https://doi.org/10.31925/farmacia.2026.2.23 **ORIGINAL ARTICLE**

EFFICACY AND SAFETY EVALUATION OF LOW MOLECULAR WEIGHT HEPARIN COMBINED WITH RIVAROXABAN IN THE TREATMENT OF ELDERLY PATIENTS WITH ACUTE PULMONARY EMBOLISM

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Abstract

This retrospective study compared the efficacy and safety of low molecular weight heparin (LMWH) combined with rivaroxaban versus LMWH plus warfarin in elderly patients with acute pulmonary embolism (PE). A total of 159 patients aged > 60 years with intermediate-low risk acute PE were included: 79 received LMWH plus warfarin and 80 received LMWH plus rivaroxaban. Clinical efficacy, coagulation parameters, biochemical markers, cardiopulmonary function, CTPA findings, and adverse events were evaluated up to 6 months after treatment. The total effective rate was significantly higher in the rivaroxaban group than in the warfarin group (86.25% *vs*. 69.62%, p = 0.042). Patients treated with rivaroxaban showed better coagulation profiles, including longer PT and lower D-dimer levels, improved oxygenation (PaO_2), and a higher thrombus lysis rate (all $p < 0.05$). In addition, bleeding events and the need for INR monitoring were significantly reduced in the rivaroxaban group. No significant differences were observed in gastrointestinal reactions or re-embolism rates. LMWH combined with rivaroxaban demonstrated superior efficacy and safety compared with the conventional warfarin regimen and may represent a preferable anticoagulation strategy in elderly patients with acute PE.

Rezumat

Studiul a comparat eficacitatea și siguranța asocierii heparinei cu greutate moleculară mică (HGMM) cu rivaroxaban față de HGMM plus warfarină la pacienții vârstnici cu embolie pulmonară (EP) acută. Au fost incluși 159 de pacienți cu vârsta > 60 ani, diagnosticați cu EP acută cu risc intermediar-scăzut: 79 au primit HGMM plus warfarină, iar 80 au primit HGMM plus rivaroxaban. Eficacitatea clinică, parametrii de coagulare, markerii biochimici, funcția cardiopulmonară, datele CTPA și reacțiile adverse au fost evaluate pe o perioadă de până la 6 luni. Rata totală de eficacitate a fost semnificativ mai mare în lotul tratat cu rivaroxaban comparativ cu lotul tratat cu warfarină (86,25% *vs*. 69,62%, p = 0,042). Pacienții din lotul cu rivaroxaban au prezentat parametri de coagulare superiori, valori mai scăzute ale D-dimerilor, oxigenare mai bună (PaO_2) și o rată mai mare de liză a trombului (toate $p < 0,05$). De asemenea, episoadele hemoragice și necesitatea monitorizării INR au fost semnificativ reduse. Nu s-au evidențiat diferențe semnificative privind reacțiile gastrointestinale sau reembolizarea. Asocierea HGMM–rivaroxaban a demonstrat eficacitate și siguranță superioare față de schema convențională cu warfarină.

Keywords: low molecular weight heparin, rivaroxaban, elderly acute pulmonary embolism, efficacy, safety

Introduction

Pulmonary embolism (PE) is an acute and critical condition characterized by the obstruction of the pulmonary artery system by various emboli, among which pulmonary thromboembolism (PTE) is the main type, closely related to the formation of deep venous thrombosis (DVT) (1, 2). Collectively referred to as venous thromboembolism (VTE), PTE is the third leading cause of cardiovascular death after coronary heart disease and stroke, with high rates of misdiagnosis, mortality, and recurrence, posing a visible threat to patients' lives (3). With the intensification of population aging, the incidence of VTE in the elderly population has markedly increased due to multiple underlying diseases, poor hemodynamic compensation, and limited mobility, resulting in worse clinical prognosis and an urgent need to explore optimized treatment regimens for this group (4).

Anticoagulation therapy is the core measure in the management of PTE. The traditional regimen combines low molecular weight heparin (LMWH) with warfarin. However, warfarin has limitations such as a narrow therapeutic window, the need for frequent international normalized ratio (INR) monitoring, and susceptibility to drug/food interactions, leading to low compliance and increased bleeding risks in elderly patients (5, 6). In recent years, novel oral anticoagulants (NOACs) like rivaroxaban have become new choices for anticoagulation therapy due to their fixed doses, no need for routine monitoring, and fewer drug interactions (7). NOACs offer advantages such as no

routine coagulation monitoring, fewer drug interactions, lower bleeding risks, rapid onset (peaking in 1 - 4 hours), and shorter half-lives (5 - 17 hours), facilitating emergency anticoagulation and dose adjustment. With their benefits of no monitoring, low bleeding risk, and convenient use, NOACs have become the preferred anticoagulant for elderly patients with acute PE (8, 9). Rivaroxaban has a rapid onset and offset of action, allowing for quick anticoagulation with a predictable pharmacokinetics that does not require frequent coagulation function monitoring and dose adjustment like warfarin, making it more convenient to use. As against vitamin K antagonist warfarin, it is less affected by food and other drugs (10). Studies have shown that rivaroxaban has a safety advantage in the treatment of elderly acute PE (11). However, there is still controversy in domestic and international guidelines regarding anticoagulation regimens for elderly patients, especially the balance strategy between bleeding and thrombotic risks. There are still some issues with the application of NOACs in elderly patients. Some elderly patients have reduced renal function, and since NOACs are excreted through the kidneys, dose adjustment is more complex in patients with renal insufficiency. NOACs are relatively expensive, increasing the economic burden on patients. Currently, there are no specific antidotes for NOACs, making it more challenging to manage severe bleeding. Many existing studies focus on the general population, and the evidence for the efficacy and safety of LMWH plus NOACs in elderly patients is still insufficient (12).

This article retrospectively analyzed the clinical data of elderly patients with acute PTE to compare the distinctions in efficacy and safety between LMWH plus rivaroxaban and the traditional warfarin regimen. It aims to provide a safer and more convenient anticoagulation treatment strategy for elderly patients and to supplement the evidence for optimizing clinical guidelines.

Materials and Methods

Research subjects

This study is a single-center retrospective cohort analysis, including elderly patients with acute PE treated at Affiliated Yangming Hospital of Ningbo University, Zhejiang, China from January 1, 2019, to September 30, 2023. The patients were divided into control group (n = 79) and observation group (n = 80) based on the anticoagulation treatment regimen. The control group was treated with LMWH plus warfarin, while the observation group was treated with LMWH plus a novel oral anticoagulant (rivaroxaban). In the observation group, there were 42 males and 38 females; the age ranged from 61 to 78 years, with an average age of (63.24 ± 1.24) years. In the control group, there were 38 males and 41 females; the age ranged from 61 to 77 years, with an average age of (63.63 ± 1.42) years. There was no statistical significance in age and gender between the two groups ($p < 0.05$), and they were comparable. The study was approved by the Affiliated Yangming Hospital of Ningbo University, Zhejiang, China ethics committee, and all patients and their families were informed and voluntarily participated in the study, signing the informed consent form.

Inclusion criteria: (i) Patients were diagnosed with elderly acute PE according to clinical diagnostic criteria (13) after admission and confirmed by CT examination; (ii) Patients were aged over 60 years and were at intermediate-low risk [simplified pulmonary embolism severity index (sPESI) score (14) ≤ 1 point]; (iii) Patients had no contraindications to anticoagulation treatment (such as active bleeding, severe liver or kidney dysfunction).

Exclusion criteria: (i) Patients with other life-threatening diseases such as malignant tumors, severe infections, ischemic stroke; (ii) Patients with incomplete clinical data.

Grouping and treatments

In the control group patients received the combination of LMWH and warfarin. LMWH calcium injection (Sichuan Fedeli Pharmaceutical Co., Ltd., China) was administered subcutaneously at a dose of 86 U/kg every 12 hours (q12h) for 7 consecutive days. Starting from the first day of treatment, warfarin sodium tablets (Shanghai Sine Pharmaceutical Co., Ltd., China) were administered orally at a dose of 2.5 mg once daily (qd) until INR reached the target range (2.0 - 3.0). After achieving the target INR, LMWH was discontinued, and oral warfarin sodium was continued until 3 months of treatment. The patients were followed up for 6 months.

In the observation group patients received the combination of LMWH and rivaroxaban. LMWH calcium injection (Sichuan Fedeli Pharmaceutical Co., Ltd., China) was administered subcutaneously at a dose of 86 U/kg every 12 hours (q12h) for 7 consecutive days. On 8th day, LMWH was discontinued, and rivaroxaban (Bayer Healthcare, Germany) was started orally for 14 days at a dose of 15 mg twice daily (bid). From 23rd day onward, the dose of rivaroxaban was adjusted to 20 mg once daily (qd) and continued until 3 months of treatment. The patients were followed up for 6 months.

Based on preliminary pilot trial data analysis, the total response rate was assumed to be 70% in the control group and 85% in the observation group. With a two-sided α set at 0.05 and a test power (1-β) of 0.80, the calculated minimum required sample size was 76 *per* group. Accounting for a 5% dropout rate, the final sample size was set at 80 *per* group, totaling 160 cases. The actual enrollment of 159 patients (79 in the control group, 80 in the observation

group) met the requirement for detecting clinically significant differences.

Observation indicators

Coagulation function indicators. Prothrombin time (PT) was detected using an automated coagulation analyzer (Sysmex CS-2500, SYSMEX Corporation, Japan). Sodium citrate-anticoagulated plasma was used as the test sample. Thromboplastin was used as the reagent. During the test, calcium ions and thromboplastin reagent were added to the sample to initiate the extrinsic coagulation pathway. The plasma coagulation time was monitored and recorded in real-time using an optical method (PT). INR was calculated based on the measured PT value and the international sensitivity index (ISI) (15) of the thromboplastin reagent. Activated partial thromboplastin time (APTT) was detected using an automated coagulation analyzer (Sysmex CS-2500, SYSMEX Corporation, Japan). Sodium citrate-anticoagulated plasma was used as the test sample. Partial thromboplastin reagent containing an activator and calcium chloride ($CaCl_2$) solution were used. During the test, the partial thromboplastin reagent was first added to the plasma sample for pre-incubation to activate contact factors, followed by the addition of pre-warmed $CaCl_2$ solution to initiate the intrinsic coagulation pathway. The time required for plasma coagulation was monitored and recorded in real-time using an optical method (APTT). D-dimer was measured using an enzyme-linked immunosorbent assay (ELISA) with an enzyme-labeled instrument (TECAN Company, Austria). Monoclonal antibodies specifically bind to D-dimer in fibrin degradation products, and the concentration was quantified based on changes in optical density (16). Fibrinogen (FIB) concentration was detected using an automated coagulation analyzer (Sysmex CS-2500, SYSMEX Corporation, Japan). Sodium citrate-anticoagulated plasma was used as the test sample. Thrombin (Multifibren U) (Tianjin Jinyuan Pharmaceutical Co., Ltd., China) was used as the reagent. During the test, an excess of thrombin reagent was added to the plasma sample. Thrombin directly acted on FIB, converting it into fibrin and forming a clot. The time required for plasma coagulation was monitored and recorded in real-time using an optical method. The measured coagulation time was inversely proportional to the FIB concentration. The final FIB concentration was calculated by comparing the coagulation time with a standard curve established using a standard with a known FIB concentration.

Biochemical indicators. C-reactive protein (CRP), brain natriuretic peptide (BNP), and N-terminal pro-brain natriuretic peptide (NT-proBNP) were detected in the subjects using ELISA method according to manufacturer instructions (TECAN Company, Austria). Cardiac troponin I (CTnI) was measured in the patients using a high-sensitivity chemiluminescent immunoassay according to manufacturer instructions (TECAN Company, Austria).

Cardiopulmonary function indicators. Respiratory rate (RR) and heart rate (HR) were monitored in real-time by a bedside monitor (Philips, the Netherlands) and the average value within 1 min at rest was recorded. Partial pressure of arterial oxygen (PaO_2) and partial pressure of arterial carbon dioxide ($PaCO_2$) were evaluated using an arterial blood gas analyzer (RapidPoint 500; Siemens, Germany) to collect radial or femoral arterial blood samples.

CT pulmonary angiography (CTPA) indicators. All patients underwent CTPA. The patients were placed in the supine position, and a non-ionic iodine contrast agent (iohexol, Shanghai Sine Pharmaceutical Co., Ltd., China) was injected through the antecubital vein. The optimal enhancement timing of the pulmonary artery trunk was determined using a bolus tracking technique (17) to trigger scanning. The scanning range covered from the lung apex to the diaphragmatic level. A multi-slice spiral CT scanner (Siemens, Germany) was used for scanning with the following acquisition parameters: tube voltage 120 kV, automatic tube current modulation, detector collimation 0.6 mm, pitch 1.0, and rotation time 0.5 s. The raw data were reconstructed into thin slices (slice thickness 1.0 mm, reconstruction interval 0.7 mm), and multi-planar reformation (MPR) and maximum intensity projection (MIP) were performed using a standard lung vascular algorithm and a soft tissue algorithm, respectively, for subsequent image analysis. Based on the obtained CTPA images, two experienced radiologists independently assessed the Qanadli score (18), the complete dissolution rate of pulmonary artery thrombi, and the incidence of pulmonary infarction without knowledge of the patient grouping information (blinding).

Adverse event recording

Bleeding events in patients were evaluated according to the International Society on Thrombosis and Haemostasis (ISTH) criteria (19) (major bleeding or clinically relevant non-major bleeding), combined with medical record documentation, a decrease in hemoglobin ($\geq$ 2 g/dL), or imaging evidence (*e.g.*, gastrointestinal endoscopy, cranial CT). Gastrointestinal reactions in patients were recorded after excluding other causes based on the patients' complaints of nausea, vomiting, and abdominal pain. New-onset PE symptoms (dyspnea, chest pain) combined with CTPA-confirmed new thrombus formation were used to diagnose re-embolism. Drug-related rashes (*e.g.*, urticaria, erythema) were assessed by a dermatologist to determine whether the patients had rashes.

Efficacy evaluation

The time points for efficacy evaluation were 1 week, 3 weeks, 3 months, and 6 months after treatment. The specific grading was following: (1) Cure: The symptoms of dyspnea and chest pain basically disappeared,

blood gas analysis was normal, and the pulmonary artery systolic pressure or hemodynamic measurement of mean pulmonary artery pressure (mPAP) was normal; (2) Visible effect: The degree of dyspnea was reduced by > 50%, the degree of chest pain was reduced by > 75%, hypoxia and hypocapnia were markedly improved, and the pulmonary artery systolic pressure or hemodynamic measurement of mPAP decreased by > 20 mmHg and 15 mmHg; (3) Improvement: The degree of dyspnea was reduced by > 20% to < 50%, the degree of chest pain was reduced by > 50%, hypoxia and hypocapnia improved, and the pulmonary artery systolic pressure or hemodynamic measurement of mPAP decreased by > 10 mmHg and 5 mmHg; (4) Effective: The degree of dyspnea improved by < 20%, chest pain was reduced by about 25%, hypoxia and hypocapnia slightly improved, and the pulmonary artery systolic pressure or hemodynamic measurement of mPAP decreased by > 10 mmHg and 5 mmHg; (5) Ineffective: There was no visible change in the degree of dyspnea and chest pain, hypoxia and hypocapnia still existed, and the pulmonary artery systolic pressure or hemodynamic measurement of mPAP decreased or increased by < 10 mmHg or 5 mmHg.

Quality control and compliance management

All reagents used in laboratory testing were original-factory-matched, and the equipment was calibrated daily. The quality control materials met the clinical laboratory improvement amendments (CLIA) standards. The operators of all testing equipment were trained uniformly. Patient compliance was assessed through medication diaries, counting remaining doses, and monthly telephone follow-ups (a compliance rate of ≥80% was considered qualified). Data were entered into an electronic data collection system by two people and regularly checked for logical errors and missing values. Intention-to-treat analysis was performed on drop-out cases, and the reasons were recorded and included in the final statistics.

Statistical methods

The baseline data and related indicators were recorded by a dedicated person using a unified form to ensure no omissions. The data were analyzed using the SPSS22.0 (IBM, USA) statistical software. Measurement data were expressed as mean ± standard deviation, and inter-group comparisons were made using the independent-samples *t*-test or the Mann-Whitney U test. Categorical data were presented as number (percentage) [n (%)], and inter-group comparisons were performed using the χ^2 test or Fisher's exact test (when the expected frequency in any cell was < 5). A p value of < 0.05 was considered statistically meaningful. To adjust for potential confounding factors, multivariate logistic regression analysis was performed for the primary outcomes (overall response rate and bleeding events), with age, sex, BMI, history of VTE, use of antiplatelet agents, and baseline estimated glomerular filtration rate included as covariates.

Results and Discussion

Contrast of primary diseases in subjects

In the control group (n = 79), 16 cases (20.25%) had DVT, 22 cases (27.85%) had myeloid joint fractures, 23 cases (29.11%) had acute exacerbation of chronic obstructive pulmonary disease (COPD), 17 cases (21.52%) had coronary heart disease, and 58 cases (73.41%) had hypertension. In the observation group (n = 80), 21 cases (26.25%) had DVT, 30 cases (37.5%) had myeloid joint fractures, 18 cases (22.5%) had acute exacerbation of COPD, 15 cases (18.75%) had coronary heart disease, and 63 cases (78.75%) had hypertension. There was no visible distinction in primary diseases between the two groups (p > 0.05) (Figure 1). In Table I, no statistically significant differences were observed in the baseline characteristics between the two groups (all p > 0.05), indicating comparability.

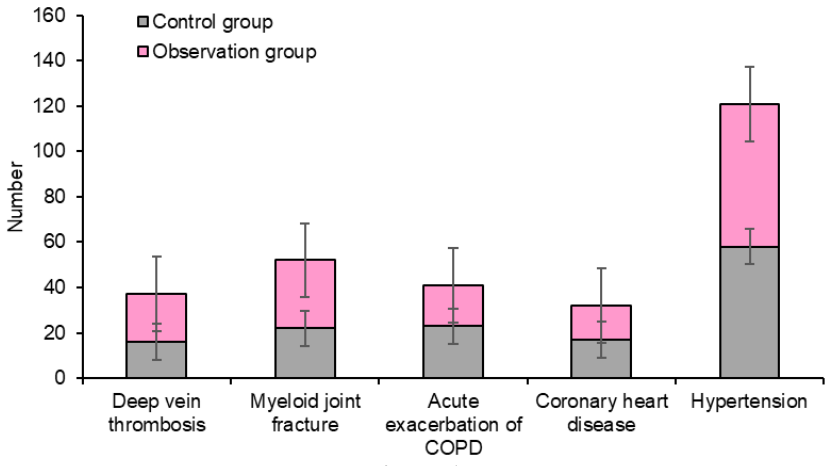

Figure 1.
Contrast of primary diseases in subjects

Table I

Comparison of baseline characteristics between the two groups

Characteristic	Observation group (n = 80)	Control group (n = 79)	p
Age (years)	63.24 ± 1.24	63.63 ± 1.42	0.105
Male, n (%)	42 (52.5%)	38 (48.1%)	0.612
Body mass index (kg/m²)	25.1 ± 3.2	24.8 ± 3.5	0.543
Smoking history, n (%)	28 (35.0%)	25 (31.6%)	0.742
History of VTE, n (%)	12 (15.0%)	10 (12.7%)	0.822
Use of antiplatelet agents, n (%)	15 (18.8%)	14 (17.7%)	1.000
Estimated glomerular filtration rate (mL/min/1.73m²)	78.5 ± 12.3	76.8 ± 13.1	0.389

Efficacy evaluation

In Figure 2, at 1 week, the visible effect rate in the observation group was 35.0% (28/80), while that in the control group was 24.05% (19/79) (p = 0.021). At 3 weeks, the cure rate in the observation group was 17.5% (14/80), compared to 5.06% (4/79) in the control group (p = 0.047). At 3 months, the total effective rate (cure + visible effect + improvement) in the observation group was 83.75% (67/80), while it was 63.29% (50/79) in the control group (p = 0.038). At 6 months, the re-embolism rate in the observation group was 2.5% (2/80), compared to 7.59% (6/79) in the control group (p = 0.042). The total effective rate in the observation group was 86.25% (69/80), markedly higher as against the control group, 69.62% (55/79) (χ^2 = 4.12, p = 0.042 < 0.05).

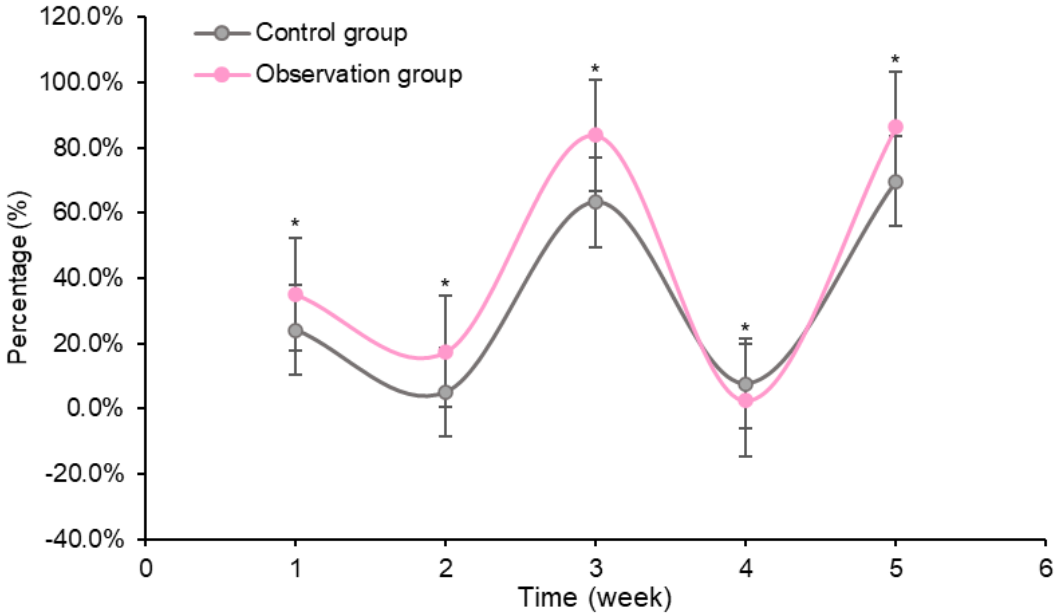

Figure 2.

Contrast of therapeutic effects

*As against control group, p < 0.05

Changes in related coagulation indicators

Before treatment, the PT was (9.87 ± 2.24) s in the observation group and (9.91 ± 2.31) s in the control group while after treatment, the PT was (18.71 ± 4.21) s in the observation group and (11.43 ± 3.17) s in the control group (Figure 3A). Before treatment, the APTT was (27.62 ± 3.5) s in the observation group and (28.11 ± 3.2) s in the control group, while after treatment, the APTT was (32.83 ± 4.5) s in the observation group and (46.37 ± 5.7) s in the control group (Figure 3B). Before treatment, the D-dimer was (5.3 ± 1.5) mg/L in the observation group and (5.2 ± 1.8) mg/L in the control group, while after treatment, the D-dimer was (0.7 ± 0.5) mg/L in the observation group and (2.7 ± 0.8) mg/L in the control group (Figure 3C). Before treatment, the FIB was (4.43 ± 0.85) g/L in the observation group and (4.51 ± 0.91) g/L in the control group while after treatment, the FIB was (3.17 ± 0.53) g/L in the observation group and (3.99 ± 0.62) g/L in the control group (Figure 3D). There were no visible distinctions in PT, APTT, D-dimer, and FIB before treatment (p > 0.05), while after treatment, the parameters in the observation group were markedly improved compared to the control group (p < 0.05).

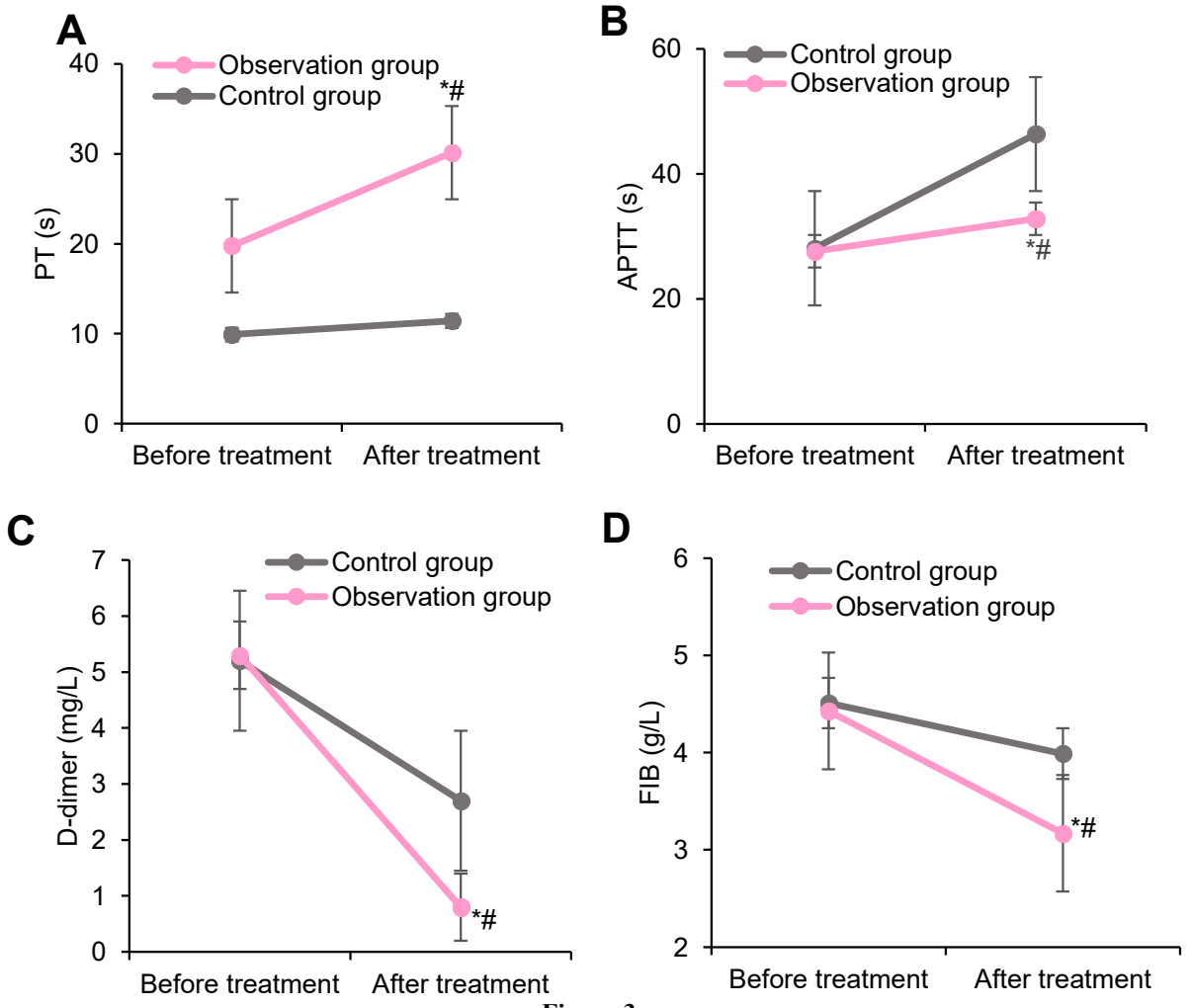

Figure 3.

Changes in coagulation indicators of subjects

A: PT; B: APTT; C: D-dimer; D: FIB. *$p < 0.05$ *vs*. control group; #$P < 0.05$ *vs*. before treatment

Contrast of biochemical indicators

Before treatment, the CRP was (6.76 ± 1.74) mg/L in the observation group and (6.83 ± 1.85) mg/L in the control group, while after treatment, the CRP was (3.11 ± 0.71) mg/L in the observation group and (4.76 ± 1.48) mg/L in the control group (Figure 4A). Before treatment, the BNP was (320 ± 83) pg/mL in the observation group and (310 ± 90) pg/mL in the control group, while after treatment, the BNP was (150 ± 46) pg/mL in the observation group and (280 ± 72) pg/mL in the control group (Figure 4B). There were no visible distinctions in CRP and BNP before treatment ($p > 0.05$). After treatment, the observation group was markedly lower than the control group, and the distinction between before and after treatment in the observation group was visible ($p < 0.05$).

Before treatment, the cTnI was (0.15 ± 0.04) ng/mL in the observation group and (0.16 ± 0.05) ng/mL in the control group while after treatment, the cTnI was (0.08 ± 0.02) ng/mL in the observation group and (0.14 ± 0.03) ng/mL in the control group (Figure 4C). Before treatment, the NT-proBNP was (1750 ± 450) ng/mL in the observation group and (1800 ± 460) ng/mL in the control group while after treatment, the NT-proBNP was (150 ± 50) ng/mL in the observation group and (800 ± 0.03) ng/mL in the control group (Figure 4D). There were no visible distinctions in NT-proBNP and cTnI before treatment ($p > 0.05$). After treatment, the distinctions in NT-proBNP and cTnI were visible, and the NT-proBNP and cTnI in the observation group were markedly lower than those in the control group ($p < 0.05$).

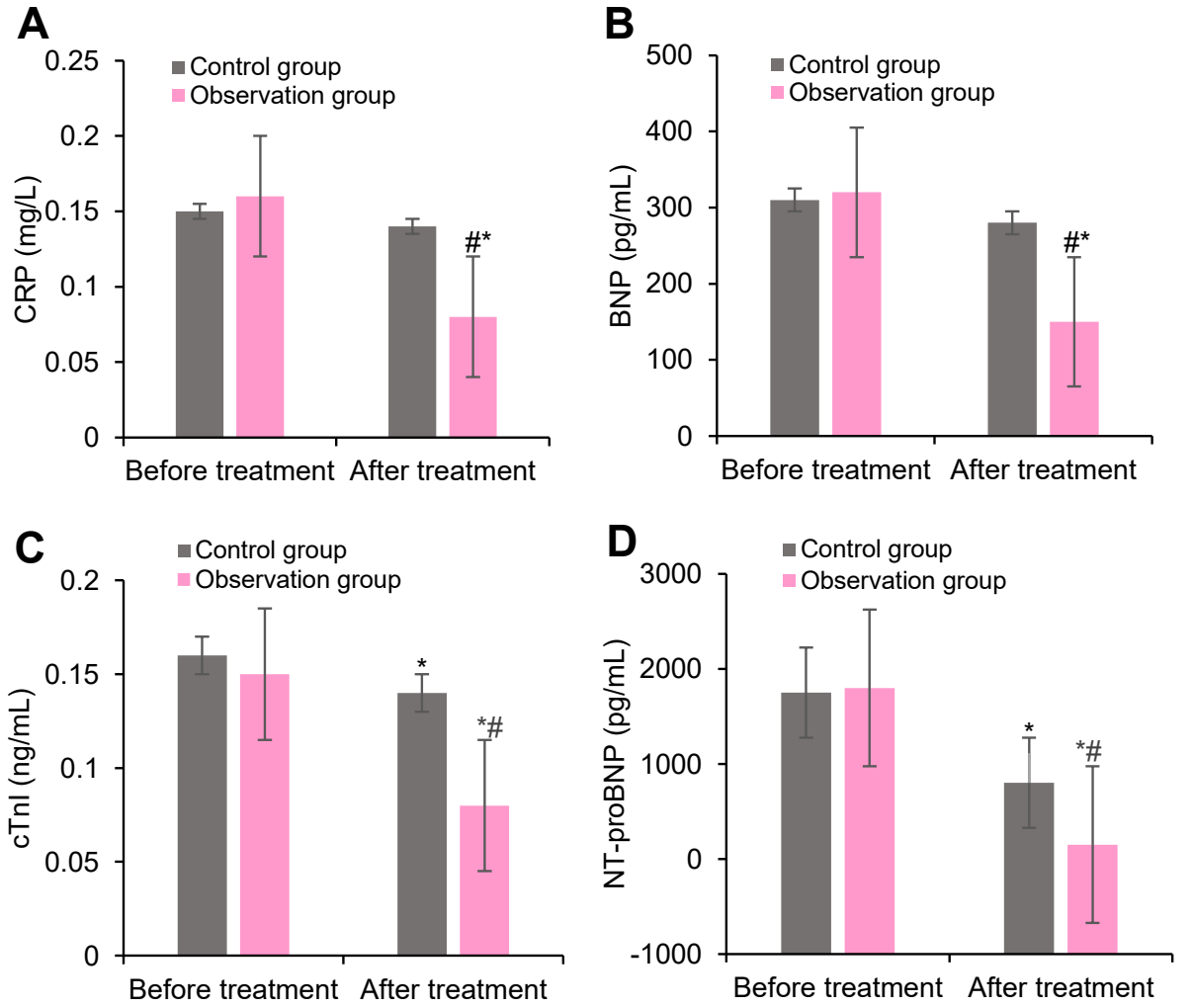

Figure 4.

Contrast of biochemical indicators

A: CRP; B: BNP; C: cTnI; D: NT-proBNP. *$p < 0.05$ *vs*. control group; #$p < 0.05$ *vs*. before treatment

Changes in cardiopulmonary indicators

Before treatment, the RR was (31.65 ± 3.74) times/min in the observation group and (32.32 ± 3.57) times/min in the control group, while after treatment, the RR was (18.11 ± 2.71) times/min in the observation group and (21.76 ± 2.48) times/min in the control group (Figure 5A). Before treatment, the HR was (98.61 ± 10.61) times/min in the observation group and (97.51 ± 11.4) times/min in the control group while after treatment, the HR was (78.32 ± 2.71) times/min in the observation group and (88.62 ± 9.82) times/min in the control group (Figure 5B). Before treatment, the PaO_2 was (66.53 ± 7.65) mmHg in the observation group and (65.82 ± 6.97) mmHg in the control group, while after treatment, the PaO_2 was (81.11 ± 6.71) mmHg in the observation group and (73.61 ± 6.43) mmHg in the control group (Figure 5C). Before treatment, the $PaCO_2$ was (53.38 ± 6.56) mmHg in the observation group and (54.75 ± 5.73) mmHg in the control group while after treatment, the $PaCO_2$ was (40.21 ± 5.18) mmHg in the observation group and (46.65 ± 5.89) mmHg in the control group (Figure 5D). There were no obvious distinctions in RR, HR, PaO_2, and $PaCO_2$ before treatment ($p > 0.05$). After treatment, significant decreases were observed in RR, HR, PaO_2, and $PaCO_2$, with the observation group showing more decrease compared to the control group ($p < 0.05$).

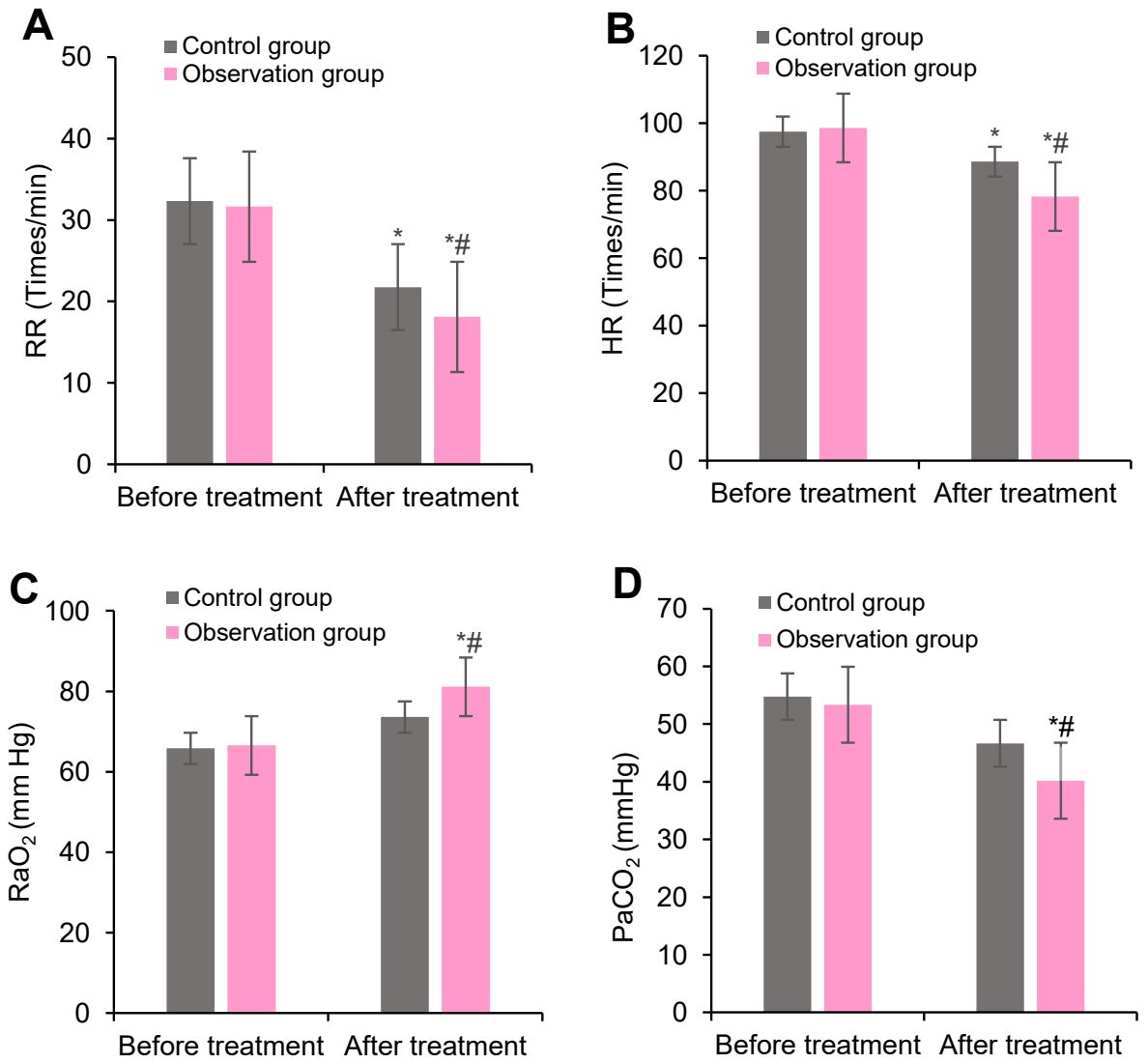

Figure 5.

Contrast of cardiopulmonary indicators before and after treatment in subjects

A: RR; B: HR; C: PaO_2; D: $PaCO_2$. *$p < 0.05$ *vs*. control group; #$p < 0.05$ *vs*. before treatment

CTPA-related indicators

Before treatment, the Qanadli score was (28.51 ± 5.34) in the observation group and (27.9 ± 5.42) in the control group. After treatment, the Qanadli score was (10.21 ± 5.34) in the observation group and (18.7 ± 5.42) in the control group. There was no obvious distinction in the Qanadli score before treatment ($p > 0.05$). After treatment, the distinction in the Qanadli score was obvious, and the Qanadli score in the observation group was markedly lower as compared to the control group ($p < 0.05$) (Figure 6A). Before treatment, the incidence of infarction was 13.75% (11/80) in the observation group and 16.46% (13/79) in the control group. After treatment, the incidence of infarction was 2.5% (2/80) in the observation group and 11.39% (9/79) in the control group. There was no obvious distinction in the incidence of infarction before treatment ($p > 0.05$). After treatment, the distinction in the incidence of infarction was obvious, and the incidence of infarction in the observation group was markedly lower as compared to the control group ($p < 0.05$) (Figure 6B). The complete dissolution rate of pulmonary artery thrombi was 0 in both groups before treatment. After treatment, the complete dissolution rate of main pulmonary artery thrombi was 78.75% (63/80) in the observation group and 43.04% (34/79) in the control group. After treatment, the incidence of infarction in the observation group was markedly lower as compared to the control group ($p < 0.05$) (Figure 6C).

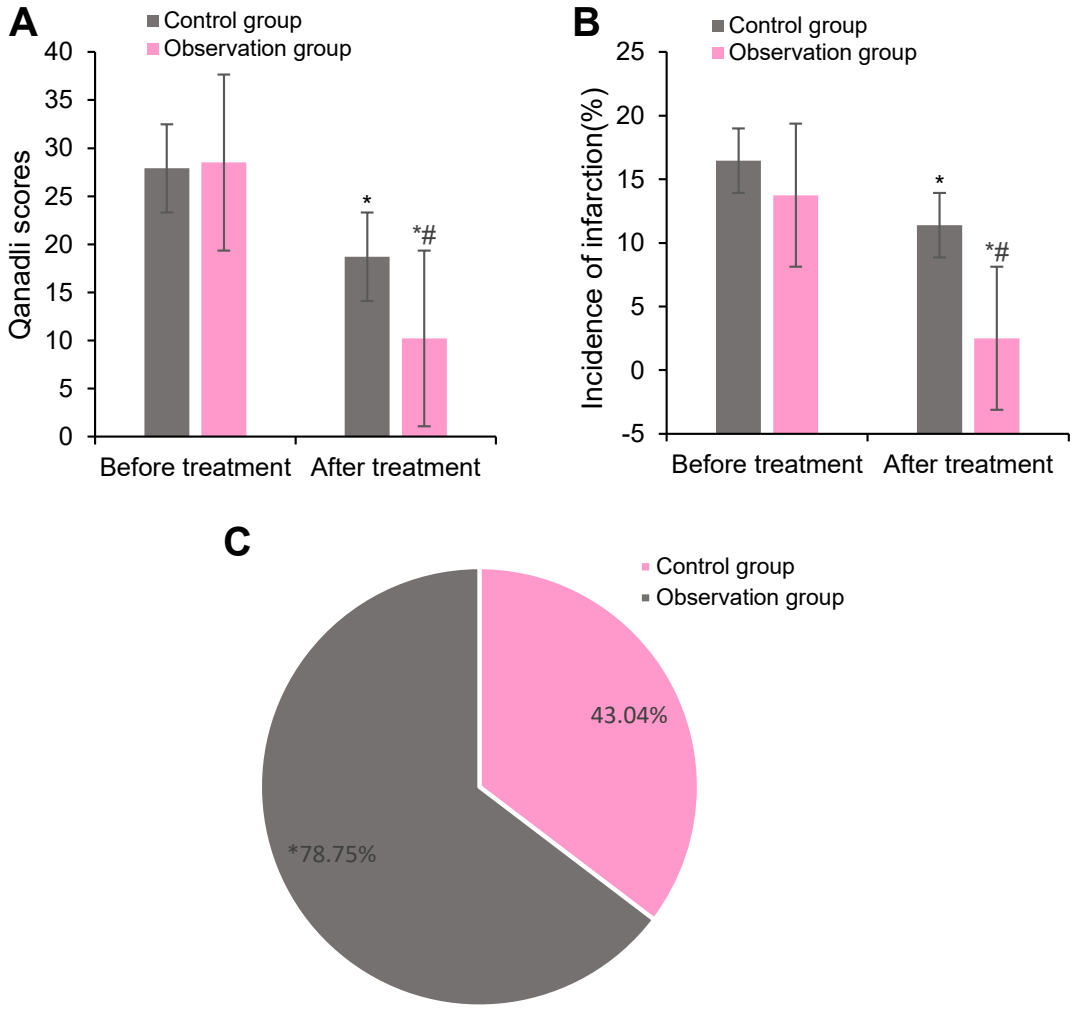

Figure 6.
CTPA-related indicators of subjects
A: Qanadli score; B: Infarction rate; C: Complete dissolution rate of pulmonary artery thrombi. *$p < 0.05$ *vs*. control group; #$p < 0.05$ *vs*. before treatment

Pulmonary artery CT images

Figure 7A shows the preprocedural pulmonary artery CT image of a 70-year-old female patient from the control group. The image reveals the partial branch occlusion in both pulmonary arteries. The patient had local obstruction of pulmonary artery blood flow due to thrombotic occlusion before treatment, with corresponding manifestations of pulmonary circulation disorders, such as dyspnea and chest pain after activity, which served as the underlying basis for potential clinical symptoms. The post-treatment CT image of the pulmonary artery shows multiple thrombi in the distal branches of multiple lobar and segmental arteries in both lungs (Figure 7B). The patient did not achieve the desired effect of thrombolysis or inhibition. The persistent thrombi would further affect pulmonary blood perfusion, increase pulmonary circulation resistance, and potentially lead to severe complications in the long term, adversely affecting the patient's prognosis.

Figure 7C shows the pulmonary artery CT image of a 65-year-old female patient from the observation group, revealing multiple filling defects in both main pulmonary arteries and their branches, and showing multiple filling defects in the main trunks and branches of both pulmonary arteries. In Figure 7C, the patient had a heavy pre-treatment pulmonary artery thrombus burden, with extensive involvement of the main trunks and branches by thrombi, and had relatively obvious clinical symptoms such as dyspnea and hypoxemia (Figure 7C). The post-treatment CT image of the pulmonary artery shows a few filling defects in the branches of both pulmonary arteries (Figure 7D). Compared with before treatment, the thrombus burden was markedly reduced, effectively decreasing the thrombi in the pulmonary arteries and improving pulmonary blood perfusion, which was conducive to the recovery of pulmonary function and correspondingly reduced the risk of severe pulmonary circulation complications. The images provided strong evi-

dence for the effectiveness of the treatment regimen from a radiological perspective.

Contrast of adverse events

The incidence of bleeding events was found to be 3.75% (3/80) in the observation group, markedly lower than the 16.46% (13/79) in the control group ($\chi^2 = 4.62$, $p = 0.032$). According to ISTH criteria, no major bleeding events occurred in the observation group, while 2 cases (2.53%, both gastrointestinal bleeding) occurred in the control group. No intracranial bleeding events were observed in either group during the follow-up period. Specifically, in terms of gastrointestinal bleeding, there were 0 cases in the observation group and 5 cases (6.33%) in the control group. The observation group had 3 cases (3.75%) of minor subcutaneous bleeding, while the control group had 7 cases (8.86%). The incidence of gastrointestinal reactions was 11.25% (9/80) in the observation group and 13.92% (11/79) in the control group ($p = 0.752$). The incidence of re-embolism was 2.5% (2/80) in the observation group and 5.06% (4/79) in the control group ($p = 0.559$). Other adverse reactions included rash, with an incidence of 3.75% (3/80) in the observation group and 6.33% (5/79) in the control group ($p = 0.643$). After a 16-week follow-up, there were no obvious distinctions in the conditions between the two groups ($p > 0.05$) (Figure 8).

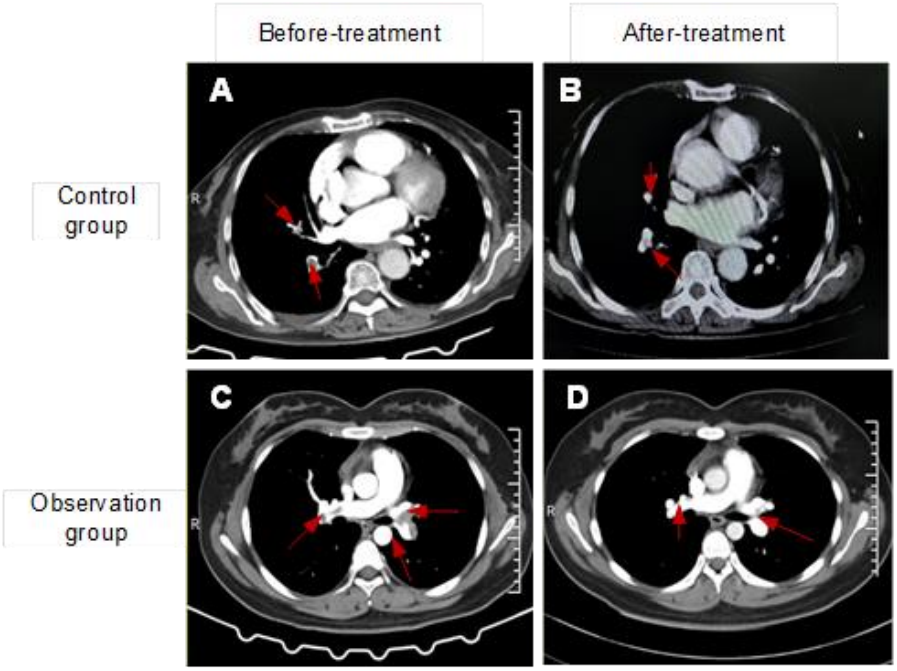

Figure 7.

Comparison of CTPA images before and after treatment in the two groups. Red arrows indicate the location of thrombi (filling defects) within the pulmonary arteries. A: Before treatment (control group); B: After treatment (control group); C: Before treatment (observation group); D: After treatment (observation group)

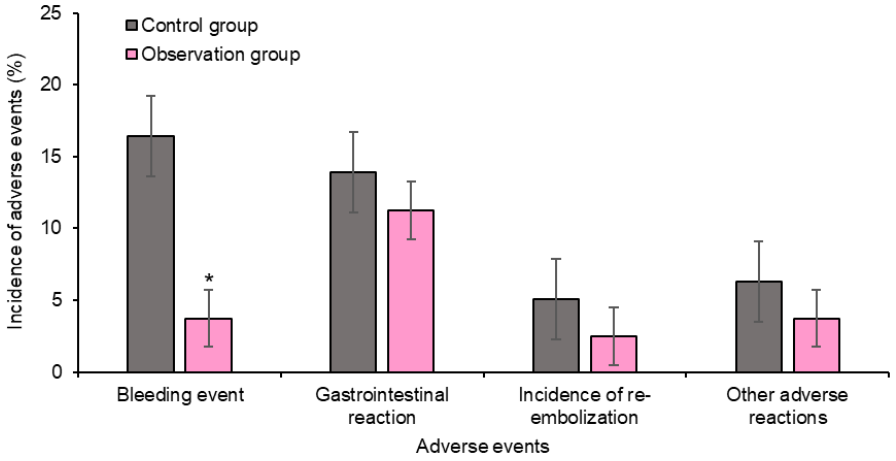

Figure 8.

Comparison of adverse events between the two groups

* $p < 0.05$ *vs*. control group

Multivariate analysis results

Multivariate logistic regression analysis, after adjusting for potential confounding factors, confirmed that the treatment regimen (LMWH plus rivaroxaban) was an independent factor associated with a higher overall response rate (OR = 2.89, 95% CI: 1.32 - 6.33, $p = 0.008$) and a lower risk of bleeding events (OR = 0.18, 95% CI: 0.05 - 0.67, $p = 0.011$).

This study compared the efficacy and safety of LMWH plus a novel oral anticoagulant (NOACs, rivaroxaban) with the traditional warfarin regimen in elderly patients with acute PE. It was found that the NOACs-based regimen had obvious advantages in improving the total effective rate, reducing bleeding risk, and enhancing coagulation function. It also reduced the clinical burden of INR monitoring. The total effective rate in the observation group was markedly higher as against the control group. Moreover, after treatment, the levels of D-dimer and the complete dissolution rate of pulmonary artery thrombi in the observation group were better than those in the control group. This result may be attributed to the direct anticoagulant effect of NOACs. By specifically inhibiting coagulation factor Xa (rivaroxaban), NOACs can rapidly block the key link in thrombus formation. As against the multi-target inhibition of warfarin, the action of NOACs is more precise and predictable, thereby accelerating thrombus dissolution and improving hemodynamics. This study conducted efficacy evaluations at early stages (1 week and 3 weeks) to capture the initial treatment response and early hemodynamic improvements, which are particularly important in the management of acute PE. Although complete thrombus resolution is an ongoing process, these early assessments reflect the rapid onset of anticoagulant effect and initial clinical stabilization, which are crucial for evaluating treatment efficacy in the acute phase.

NOACs are administered at a fixed dose and do not require frequent monitoring of coagulation indicators, reducing the risk of unstable efficacy caused by INR fluctuations during treatment (20). Cohen *et al*. (2015) (21) stated that anticoagulants have considerable potential to improve outcomes in VTE. Sharifi *et al*. (2015) (22) indicated that for PE patients, shifting from an "anticoagulation-first" to a "thrombolysis-first" approach simplifies treatment and makes it safer and more effective. In this article, the observation group had higher obvious effect rates at 1 week, cure rates at 3 weeks, and total effective rates at 3 months than the control group. This may be related to the mechanism of action of NOACs in directly inhibiting coagulation factor Xa (rivaroxaban). These drugs can rapidly block the coagulation cascade, reducing fibrin deposition. Traditional warfarin relies on vitamin K antagonism, has a slow onset of action, and needs to be overlapped with heparin for 5 - 7 days, which may delay thrombus clearance. A 6-month follow-up showed that the reembolism rate in the observation group was lower as against the control group, suggesting that NOACs may provide more sustained anticoagulant protection by stably inhibiting the activity of coagulation factors. Elderly patients often have reduced activity and poor vascular elasticity, making them prone to residual thrombi. The strong anticoagulant properties of NOACs may more effectively inhibit thrombus recurrence. This article is consistent with the conclusions of several recent RCT studies, further supporting the central role of NOACs in the treatment of acute PE (23, 24). It should be noted that approximately 30% of rivaroxaban is excreted renally. Although this study excluded patients with severe renal impairment and the baseline renal function was comparable between the two groups, close monitoring of renal function and appropriate dose adjustments remain crucial when using NOACs in elderly patients in clinical practice.

Ageno *et al*. (2022) (25) reported that rivaroxaban can reduce the risk of recurrent VTE in patients with symptomatic isolated distal DVT. Limbrey and Howard (2015) (26) indicated that rivaroxaban and apixaban have been shown to reduce the risk of recurrent VTE relative to placebo when administered for more than 12 months. Türk *et al*. (2016) (27) noted that the cost of maintenance therapy with novel oral anticoagulants is lower than that with warfarin. For patients with a low risk of complications, alternative regimens that do not require hospitalization may be less expensive. In this article, the incidence of bleeding events in the observation group was only 4.8%, with no gastrointestinal bleeding, while the control group had 3 cases of gastrointestinal bleeding. This is related to the fact that NOACs do not affect vitamin K-dependent coagulation factors and only specifically inhibit a single coagulation target, avoiding the extensive interference of warfarin with overall coagulation function (28). Elderly patients often have reduced liver and kidney function, and the metabolism of warfarin is easily affected. In contrast, the pharmacokinetics of NOACs are more predictable, and there is no need for frequent INR monitoring, which further reduces the risk of bleeding caused by improper dosing (29). There were no obvious distinctions in the incidence of gastrointestinal reactions and rashes, indicating that NOACs have a smaller impact on the common gastrointestinal underlying diseases in elderly patients. The observation group did not need to monitor coagulation indicators routinely, reducing the burden of elderly patients traveling to and from the hospital and improving treatment compliance (a compliance rate of $\geq$ 80% was considered qualified). This is particularly important for the elderly population with multiple chronic diseases that require comprehensive management. Elderly patients often have

reduced kidney function (with a decrease in estimated glomerular filtration rate), and about 30% of rivaroxaban is excreted through the kidneys, so the dose needs to be adjusted according to kidney function (30, 31). This article included intermediate-low-risk patients (excluding those with severe liver and kidney dysfunction), but in clinical practice, it is necessary to be vigilant about the potential impact of kidney function fluctuations on drug accumulation and avoid bleeding risks. Although warfarin is less expensive, it requires frequent INR monitoring and is easily affected by diet and drugs (such as antibiotics and antifungal agents). In this article, 73.81% of patients in the control group had comorbid hypertension and may need to require long-term use of antiplatelet drugs (such as aspirin). The combination of warfarin and antiplatelet drugs can further increase the risk of bleeding. In contrast, NOACs have fewer interactions with antiplatelet drugs and are more suitable for elderly patients with multiple comorbidities.

This article was a single-center retrospective analysis with a small sample size and no subgroup analysis of the efficacy distinctions between different NOACs (rivaroxaban). Elderly patients often have comorbidities such as tumors and chronic infections that are prone to thrombosis. This article excluded this population, so caution is required when extrapolating the conclusions. Future multicenter, prospective studies are needed to further verify the safety of NOACs in elderly patients over 80 years old, those with renal insufficiency, and those with complex comorbidities. It is also necessary to explore the possibility of combining NOACs with new thrombolytic drugs to optimize individualized treatment for elderly patients with PE.

Conclusions

This retrospective cohort study confirmed that in elderly patients with intermediate-low risk acute PE, the LMWH combined with rivaroxaban regimen demonstrated superior efficacy and a lower risk of bleeding compared to the conventional warfarin-based regimen. However, given the single-center, retrospective design of this study and the exclusion of high-risk PE patients, these findings require further validation through larger-scale, prospective, multicenter randomized controlled trials. Considering its convenience of administration and lack of requirement for routine monitoring, the LMWH plus rivaroxaban regimen may serve as a preferred anticoagulation strategy for elderly patients with intermediate-low risk PE, particularly for those with comorbidities or difficulties in tolerating frequent monitoring. In clinical practice, individualized dose adjustment based on renal function is recommended, with vigilance for potential bleeding risks.

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Ethics approval and consent to participate

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AI use disclosure

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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