Chinese outpatients with suspected venous thromboembolism. Thrombosis research. 2015;136(4):739-43.
4. Mullier F, Vanpee D, Jamart J, Dubuc E, Bailly N, Douxfils J, et al. Comparison of five D-dimer reagents and application of an age-adjusted cut-off for the diagnosis of venous thromboembolism in emergency department. Blood Coagul Fibrinolysis. 2014;25(4):309-15.
5. Takach Lapner S, Julian JA, Linkins LA, Bates SM, Kearon C. Questioning the use of an age-adjusted D-dimer threshold to exclude venous thromboembolism: analysis of individual patient data from two diagnostic studies. J Thromb Haemost. 2016;14(10):1953-9.
6. Condliffe R. Pathways for outpatient management of venous thromboembolism in a UK centre. Thromb J. 2016;14:47.
7. Farm M, Siddiqui AJ, Onelov L, Jarnberg I, Eintrei J, Maskovic F, et al. Age-adjusted D-dimer cut-off leads to more efficient diagnosis of venous thromboembolism in the emergency department: a comparison of four assays. J Thromb Haemost. 2018;16(5):866-75.
8. Harper P, Theakston E, Ahmed J, Ockelford P. D-dimer concentration increases with age reducing the clinical value of the D-dimer assay in the elderly. Internal medicine journal. 2007;37(9):607-13.
9. Nobes J, Messow CM, Khan M, Hrobar P, Isles C. Age-adjusted D-dimer excludes pulmonary embolism and reduces unnecessary radiation exposure in older adults: retrospective study. Postgrad Med J. 2017;93(1101):420-4.
10. Li Q, Chen X, Wang Y, Li L. Analysis of the occurrence of deep venous thrombosis in lower extremity fractures: A clinical study. Pak J Med Sci. 2018;34(4):828-32.
11. Protty MB, Aithal S, Hickey B, Pettit R, Johansen A. Mechanical prophylaxis after hip fracture: what is the risk of deep vein thrombosis? A retrospective observational study. BMJ Open. 2015;5(2):e006956.
12. Zuo J, Hu Y. Admission deep venous thrombosis of lower extremity after intertrochanteric fracture in the elderly: a retrospective cohort study. J Orthop Surg Res. 2020;15(1):549.
13. Luo Z, Chen W, Li Y, Wang X, Zhang W, Zhu Y, et al. Preoperative incidence and locations of deep venous thrombosis (DVT) of lower extremity following ankle fractures. Sci Rep. 2020;10(1):10266.
14. Shin WC, Lee SM, Suh KT. Recent Updates of the Diagnosis and Prevention of Venous Thromboembolism in Patients with a Hip Fracture. Hip Pelvis. 2017;29(3):159-67.
15. Williams JR, Little MT, Kramer PA, Benirschke SK. Incidence of Preoperative Deep Vein Thrombosis in Calcaneal Fractures. J Orthop Trauma. 2016;30(7):e242-5.
16. Zhang W, Huai Y, Wang W, Xue K, Chen L, Chen C, et al. A Retrospective cohort study on the risk factors of deep vein thrombosis (DVT) for patients with traumatic fracture at Honghui Hospital. BMJ Open. 2019;9(3):e024247.
17. Robert-Ebadi H, Robin P, Hugli O, Verschuren F, Trinh-Duc A, Roy PM, et al. Impact of the Age-Adjusted D-Dimer Cutoff to Exclude Pulmonary Embolism: A Multinational Prospective Real-Life Study (the RELAX-PE Study). Circulation. 2021;143(18):1828-30.

18. Wu JX, Qing JH, Yao Y, Chen DY, Jiang Q. Performance of age-adjusted D-dimer values for predicting DVT before the knee and hip arthroplasty. J Orthop Surg Res. 2021;16(1):82.
19. Zhang J, Fang Y, Pang H, Tao Y, Zhou J, Zhu S, et al. Association of age-adjusted D-dimer with deep vein thrombosis risk in patients with spinal cord injury: a cross-sectional study. Spinal Cord. 2021.
20. Douma R, le Gal G, Söhne M, Righini M, Kamphuisen P, Perrier A, et al. Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts. BMJ (Clinical research ed). 2010;340:c1475.
21. Bates S, Kearon C, Crowther M, Linkins L, O'Donnell M, Douketis J, et al. A diagnostic strategy involving a quantitative latex D-dimer assay reliably excludes deep venous thrombosis. Annals of internal medicine. 2003;138(10):787-94.
22. Douma RA, Tan M, Schutgens RE, Bates SM, Perrier A, Legnani C, et al. Using an age-dependent D-dimer cut-off value increases the number of older patients in whom deep vein thrombosis can be safely excluded. Haematologica. 2012;97(10):1507-13.
23. Gomez-Jabalera E, Bellmunt Montoya S, Fuentes-Camps E, Escudero Rodriguez JR. Age-adjusted D-dimer for the diagnosis of deep vein thrombosis. Phlebology. 2018;33(7):458-63.
24. Riva N, Camporese G, Iotti M, Bucherini E, Righini M, Kamphuisen PW, et al. Age-adjusted D-dimer to rule out deep vein thrombosis: findings from the PALLADIO algorithm. J Thromb Haemost. 2018;16(2):271-8.
25. Dutton J, Dachsel M, Crane R. Can the use of an age-adjusted D-dimer cut-off value help in our diagnosis of suspected pulmonary embolism?. Clinical medicine (London, England). 2018;18(4):293-6.
26. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. Archives of surgery (Chicago, Ill : 1960). 1972;104(2):134-44.
27. Niikura T, Sakai Y, Lee SY, Iwakura T, Nishida K, Kuroda R, et al. D-dimer levels to screen for venous thromboembolism in patients with fractures caused by high-energy injuries. J Orthop Sci. 2015;20(4):682-8.
28. Sasaki S, Miyakoshi N, Matsuura H, Saito H, Nakanishi T, Kudo Y, et al. Prospective study on the efficacies of fondaparinux and enoxaparin in preventing venous thromboembolism after hip fracture surgery. J Orthop Sci. 2011;16(1):64-70.
29. Sasaki S, Miyakoshi N, Matsuura H, Saitoh H, Kudoh D, Shimada Y. Prospective randomized controlled trial on the effect of fondaparinux sodium for prevention of venous thromboembolism after hip fracture surgery. J Orthop Sci. 2009;14(5):491-6.
30. Xing F, Li L, Long Y, Xiang Z. Admission prevalence of deep vein thrombosis in elderly Chinese patients with hip fracture and a new predictor based on risk factors for thrombosis screening. BMC Musculoskelet Disord. 2018;19(1):444.
31. Senior K, Burles K, Wang D, Grigat D, Innes GD, Andruchow JE, et al. Age-adjusted D-dimer thresholds in the investigation of suspected pulmonary embolism: A retrospective evaluation in patients ages 50 and older using administrative data. CJEM. 2018;20(5):725-31.
32. Righini M, Nendaz M, Le Gal G, Bounameaux H, Perrier A. Influence of age on the cost-effectiveness of diagnostic strategies for suspected pulmonary embolism. Journal of thrombosis and haemostasis : JTH. 2007;5(9):1869-77.

33. Jimenez-Guiu X, Romera-Villegas A, Huici-Sanchez M, Martinez-Rico C, Vila-Coll R. Role of an age-adjusted D-dimer cutoff level in the diagnosis algorithm of lower limb deep venous thrombosis in outpatients. Journal of vascular surgery Venous and lymphatic disorders. 2020;8(5):734-40.
34. Alhassan S, Sayf A, Arsene C, Krayem H. Suboptimal implementation of diagnostic algorithms and overuse of computed tomography-pulmonary angiography in patients with suspected pulmonary embolism. Annals of thoracic medicine. 2016;11(4):254-60.
35. Yin F, Wilson T, Della Fave A, Larsen M, Yoon J, Nugusie B, et al. Inappropriate use of D-dimer assay and pulmonary CT angiography in the evaluation of suspected acute pulmonary embolism. American journal of medical quality : the official journal of the American College of Medical Quality. 2012;27(1):74-9.
36. Oude Elferink R, Loot A, Van De Klashorst C, Hulsebos-Huygen M, Piersma-Wichers M, Oudega R. Clinical evaluation of eight different D-dimer tests for the exclusion of deep venous thrombosis in primary care patients. Scandinavian journal of clinical and laboratory investigation. 2015;75(3):230-8.
37. Parry BA, Chang AM, Schellong SM, House SL, Fermann GJ, Deadmon EK, et al. International, multicenter evaluation of a new D-dimer assay for the exclusion of venous thromboembolism using standard and age-adjusted cut-offs. Thromb Res. 2018;166:63-70.

Figures

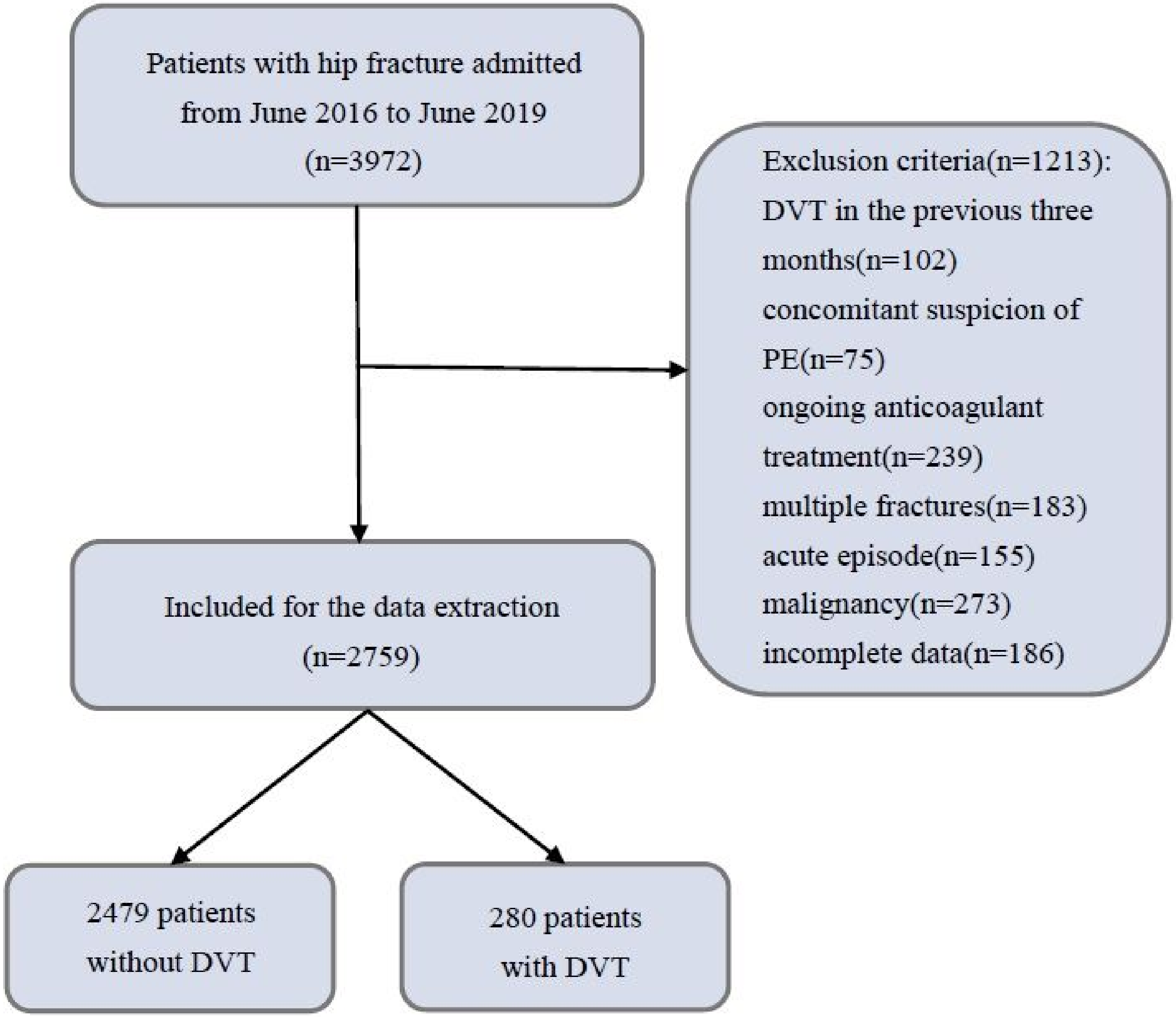

Figure 1

flow diagram of the study. Of 3972 aged patients with hip fracture admitted to hospital. 1213 patients who did not meet the inclusion criteria were excluded. Of the 2759 left. Of those patients, 2479 did not had DVT and 280 did.

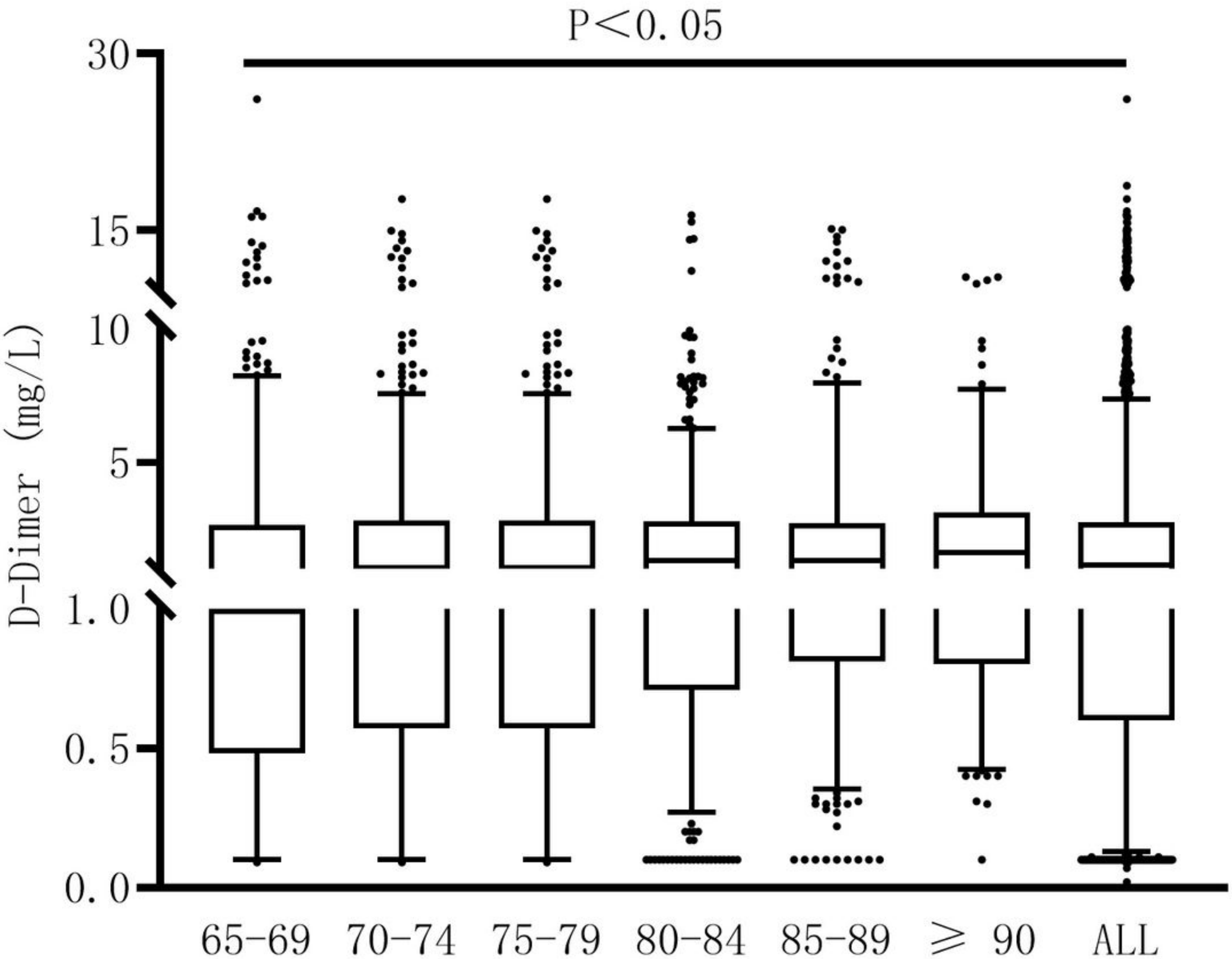

Figure 2

the D-dimer level of all patients and six 5-year age groups. The level of D-dimer in each group was shown as box plots with a percentile of 5-95%. Comparison of 7 groups: $p<0.05$.

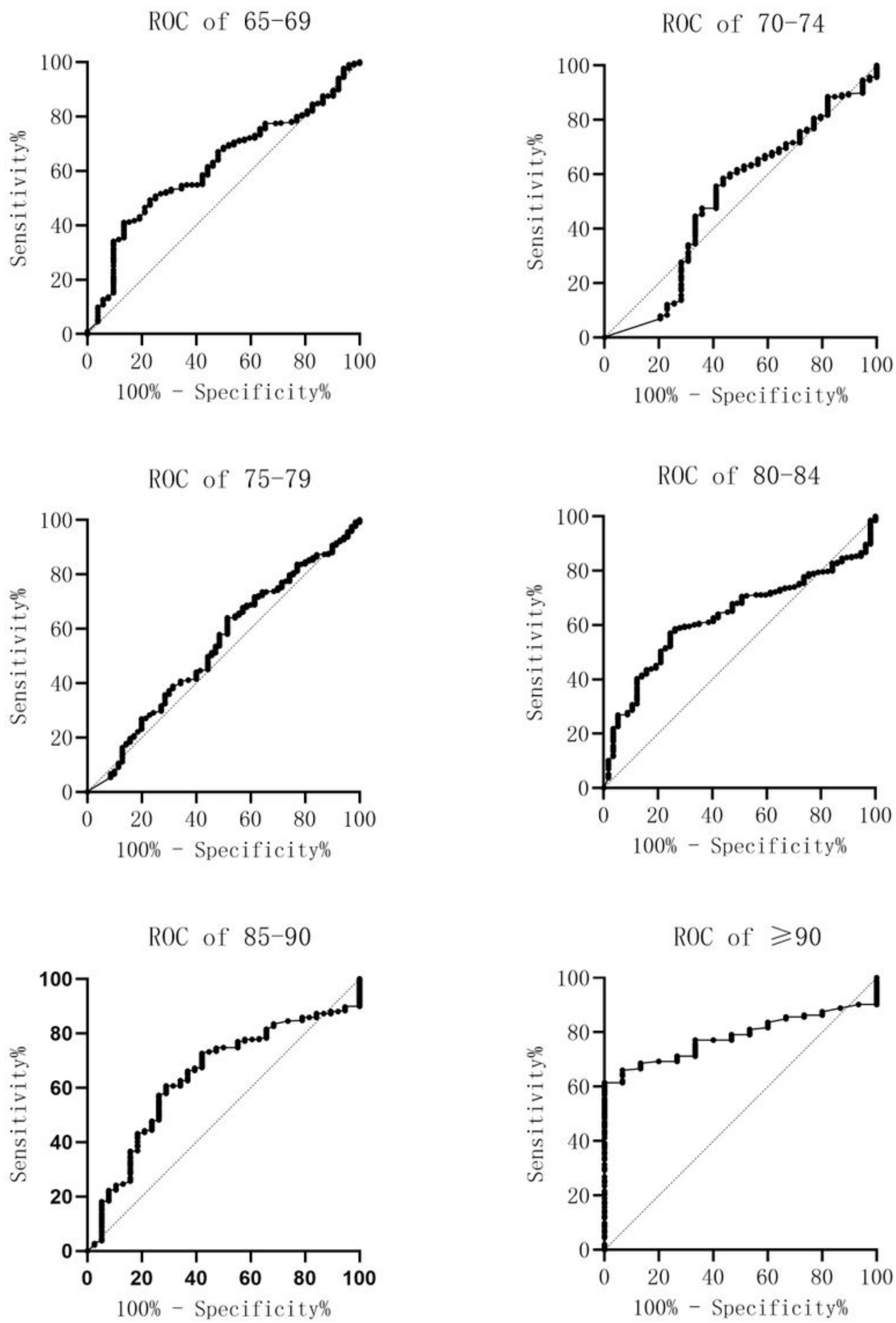

Figure 3

receiver operating characteristic (ROC) curves of the D-dimer test for each 5-year-apart age group. The optimal cutoff value for each group was determined when the Youden index was at its maximum.

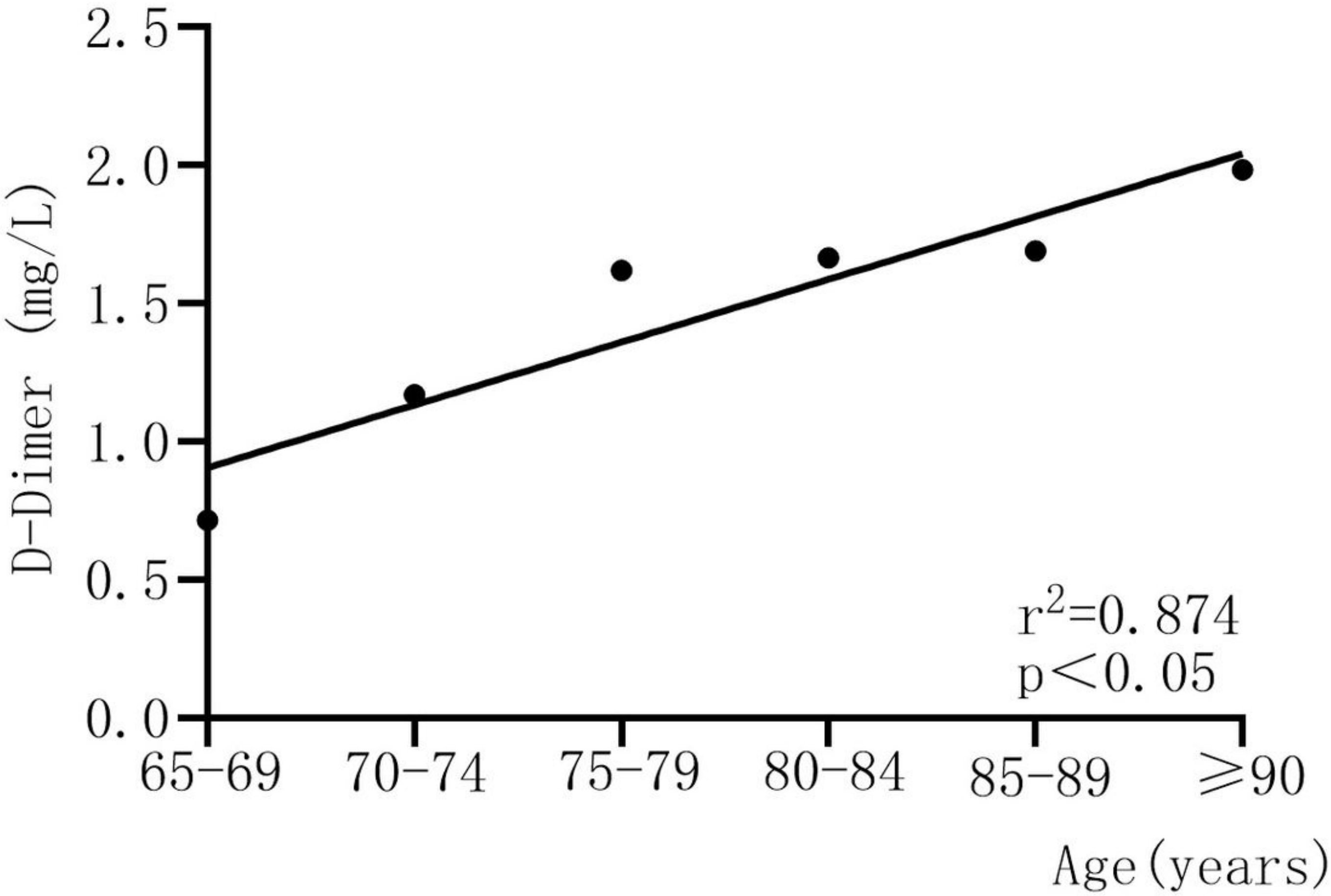

Figure 4

linear regression analysis of optimal cutoff value and 5-year age groups. Through linear regression analysis, the regression coefficient (r, corresponding to the slope of the regression line) was determined (here :0.23; 95% confidence interval 0.11-0.35). This coefficient represented an increase in the level of D-dimer per 5 years. By dividing the regression coefficient by 5, the annual increase in the level of D-dimer was obtained. In determining the new age-adjusted D-dimer threshold, the calculated coefficient was used as a multiplier for the patient's age.