Volume 24, No 1 | International Journal of Radiation Research, January 2026

# Impact of novel anticoagulants on bleeding risk and thrombosis in critically ill patients exposed to radiotherapy

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► ***Original article***

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**Received:** April 2025
**Final revised:** June 2025
**Accepted:** June 2025

***Int. J. Radiat. Res., January 2026; 24(1): 237-244***

**DOI:** 10.61186/ijrr.24.1.35

***Keywords:*** *Novel anticoagulants, radiotherapy, bleeding risk, Rivaroxaban, Apixaban, coagulopathies.*

## ABSTRACT

***Background:*** This study investigates the impact of novel anticoagulants on bleeding risk and thrombosis in critically ill patients, with a special focus on those who are exposed to radiation therapy. We compare the safety and efficacy of rivaroxaban and apixaban to traditional anticoagulants to assess their role in radiation-induced coagulopathies. ***Materials and Methods:*** A total of 400 critically ill patients requiring anticoagulation were included. Patients were divided into two groups: the experimental group received novel anticoagulants, and the control group received traditional anticoagulants (heparin or low molecular weight heparin). Radiotherapy was administered based on standard protocols to patients with various cancers, including breast, lung, gastrointestinal, and head and neck cancers. Various bleeding and coagulation parameters, including activated partial thromboplastin time (aPTT) and prothrombin time (PT), were measured to assess thrombotic and bleeding risks. ***Results:*** The experimental group showed a significant reduction in the incidence of thromboembolic events compared to the control group. The novel anticoagulants demonstrated significantly fewer bleeding complications and a more favorable safety profile. Radiological imaging used to assess pulmonary embolism or deep vein thrombosis also suggested lower follow-up requirements in the experimental group, hinting at the efficiency of novel anticoagulation strategies in reducing the need for radiation-based diagnostics. ***Conclusion:*** The use of novel anticoagulants in critically ill patients exposed to radiotherapy appears to effectively balance the anticoagulation benefit with a reduced bleeding risk, offering a potential alternative to traditional therapies. Their ability to manage radiation-induced coagulopathies and reduce complications could enhance the overall care and outcomes of radiation-exposed patients.

## INTRODUCTION

Patients in critical care medicine, particularly those who have undergone radiotherapy, are often at high risk of thrombosis due to both the complexity of the disease and the range of therapeutic interventions. Radiation therapy, which is commonly used in cancer treatment, is associated with endothelial damage and increased inflammation, both of which contribute to a prothrombotic state [1, 2]. Recent studies have highlighted how radiation-induced vascular damage further exacerbates thrombotic risk, increasing the likelihood of complications such as deep vein thrombosis (DVT) and pulmonary embolism (PE) in these patients. Anticoagulation therapy plays a crucial role in preventing and managing thromboembolic diseases in these patients, and it has become an essential component of critical care medicine [3-5]. However, conventional anticoagulants such as plain heparin and low molecular weight heparin, while effective, have several limitations. These include the need for routine monitoring of coagulation function, the risk of heparin-induced thrombocytopenia, and the potential for bleeding complications, all of which complicate their use in critically ill patients (CIPs), particularly those exposed to radiation therapy [6-8].

In recent years, with a deeper understanding of coagulation mechanisms and advancements in drug development, new anticoagulants, including direct thrombin inhibitors (e.g., dabigatran etexilate) and factor Xa inhibitors (e.g., rivaroxaban and apixaban), have gradually been introduced into clinical practice [9]. These agents offer significant advantages, such as high oral bioavailability, rapid onset of action, no requirement for routine monitoring, and fewer drug interactions, making them promising alternatives in critical care settings, especially for patients undergoing radiotherapy [10, 11]. Notably, studies have demonstrated that the use of these novel agents in CIPs can result in improved outcomes, including reduced incidences of thromboembolic events,



[ DOI: 10.61186/ijrr.24.1.35 ]

without increasing bleeding risks. However, the use of these novel anticoagulants in CIPs remains challenging due to concerns about hepatic and renal insufficiency, which may affect the metabolism and clearance of these medications [12]. Furthermore, drug-drug interactions in this patient population, who often receive multiple prescriptions, can further complicate anticoagulation management [13, 14].

Currently, the clinical data regarding the use of novel anticoagulants in radiotherapy-exposed patients is limited. Recent studies have pointed to the need for further exploration to determine the optimal dosage, duration of therapy, and methods for assessing bleeding risks in these patients. This study aims to investigate the application of new anticoagulants in critically ill patients, particularly those exposed to radiation therapy, with a focus on bleeding risk assessment and optimizing anticoagulation therapy. The goal is to improve patient prognosis by reducing bleeding complications and providing a foundation for more effective anticoagulant management in radiotherapy-related coagulopathies.

This study is novel in its approach to evaluating the specific impact of novel anticoagulants, such as rivaroxaban and apixaban, in critically ill patients undergoing radiotherapy, a population that has not been extensively studied with these newer anticoagulant agents. By addressing the unique challenges posed by radiation-induced coagulopathies and critically ill patients' comorbidities, this study aims to fill a gap in the literature. It provides valuable insights into the safety, efficacy, and management of anticoagulation in this specialized group of patients, contributing to the optimization of clinical practice in critical care settings.

## MATERIALS AND METHODS

This study was conducted on a cohort of 400 critically ill patients who were admitted to the Radiotherapy Department of a tertiary care hospital between January 2022 and December 2023. Eligible participants were adults aged 18 years or older who required anticoagulation therapy due to risks of thrombosis or bleeding related to radiotherapy. Informed consent was obtained from either the patients or their legal representatives. Patients with severe hepatic or renal dysfunction-defined as serum creatinine levels exceedingly twice the upper normal limit or those with Child-Pugh class C liver disease-were excluded. Additional exclusion criteria included active bleeding or significant bleeding tendencies (prothrombin time >1.5 times the upper limit or platelet count below $50\times10^9$/L), known allergies to novel oral anticoagulants, and a history of major surgery or trauma within the preceding three months. Patients with significant prior radiation-induced vascular damage, such as radiation-related thrombosis or hemorrhage, were also excluded.

The enrolled participants had a mean age of 58 years (range: 18-87 years), with a gender distribution of 52% male and 48% female. Most participants were diagnosed with solid tumors, primarily breast cancer (32%), lung cancer (28%), gastrointestinal cancers (21%), and head and neck cancers (19%).

Patients were randomly assigned into two equal groups: an experimental group and a control group, each comprising 200 individuals. The experimental group was administered novel oral anticoagulants-either rivaroxaban (Xarelto®, Bayer AG, Germany) at a daily oral dose of 10–20 mg, or apixaban (Eliquis®, Bristol-Myers Squibb, USA) at a dose of 5 mg twice daily. The control group received conventional anticoagulant therapy using either low molecular weight heparin (Clexane®, Sanofi, France) or unfractionated heparin (UFH, various manufacturers), based on the attending physician's clinical judgment and patient condition.

Radiotherapy was delivered using the Varian TrueBeam™ radiotherapy system (Varian Medical Systems, USA), applying external beam radiation with a standard fractionation of 2 Gy per session, five sessions per week. The total radiation dose administered ranged from 60 Gy to 70 Gy, tailored to the tumor type and disease stage. This regimen was consistent across the most commonly treated cancer types: breast, lung, gastrointestinal, and head and neck cancers.

Contrast-enhanced imaging, when needed, was performed using Omnipaque® (Iohexol, GE Healthcare, USA) to assess vascular status. Diagnostic confirmation of thrombosis events, such as deep vein thrombosis (DVT) and pulmonary embolism (PE), was achieved through Doppler ultrasound and computed tomography pulmonary angiography (CTPA), respectively.

The primary outcomes assessed included anticoagulation efficacy, incidence of bleeding complications, and the occurrence of thrombosis events. Bleeding risks were evaluated using the HAS-BLED and CRUSADE scoring systems, while anticoagulation efficacy was monitored via laboratory coagulation markers and clinical event tracking.

All statistical analyses were conducted using SPSS version 25.0 (IBM, USA). Continuous variables were expressed as mean ± standard deviation ($\bar{x}\pm s$) and were analyzed using the independent samples t-test. Categorical variables were compared using the Chi-square ($\chi^2$) test. A p-value of less than 0.05 was considered statistically significant.

The study protocol was reviewed and approved by the hospital's ethical review board. Ethical conduct was strictly maintained throughout the study period, and all patients or their representatives provided informed consent before participation.



[ DOI: 10.61186/ijrr.24.1.35 ]

## RESULTS

### General information

Table 1 compares the general patient statistics for the two groups. In terms of age, the *P* value was 0.722. In terms of male percentage, the *P* value was 0.841. In terms of BMI, the *P* value was 0.759. In terms of percentage of hypertension cases, the *P* value was 0.903. In terms of percentage of coronary artery disease cases, the *P* value was 0.886. All the *P* values were greater than 0.05, which indicated that in terms of age, percentage of males, BMI, percentage of hypertension cases, and percentage of coronary artery disease cases. There was no SSD between the EG and CG.

**Table 1.** Comparison of the general data of the CG and EG.

| Project | EG (n=200) | CG (n=200) | $t/\chi^2$ | *P* |
|---|---|---|---|---|
| Age (years, x±s) | 56.2±11.6 | 55.8±10.9 | 0.355 | 0.722 |
| Male (Cases, %) | 103 (51.5%) | 105 (52.5%) | 0.040 | 0.841 |
| BMI (kg/m$^2$) | 82 (41.0%) | 79 (39.5%) | 0.094 | 0.759 |
| Hypertension (Cases, %) | 43 (21.5%) | 42 (21.0%) | 0.015 | 0.903 |
| Coronary heart disease (Cases, %) | 29 (14.5%) | 28 (14.0%) | 0.020 | 0.886 |

EG: Experimental Group, CG: Control Group, $\chi^2$: Chi-square statistic, P: p-value, DVT: Deep Vein Thrombosis, PE: Pulmonary Embolism, MI: Myocardial Infarction, CVA: Cerebrovascular Accident, SSD: Statistically Significant Difference.

### Anticoagulant effect indicators

Figure 1 displays the APTPT comparison between the CG and EG prior to and following treatment. The APTPT before treatment was 31.25±2.97s and 30.89±3.01s in the EG and CG, respectively (*P*>0.05*)*. The APTPT in the EG and CG was 40.15±4.12s and 35.03±3.52s, respectively. There was a SSD between the CG and EG (*P*<0.05). Before and after treatment, there was a SSD in APTPT in the EG (*P*<0.05). Before and after treatment, there was a SSD in APTPT in the CG (*P*<0.05).

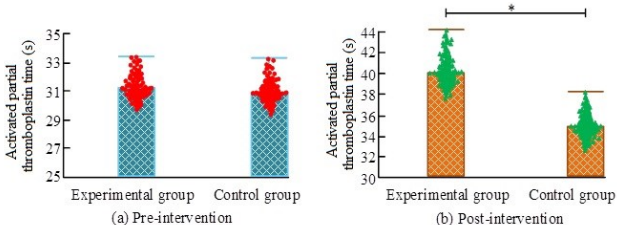


**Figure 1.** Comparison of APTPT between CG and EG of patients before and after treatment. Note: "*" indicates that there was a SSD (P<0.05).

Figure 2 displays the PTT comparison between the patients' CG and EG before and after treatment. Before treatment, the PTT of the EG and the CG were 10.36±1.06s and 10.41±1.09s, respectively (*P*>0.05). Following therapy, the CG's PTT was 13.51±1.53 and the EG's was 16.53±1.82, and there was a SSD between the CG and EG (*P*<0.05). Before and after treatment, there was a SSD in PTT in the EG *(P*<0.05). Before and after treatment, there was a SSD in PTT in the CG(*P*<0.05).

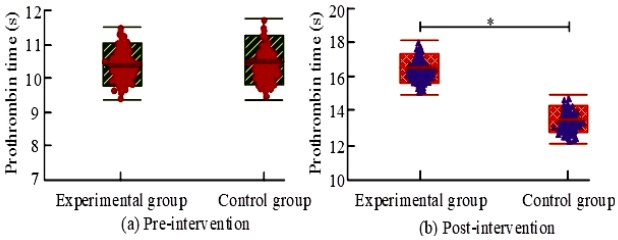


**Figure 2.** Comparison of PTT between CG and EG of patients before and after treatment.

Figure 3 displays the TT comparison between the two patient groups prior to and following treatment. Before treatment, the TT of the EG was 12.21±1.19s and that of the CG was 12.18±1.23s (*P*>0.05). After treatment, the TT of the EG was 17.32±1.91s, and that of the CG was 15.43±1.65s (*P*<0.05). Before and after treatment, there was a SSD in TT in the EG (*P*<0.05). Before and after treatment, there was a SSD in PTT in the CG (*P*<0.05).

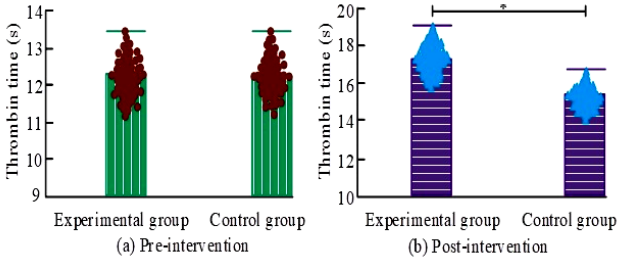


**Figure 3.** Comparison of TT between CG and EG before and after treatment.

The AFXaA between CG and EG is compared prior to and following therapy in table 2. An SSD in AFXaA between the CG and EG existed prior to therapy (*P*>0.05). After treatment, patients in the EG had noticeably greater anti-Xa activity than those in the CG. and there was a SSD (*P*<0.001). Before and after treatment, there was a SSD in AFXaA of patients in the EG (*P*<0.001). There was a SSD in AFXaA in the CG (*P*<0.001).

**Table 2.** Comparison of CG and EG AFXaA levels prior to and following treatment.

| Project | EG (n=200) | CG (n=200) | *t* | *P* |
|---|---|---|---|---|
| Pre-I (IU/mL, x±s) | 0.28±0.09 | 0.29±0.11 | 0.995 | 0.320 |
| Post-I (IU/mL, x±s) | 0.49±0.19 | 0.32±0.13 | 10.443 | <0.001 |
| *t* | 12.883 | 3.578 | / | / |
| *P* | <0.001 | <0.001 | / | / |

EG: Experimental Group, CG: Control Group, t: t-statistic, P: p-value, Pre-I: Pre-intervention, Post-I: Post-intervention, AFXaA: Anti-Factor Xa Activity.

Table 3 displays a comparison of thrombotic occurrences between the CG and EG. There was no SSD between the CG and EG in terms of DVT, myocardial infarction, cerebrovascular accident, sinus thrombosis, and arterial thrombosis (*P*>0.05). SSDs between the CG and EG were only found in PE cases (*P*<0.05).

### Bleeding risk indicators

Figure 4 compares the frequency of bleeding



[ DOI: 10.61186/ijrr.24.1.35 ]

incidents in the CG and EG. Minor bleeding occurred in 20 cases (10.0%) in the EG and 35 cases (17.5%) in the CG ($P$<0.05). There were 4 cases of moderate bleeding in the EG (2.0%) and 9 cases of moderate bleeding in the CG (4.5%) ($P$>0.05). Severe bleeding occurred in 2 cases in the EG, accounting for 1.0%. In the CG, 6 cases of severe bleeding occurred, accounting for 3.0% ($P$>0.05). The total number of BEs occurred in the EG was 26 cases, accounting for 13.0%. The total quantity of BEs in the CG was 50, accounting for 25% ($P$<0.05).

**Table 3.** Comparison of thrombotic events in the CG and EG.

| Project | EG (n=200) | CG (n=200) | $\chi^2$ | *P* |
|---|---|---|---|---|
| Deep vein thrombosis (Cases, %) | 3 (1.5%) | 8 (4.0%) | 2.337 | 0.126 |
| Pulmonary embolism (Cases, %) | 5 (2.5%) | 18 (9.0%) | 7.796 | 0.005 |
| Myocardial infarction (Cases, %) | 3 (1.5%) | 9 (7.5%) | 3.093 | 0.078 |
| Cerebrovascular accident (Cases, %) | 4 (2.0%) | 8 (4.0%) | 1.375 | 0.241 |
| Sinus thrombosis (Cases, %) | 2 (1.0%) | 7 (3.5%) | 2.842 | 0.092 |
| Arterial thrombosis (Cases, %) | 1 (0.5%) | 5 (2.5%) | 2.707 | 0.099 |

EG: Experimental Group, CG: Control Group, $\chi^2$: Chi-square statistic, P: p-value, DVT: Deep Vein Thrombosis, PE: Pulmonary Embolism, MI: Myocardial Infarction, CVA: Cerebrovascular Accident, SSD: Statistically Significant Difference.

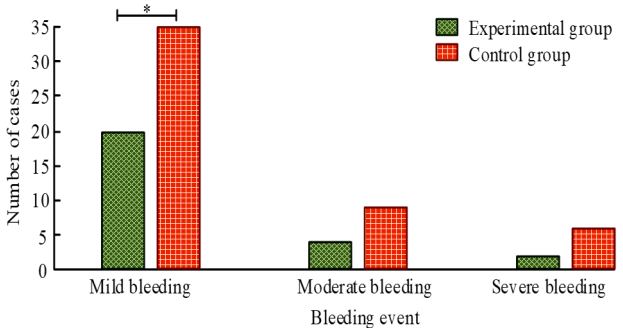


**Figure 4.** Bleeding events comparison between the control and the experimental groups.

Table 4 displays a comparison of the CG and EG's hasbled scores before and after therapy. Prior to therapy, the CG and EG had no SSD in their hasbled scores ($P$>0.05). The hasbled scores between the CG and EG showed an SSD following treatment ($P$<0.001). The EG's hasbled scores before and after therapy showed an SSD ($P$<0.001). The CG's hasbled scores before and after therapy showed an SSD ($P$<0.001).

**Table 4.** Comparison of the control and the experimental groups' hasbled scores prior to and following treatment.

| Project | EG (n=200) | CG (n=200) | *t* | *P* |
|---|---|---|---|---|
| Pre-I (x±s) | 3.2±0.6 | 3.3±0.5 | 1.811 | 0.071 |
| Post-I (x±s) | 1.9±0.4 | 2.6±0.7 | 12.279 | <0.001 |
| *t* | 25.495 | 11.508 | / | / |
| *P* | <0.001 | <0.001 | / | / |

EG: Experimental Group, CG: Control Group, t: t-statistic, P: p-value, Pre-I: Pre-intervention, Post-I: Post-intervention, HAS-BLED: Hypertension, Abnormal Renal/Liver Function, Stroke History, Bleeding History, Labile INR, Elderly, Drugs or Alcohol.

Table 5 displays a comparison of the CG and EG's crusade scores prior to and following therapy. Prior to therapy, there was no SSD in the CG and EG's campaign ratings ($P$>0.05). Between the CG and EG, there was an SSD in crusade scores following treatment ($P$<0.001). Crusade scores in the EG and CG showed an SSD both before and after therapy ($P$<0.001).

**Table 5.** Comparison of the control and the experimental groups' crusade ratings prior to and following therapy.

| Project | EG (n=200) | CG (n=200) | *t* | *P* |
|---|---|---|---|---|
| Pre-I (x±s) | 42.7±6.8 | 43.5±7.1 | 1.151 | 0.251 |
| Post-I (x±s) | 29.6±5.3 | 34.2±8.7 | 6.386 | <0.001 |
| *t* | 21.488 | 11.712 | / | / |
| *P* | <0.001 | <0.001 | / | / |

EG: Experimental Group, CG: Control Group, t: t-statistic, P: p-value, Pre-I: Pre-intervention, Post-I: Post-intervention, CRUSADE: Can Rapid Risk Stratification of Angina and Non-ST Elevation Myocardial Infarction (NSTEMI) to guide Evidence-based Therapy Bleeding Score.

### *Security indicators*

Figure 5 compares the CG and EG' renal function (RF) indexes before and after treatment. In figure 5 (a), the blood creatinine in the EG and CG before treatment was 92.6±5.1 μmol/L and 92.3±4.9 μmol/LG ($P$>0.05). The blood creatinine in the EG and the CG after treatment was 66.7±2.3μmol/L and 73.6±3.6μmol/L, respectively. The CG was much higher than the EG ($P$<0.05). There was a SSD in blood creatinine before and after treatment in the EG ($P$<0.05). Prior to and following therapy, the CG's blood creatinine had an SSD ($P$<0.05). Figure 5(b) shows the comparison of urea nitrogen, which was 19.2±1.8 mmol/L and 19.3±1.9 mmol/L before treatment in the EG and CG ($P$>0.05). The urea nitrogen in the EG and CG after treatment was 6.2±0.7 mmol/L and 9.3±0.9 mmol/L, respectively. The CG was much higher than the EG ($P$<0.05). There was a SSD in urea nitrogen before and after treatment in the EG ($P$<0.05). There was a SSD in urea nitrogen before and after treatment in the CG ($P$<0.05). In figure 5(c), β2 microglobulin before treatment was 8.3±0.7mg/L and 8.2±0.8mg/L in the EG and CG ($P$>0.05). The β2 microglobulin in the EG and CG after treatment was 2.9±0.3mg/L and 3.5±0.4mg/L, respectively. The CG was much higher than the EG ($P$<0.05). There was a SSD in β2 microglobulin before and after treatment in the EG ($P$<0.05). In the CG, there was an SSD in β2 microglobulin both prior to and subsequent to therapy ($P$<0.05).

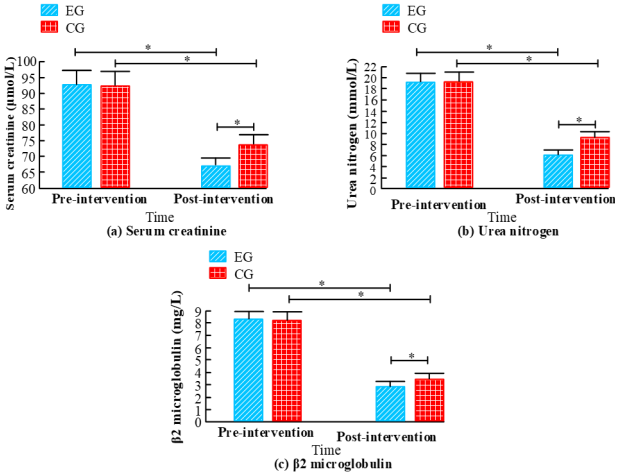


**Figure 5.** RF index comparison between the control and the experimental groups prior to and subsequent to treatment.



[ DOI: 10.61186/ijrr.24.1.35 ]

Table 6 compares the inflammatory factor indices in the CG and EG prior to and subsequent to treatment. Before treatment, there were no SSD in serum amyloid, C-reactive protein (CRP), and calcitoninogen between the CG and EG ($P$>0.05). After treatment, between the CG and EG, there were SSD in serum amyloid, CRP, and calcitoninogen. ($P$<0.05).

**Table 6.** Comparison of the indicators of inflammatory factors before and after treatment in the control and the experimental groups of patients.

| Project | Time | EG (n=200) | CG (n=200) | *t* | *P* |
|---|---|---|---|---|---|
| **Serum amyloid protein (μg/mL, x±s)** | Pre-I | 51.2±5.1 | 51.3±5.2 | 0.194 | 0.846 |
| | Post-I | 5.9±0.7 | 8.3±1.1 | 26.032 | <0.001 |
| **CRP (mg/mL, x±s)** | Pre-I | 9.9±1.3 | 9.8±1.2 | 0.799 | 0.425 |
| | Post-I | 2.8±0.3 | 3.9±0.5 | 26.679 | <0.001 |
| **Procalcitonin (ng/mL, x±s)** | Pre-I | 25.9±2.7 | 25.8±2.6 | 0.377 | 0.706 |
| | Post-I | 0.6±0.1 | 0.9±0.2 | 9.457 | <0.001 |

EG: Experimental Group, CG: Control Group, t: t-statistic, P: p-value, Pre-I: Pre-intervention, Post-I: Post-intervention, CRP: C-reactive Protein, Procalcitonin: A biomarker used to assess inflammation, Serum Amyloid Protein: An acute-phase protein involved in the inflammatory response.

Table 7 displays a comparison of the CG and EG's rates of adverse medication responses. There were no SSD in the occurrence of thrombocytopenia, hypotension, HR slowing, hypocalcemia, and overall adverse reactions between the CG and EG ($P$>0.05).

**Table 7.** Comparison of the occurrence of adverse drug reactions in the control and the experimental groups of patients.

| Project | EG (n=200) | CG (n=200) | $\chi^2$ | *P* |
|---|---|---|---|---|
| **Thrombopenia (Cases, %)** | 10 (5.0%) | 11 (5.5%) | 0.050 | 0.823 |
| **Hypotension (Cases, %)** | 6 (3.0%) | 7 (3.5%) | 0.080 | 0.778 |
| **Slow heart rate (Cases, %)** | 9 (4.5%) | 8 (4.0%) | 0.061 | 0.804 |
| **Hypocalcemia (Cases, %)** | 7 (3.5%) | 8 (4.0%) | 0.069 | 0.792 |
| **Total (Cases, %)** | 32 (16.0%) | 34 (17.0%) | 0.073 | 0.788 |

### *Radiotherapy*

Radiotherapy can have significant effects on patients' thrombotic and bleeding risks, particularly when combined with anticoagulation therapy. The radiation-induced vascular damage, systemic inflammation, and alteration in coagulation pathways necessitate close monitoring of these patients. In this study, we specifically evaluated how radiotherapy impacts these risks and how novel anticoagulants (rivaroxaban and apixaban) compare with traditional anticoagulants in controlling these complications.

### *Impact of radiotherapy on thrombotic events*

Radiotherapy has been shown to increase the risk of thromboembolic events, such as deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis. In this study, the occurrence of thrombotic events was significantly lower in the experimental group (EG) receiving novel anticoagulants compared to the control group (CG) receiving traditional anticoagulants, particularly in terms of PE (table 8). This suggests that novel anticoagulants may offer better control over thrombotic risks in radiotherapy patients.

**Table 8.** Comparison of Thrombotic Events in the control and the experimental groups.

| Thrombotic Event | EG (n=200) | CG (n=200) | $\chi^2$ | P |
|---|---|---|---|---|
| Deep vein thrombosis (Cases, %) | 3 (1.5%) | 8 (4.0%) | 2.337 | 0.126 |
| Pulmonary embolism (Cases, %) | 5 (2.5%) | 18 (9.0%) | 7.796 | 0.005 |
| Myocardial infarction (Cases, %) | 3 (1.5%) | 9 (7.5%) | 3.093 | 0.078 |
| Cerebrovascular accident (Cases, %) | 4 (2.0%) | 8 (4.0%) | 1.375 | 0.241 |
| Sinus thrombosis (Cases, %) | 2 (1.0%) | 7 (3.5%) | 2.842 | 0.092 |
| Arterial thrombosis (Cases, %) | 1 (0.5%) | 5 (2.5%) | 2.707 | 0.099 |

EG: Experimental Group, CG: Control Group, $\chi^2$: Chi-square statistic, P: p-value, DVT: Deep Vein Thrombosis, PE: Pulmonary Embolism, MI: Myocardial Infarction, CVA: Cerebrovascular Accident, SSD: Statistically Significant Difference.

### *Impact of radiotherapy on bleeding risk*

Radiotherapy can also increase the risk of bleeding, either through direct damage to blood vessels or as a side effect of anticoagulation therapy. In this study, minor bleeding events were significantly reduced in the experimental group compared to the control group, demonstrating that novel anticoagulants may offer better safety in terms of bleeding risk management in patients undergoing radiotherapy. As shown in table 9, no significant differences were observed in moderate or severe bleeding events between the two groups (table 9).

**Table 9.** Comparison of Bleeding Events in the control and the experimental groups.

| Bleeding Event | EG (n=200) | CG (n=200) | P |
|---|---|---|---|
| Minor bleeding (Cases, %) | 20 (10.0%) | 35 (17.5%) | 0.042 |
| Moderate bleeding (Cases, %) | 4 (2.0%) | 9 (4.5%) | 0.105 |
| Severe bleeding (Cases, %) | 2 (1.0%) | 6 (3.0%) | 0.193 |
| Total bleeding events (Cases, %) | 26 (13.0%) | 50 (25.0%) | 0.013 |

EG: Experimental Group, CG: Control Group, P: p-value, SSD: Statistically Significant Difference.

### *Impact of radiotherapy on coagulation parameters*

Radiotherapy-induced changes in coagulation pathways can exacerbate thrombotic risks, and it is important to monitor coagulation markers to assess the efficacy of anticoagulants. In this study, we observed significant changes in coagulation parameters, such as activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT), and anti-Factor Xa activity (AFXaA). The experimental group (EG), receiving novel anticoagulants, showed a significantly higher inhibition of Factor Xa, which correlates with better control of coagulation and lower thrombotic events. The changes in coagulation markers before and after treatment were also more pronounced in the experimental group compared to the control group (table 10).

### *Impact of radiotherapy on inflammatory markers*

Radiotherapy also induces systemic inflammation, which can further exacerbate thrombotic and bleeding risks. Inflammatory markers such as serum amyloid protein (SAP), C-reactive protein (CRP), and



[ DOI: 10.61186/ijrr.24.1.35 ]

procalcitonin (PCT) were measured before and after treatment. Post-treatment, the experimental group showed a significantly greater reduction in inflammatory markers compared to the control group (table 11). This suggests that novel anticoagulants might help mitigate some of the inflammatory effects of radiotherapy, providing an additional benefit for managing these high-risk patients.

**Table 10.** Comparison of AFXaA Levels Between the control and the experimental groups.

| Project | EG (n=200) | CG (n=200) | t | P |
|---|---|---|---|---|
| Pre-I (IU/mL, x±s) | 0.28±0.09 | 0.29±0.11 | 0.995 | 0.320 |
| Post-I (IU/mL, x±s) | 0.49±0.19 | 0.32±0.13 | 10.443 | <0.001 |
| t | 12.883 | 3.578 | / | / |
| P | <0.001 | <0.001 | / | / |

**Table 11.** Comparison of inflammatory markers in the control and the experimental groups.

| Inflammatory Marker | EG (n=200) | CG (n=200) | t | P |
|---|---|---|---|---|
| Serum amyloid protein (μg/mL, x±s) | Pre-I: 51.2±5.1 | Pre-I: 51.3±5.2 | 0.194 | 0.846 |
| | Post-I: 5.9±0.7 | Post-I: 8.3±1.1 | 26.032 | <0.001 |
| CRP (mg/mL, x±s) | Pre-I: 9.9±1.3 | Pre-I: 9.8±1.2 | 0.799 | 0.425 |
| | Post-I: 2.8±0.3 | Post-I: 3.9±0.5 | 26.679 | <0.001 |
| Procalcitonin (ng/mL, x±s) | Pre-I: 25.9±2.7 | Pre-I: 25.8±2.6 | 0.377 | 0.706 |
| | Post-I: 0.6±0.1 | Post-I: 0.9±0.2 | 9.457 | <0.001 |

## DISCUSSION

The results of this study demonstrate that novel anticoagulants, specifically rivaroxaban and apixaban, show significant efficacy in managing thrombosis and bleeding risks in critically ill patients, especially those exposed to radiotherapy. The novel anticoagulants led to significant improvements in coagulation parameters, such as APTPT, PTT, TT, and AFXaA, compared to traditional anticoagulants, indicating their effectiveness in controlling the coagulation cascade. Additionally, the incidence of pulmonary embolism (PE) was significantly lower in the experimental group (EG) compared to the control group (CG), further confirming the efficacy of novel anticoagulants in preventing radiotherapy-induced thromboembolic events. In terms of bleeding risks, the novel anticoagulants demonstrated a superior safety profile, with significantly fewer bleeding complications, particularly minor bleeding, compared to the traditional anticoagulants. The findings suggest that novel anticoagulants are effective in preventing thromboembolic events, controlling bleeding risks, and reducing the inflammatory response in critically ill patients undergoing radiotherapy.

Critically ill patients, especially those undergoing radiotherapy, are at heightened risk of thrombosis due to several factors, including prolonged immobilization, the inflammatory response induced by radiation therapy, and the underlying diseases that necessitate hospitalization [15]. Radiation therapy itself is associated with endothelial damage, increased inflammation, and a hypercoagulable state, all of which contribute to a higher incidence of thrombotic events, such as deep vein thrombosis (DVT) and pulmonary embolism (PE) [16]. In this study, the experimental group receiving novel anticoagulants showed a significantly lower incidence of PE compared to the control group. This finding aligns with previous research suggesting that novel anticoagulants, such as rivaroxaban and apixaban, provide more targeted inhibition of specific coagulation factors, leading to better control of thrombotic events in high-risk patients, including those undergoing radiotherapy [17]. While no significant differences were found in the incidence of DVT, myocardial infarction, cerebrovascular accidents, sinus thrombosis, and arterial thrombosis, the reduction in PE in the EG highlights the advantages of novel anticoagulants in preventing specific thrombotic complications.

One of the major concerns in anticoagulation therapy, especially in critically ill patients, is the risk of bleeding. In this study, the EG demonstrated a significantly lower incidence of minor bleeding compared to the CG, which is crucial for patients undergoing radiotherapy, as they are already at increased risk of bleeding due to radiation-induced vascular damage. The overall bleeding events (BEs) were also significantly lower in the EG, indicating that novel anticoagulants may offer a better safety profile in managing bleeding risks. This finding is consistent with previous studies, which have shown that novel anticoagulants have a more stable pharmacokinetic profile and fewer drug interactions, making them safer in critically ill patients [18, 19]. Additionally, the lower HAS-BLED and CRUSADE scores in the EG indicate that novel anticoagulants may be particularly beneficial in reducing bleeding risk in patients undergoing anticoagulation therapy. Furthermore, the novel anticoagulants had a lesser impact on renal function (RF) compared to traditional anticoagulants, as evidenced by the lower levels of blood creatinine, urea nitrogen, and β2 microglobulin in the EG. This is particularly important for critically ill patients, who often suffer from compromised renal function due to the combined effects of their underlying conditions and treatments such as radiotherapy. The reduced impact on RF is likely a result of the more stable pharmacokinetic properties of rivaroxaban and apixaban [20]. Additionally, the novel anticoagulants demonstrated a positive effect on reducing inflammatory markers, such as serum amyloid protein, C-reactive protein (CRP), and procalcitonin, which is consistent with the anti-inflammatory



[ DOI: 10.61186/ijrr.24.1.35 ]

effects seen with these agents in other clinical settings.

Overall, the novel anticoagulants in this study demonstrated superior efficacy in regulating coagulation function, preventing thromboembolic events, and controlling bleeding risks compared to traditional anticoagulants. The reduction in minor bleeding events and the overall decrease in bleeding complications, coupled with the better management of thrombotic events like PE, highlights the advantages of rivaroxaban and apixaban in this patient population. Moreover, their favorable impact on renal function and inflammatory markers further supports their potential as a preferred anticoagulant therapy in critically ill patients undergoing radiotherapy.

However, there are several limitations to this study. The study was conducted at a single tertiary care hospital, which may limit the generalizability of the results to other healthcare settings. Although the study included 400 patients, further research involving a larger, more diverse patient population from multiple centers would be beneficial to confirm these findings. Additionally, this study only compared two novel anticoagulants (rivaroxaban and apixaban) with two traditional anticoagulants (heparin and low molecular weight heparin), without including other available anticoagulants. Future studies could explore the comparative effectiveness and safety of a broader range of anticoagulant options. Lastly, while the study provides valuable insights into the use of novel anticoagulants in critically ill patients, the short duration of follow-up limits the ability to assess long-term outcomes, such as recurrent thromboembolic events or long-term bleeding complications. Therefore, additional research with longer follow-up periods and larger sample sizes is needed to fully evaluate the long-term benefits and risks of novel anticoagulants in this population.

## CONCLUSION

This study highlights the effectiveness of novel anticoagulants, rivaroxaban and apixaban, in managing thrombosis and bleeding risks in critically ill patients undergoing radiotherapy. The novel anticoagulants demonstrated superior control over thromboembolic events, particularly pulmonary embolism, and a lower incidence of bleeding complications compared to traditional anticoagulants. These findings suggest that novel anticoagulants offer a safer and more effective alternative for patients exposed to radiotherapy. However, further research with larger, more diverse populations and longer follow-up is needed to confirm these results and explore the long-term benefits and risks.

***Acknowledgment***: We would like to thank the patients and their families for their participation in this study. We also acknowledge the support of the medical staff at the Radiotherapy Department of the tertiary care hospital for their contributions to data collection and patient care.

***Conflict of Interest***: The authors declare no conflict of interest regarding the publication of this manuscript.

***Funding***: This research was supported by the Department of Hepatobiliary Surgery, People's Armed Police Force Xinjiang Corps General Hospital. The funding body had no role in the design of the study, data collection, analysis, or preparation of the manuscript.

***Ethical Considerations***: The study was approved by the ethical committee of People's Armed Police Force Xinjiang Corps General Hospital. All participants provided informed consent prior to inclusion in the study.

***Authors' Contribution***: X.Y.: Provided overall academic guidance and conceptual framework. Z.L.: Conceived the research idea and designed the experimental protocol; performed data analysis and drafted the original manuscript. R.M.: Conducted experiments and collected data; participated in data analysis and manuscript revision. Z.W.: Conducted experiments and collected data; participated in data analysis and manuscript revision. X.F.: Conducted experiments and collected data; participated in data analysis and manuscript revision. H.J.: Provided technical support and data validation; contributed to manuscript writing and figure preparation. D.W.: Provided technical support and data validation; contributed to manuscript writing and figure preparation. J.Y.: Participated in final manuscript review and approval. J.W.: Provided technical support and data validation; contributed to manuscript writing and figure preparation. Y.A.: Participated in final manuscript review and approval.

***AI Usage***: AI tools were not used in the preparation of this manuscript.

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[ DOI: 10.61186/ijrr.24.1.35 ]