

## Research Article

# Impact of anticoagulation therapy on surgical timing, hospital stay, and postoperative outcomes in proximal femur fracture patients

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## ABSTRACT

**Objective:** This study aimed to evaluate the association between preoperative anticoagulant use and time to surgery, hospital length of stay, and 30-day postoperative complications in elderly patients with proximal femur fractures.

**Methods:** This study included 572 patients with low-energy proximal femur fractures who required surgical treatment. Patients were categorized into two groups based on anticoagulation therapy use. The following data was collected and compared between the groups: time from hospitalization to surgery, hospital length of stay, percent changes in hemoglobin and other post-operative complications: death, cardiac complications, sepsis, deep venous thrombosis, pneumonia, urinary tract infection, surgical site infection, pressure ulcers, acute kidney injury and delirium. Multivariate regression analysis was performed to analyze possible confounders.

**Results:** The median age of study participants was 83 years. 78.2% being female. Anticoagulation therapy was used by 19.9% of patients, predominantly non-vitamin K oral anticoagulants. Patients receiving anticoagulants experienced significantly longer hospital stays (median 9 vs. 7 days;  $P < .05$ ) and surgical delays (median 3 vs. 2 days;  $P < .0001$ ) compared to those without anticoagulation. Complication rates and hemoglobin level changes did not differ significantly among the groups ( $P > .05$ ). Multivariate analysis identified age, time to surgery, and hospital length of stay as independent predictors of 30-day postoperative complications, with age and hospital stay also significantly associated with 30-day mortality.

**Conclusion:** Anticoagulation therapy did not directly increase 30-day postoperative complications or mortality but was associated with surgical delays and prolonged hospital stays, which negatively impacted outcomes. Delayed surgery and extended hospitalization emerged as key risk factors. These findings underscore the clinical importance of minimizing surgical delays in anticoagulated patients to improve postoperative outcomes.

**Level of Evidence:** Level II, Prognostic study.

## Introduction

Hip fractures remain the leading cause of morbidity and mortality in the elderly trauma population, and the notable prevalence of anticoagulant usage among these geriatric patients, often due to underlying cardiovascular comorbidities, further complicates their clinical management and outcomes.<sup>1,2</sup> The arrival of novel oral anticoagulants (NOACs), including dabigatran, rivaroxaban, and apixaban, has almost doubled global anticoagulant utilization.<sup>3</sup> Consequently, the management of hip fractures in NOAC-receiving patients still poses a challenge. These individuals frequently encounter surgical delays and prolonged hospitalization periods relative to non-anticoagulated patients.<sup>4</sup>

While perioperative management of anticoagulant therapy in surgery necessitates a delicate balance between bleeding and thrombotic risks, a 2021 survey revealed that 73.6% of surgeons believe adequate clinical guidelines for anticoagulated patients with hip fractures are lacking.<sup>5</sup> A new retrospective study by

Fenwick et al<sup>6</sup> demonstrated that a structured surgical timing protocol based on renal function and pharmacokinetics of the direct oral anticoagulants (DOACs) enables safe operative management of hip fractures within a 48-hour window. Patients with adequate renal function underwent surgery within 24 hours, while those with impaired clearance or on dabigatran were delayed to 24-72 hours based on drug-specific half-lives. Despite longer surgical delays in the anticoagulated cohort, mortality did not increase when surgery occurred within 48 hours; however, delays beyond 48 hours were associated with significantly higher mortality (9.8%;  $P < .001$ ).<sup>6</sup> Current American College of Chest Physicians (ACCP) guidelines recommend withholding DOACs for 24-48 hours prior to elective surgery, with extended interruption—up to 96 hours—for dabigatran in patients with reduced renal function. Postoperative resumption is advised within 24-72 hours once adequate hemostasis is achieved. For patients treated with vitamin K antagonists such as warfarin, the ACCP recommends discontinuation at least 5 days before surgery, with a target international normalized ratio (INR) of  $\leq 1.5$  prior to intervention.<sup>7</sup>

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This evidence supports individualized but timely surgery in DOAC-treated patients, minimizing bleeding risk while preserving the benefits of early intervention.

This study aims to evaluate the association between preoperative anticoagulant use and time to surgery, hospital length of stay, postoperative complications, and patient mortality, with the specific objective of determining whether current perioperative management strategies influence these outcomes and highlight the need for more standardized, evidence-based protocols.

## Material and methods

### Study design

This prospective, single-center, observational study included 572 patients with proximal (pertrochanteric, subtrochanteric, femoral neck) femur fractures who received surgical treatment between December 2022 and November 2023 at a tertiary trauma center. For each patient, the following information was recorded: age, sex, dates of admission and surgery, hospitalization period, time to surgery, ASA score, type of hip fracture, surgical method, type of anesthesia, hemoglobin pre and post-surgery, anticoagulant drug usage, 30-day postoperative complications, and mortality.

Patients were categorized into 2 groups based on anticoagulation status, which was ascertained from their chronic medication lists at the time of admission: no anticoagulant use (control group) and patients receiving anticoagulation therapy (including non-vitamin K antagonist oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) and warfarin). While data on the precise timing of the last medication dose were not available for all patients, it was assumed that patients were managed according to established medication cessation protocols, and the time of the last medication was set as the time of hospitalization. To evaluate the impact of both the time from hospitalization to surgery and anticoagulation treatment on postoperative complications, the anticoagulation therapy cohort was divided into 2 subgroups: patients who underwent surgery within 48 hours and those who waited longer.

Although direct measurement of blood loss was not possible, the percentage change in hemoglobin levels was calculated using a formula proposed by Schermann et al.<sup>8</sup> This formula determines hemoglobin change by the difference between pre- and postoperative hemoglobin levels divided by preoperative hemoglobin level and multiplied by 100.<sup>8</sup> In this patient cohort, blood transfusion therapy was administered when the hemoglobin level was below 80 g/L or in cases of acute ongoing bleeding with a significant decline in hemoglobin. To

ensure accurate statistical evaluation of the percentage change in hemoglobin levels, outliers were identified and removed.

### Surgical techniques

Perioperative anticoagulation management followed standardized institutional protocols. Patients receiving warfarin were administered vitamin K, with INR levels monitored to guide the timing of surgery. For individuals on apixaban or rivaroxaban, plasma drug concentrations were measured, and surgery was performed once levels declined below 30 ng/mL. In patients treated with dabigatran or edoxaban, surgical intervention was postponed for 48 hours to allow for adequate drug clearance. Anticoagulation therapy was resumed on the first postoperative day.

Anesthetic management for all patients consisted of either general or neuraxial anesthesia, selected at the discretion of the attending anesthesiologist. Regional anesthesia was performed on 90.53% of the patients, while general anesthesia was administered to 9.47%. The majority of patients (88.21%) had an ASA grade 3, while an additional substantial proportion (4.46%) were classified as ASA grade 4, indicating a generally high preoperative risk profile within the study cohort. Tranexamic acid was administered preoperatively in all surgical cases.

The largest group consisted of patients who had sustained femoral head or neck (intracapsular) fractures (49.65%). A significant portion also suffered from pertrochanteric femoral fractures (44.93%), while a smaller proportion experienced subtrochanteric fractures (5.42%). Details regarding the surgical techniques employed for each fracture type are provided in Table 1. All procedures were either performed or directly supervised by a consultant orthopedic surgeon.

### Follow-up and outcomes

After surgery, patients were followed up for 30 days. On the 30th day, the patient or his surrogate was contacted for an interview. Furthermore, the patient's electronic medical history was analyzed during the interview. The following complications were recorded: pneumonia, cardiac complications, surgical site infection, urinary tract infection, deep venous thrombosis, acute renal failure, readmission, reoperation, death, sepsis, delirium, and pressure sores.

### Inclusion and exclusion criteria

This study included patients aged 65 years or older who experienced low-energy (simple fall) proximal femur fracture (pertrochanteric, subtrochanteric, femoral neck) and required surgical treatment. However, individuals with open fractures, fractures involving neurovascular bundle injuries, polytrauma or high-energy trauma, documented alcohol or psychoactive substance dependence, pregnancy, or insufficient data were excluded from the study.

## HIGHLIGHTS

- This study demonstrates that preoperative anticoagulant therapy in elderly patients with proximal femur fractures does not significantly increase the incidence of postoperative complications when compared to patients without anticoagulation.
- While anticoagulant use correlates with a statistically significant prolongation of time to surgical intervention and increased hospital length of stay, this delay did not translate to a higher rate of adverse outcomes.
- Analysis revealed no statistically significant differences in perioperative hemoglobin level changes between patients receiving anticoagulation and those who did not, suggesting that anticoagulation does not substantially elevate the risk of significant blood loss in this patient population.
- Age and prolonged hospital stay were significant risk factors for both 30-day mortality and postoperative complications, while delayed surgery independently predicted 30-day postoperative complications.

Table 1. Distribution of surgical procedures by fracture type

	Femoral head or neck (intracapsular) fractures n = 284	Petrochanteric fractures n = 257	Subtrochanteric fractures n = 31
Surgical method	n (%)	n (%)	n (%)
HA	184 (64.79)	4 (1.56)	0 (0)
THA	63 (22.18)	3 (1.17)	0 (0)
PFN	4 (1.41)	199 (77.43)	31 (100)
DHS	16 (5.63)	51 (19.84)	0 (0)
CS	17 (5.99)	0 (0)	0 (0)

CS, cannulated screws; DHS, dynamic hip screw; HA, hip hemiarthroplasty; PFN, proximal femoral nailing; THA, total hip arthroplasty.

### Statistical methods

The data was registered in Microsoft Excel and analyzed using IBM SPSS Statistics v. 30.0 (IBM SPSS Corp.; Armonk, NY, USA) / R Commander version: 2.9-5 (John Fox et al., Department of Sociology, McMaster University; Hamilton, Ontario, Canada). To test the normality of the data, the Kolmogorov-Smirnov test was chosen, which is recommended for large sample sizes ( $n \geq 50$ ).<sup>9</sup> Data were presented as numbers (percentages) for categorical variables and median (Q1; Q3) or mean (SD) for continuous variables. Statistical differences for variables with a normal distribution were evaluated with Student's t-test, while the Wilcoxon test was used for non-normally distributed data. The chi-square test of independence and Fisher's exact test were applied to determine statistical differences between nominal variables. A sample size of 572 participants was calculated to achieve 81.4% statistical power (post hoc analysis) to detect a medium effect size ( $r=0.306$ ) for the primary outcome, ensuring adequate power to reliably detect meaningful differences. Differences were considered statistically significant if  $P < .05$ . A one-way ANOVA was used to analyze statistical differences and compare means between more than 2 groups. Multivariate logistic regression analyses were performed to determine independent predictors of 30-day postoperative complications and mortality.

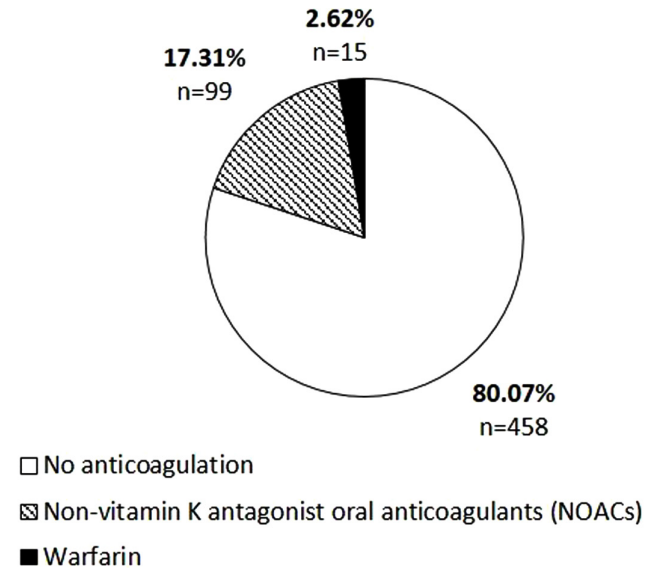
This study was approved by the Lithuanian Bioethics Research Ethics Committee, Issue No. 2022/11-1473-941, Date: 22.11.2022.

Written informed consent was obtained from all individual participants included in the study.

### Results

The median age of study participants was 83 years (Q1: 77, Q3: 88), and the majority were women (78.15%). A total of 19.93% ( $n=114$ ) of patients with a proximal femur fracture who presented for surgical management were undergoing anticoagulation therapy. The majority were treated with non-vitamin k antagonist oral anticoagulants (rivaroxaban, apixaban, endoxaban, and dabigatran), though some patients received warfarin (Figure 1).

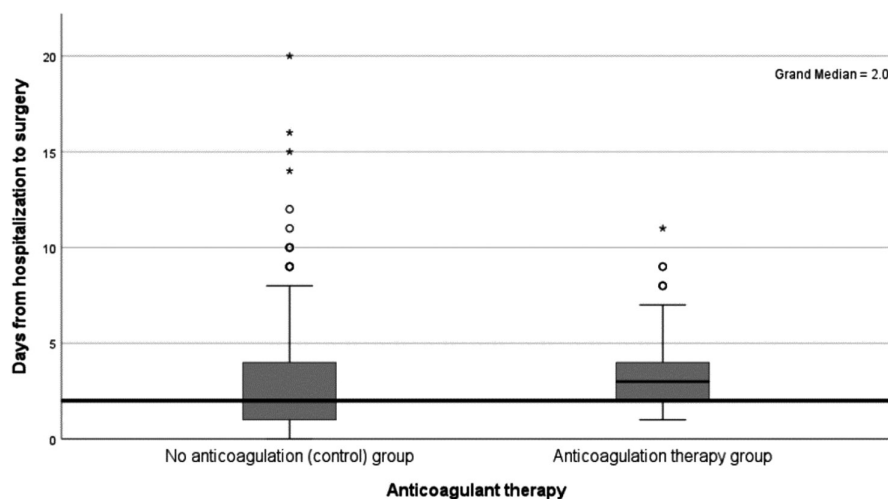
Statistically significant differences were found in both the number of days spent in the hospital ( $P < .05$ ; 95% CI:  $-0.26$  to  $-0.03$ ) and the time between hospitalization and surgery ( $P < .0001$ ; 95% CI:  $-0.37$



**Figure 1.** Incidence rates of anticoagulation therapy use among patients with proximal femur fractures requiring surgical treatment.

to  $-0.17$ ) when comparing patients receiving anticoagulation therapy and those who were not. The median time from hospitalization to surgery was 3 days (Q1: 2; Q3: 4) in the anticoagulation therapy group and 2 days (Q1: 1; Q3: 4) in the control group (Figure 2). In addition, patients receiving warfarin experienced a longer median surgical delay compared to those on NOAC therapy: 5 days (Q1: 2.5, Q3: 5.5) and 3 days (Q1: 2, Q3: 4), respectively ( $P < .05$ ). Despite this, patients receiving anticoagulation therapy spent more time in the hospital, with a median duration of 9 days (Q1: 6, Q3: 11), while patients without anticoagulation therapy had a significantly shorter stay, with a median of 7 days (Q1: 6, Q3: 10).

In the anticoagulation therapy group, 64.04% ( $n=73$ ) of patients undergoing surgery waited more than 48 hours. To assess the potential influence of anticoagulant therapy and surgical delay on 30-day postoperative complications, the study cohort was divided into 3 groups: a control group with no anticoagulation ( $n=458$ ), an anticoagulation group with surgery performed within 48 hours ( $n=41$ ),



**Figure 2.** Median time from hospitalization to surgery. The Y-axis represents the number of days waited from hospitalization to surgery, while the X-axis categorizes patients into 2 study groups: no anticoagulation (control) and anticoagulation therapy. The grand median (long black line) is 2.0 days, aligning with the no anticoagulation group's median, while the median for the anticoagulation therapy group is shown as a short black line. Outliers, represented by small circles and asterisks, indicate patients who experienced significantly longer surgical delays.

**Table 2.** Incidence rates of postoperative complications and statistical differences among 3 study groups: a control group with no anticoagulation, a group receiving anticoagulation therapy who underwent surgical treatment within 48 hours, and a group receiving anticoagulation therapy who waited more than 48 hours before surgery

	No anticoagulation (control) group n=458	Anticoagulation therapy group (surgery < 48 hours) n=41	Anticoagulation therapy group (surgery > 48 hours) n=73	P
Postoperative complications	n (%)	n (%)	n (%)	
Deaths	36 (7.86)	2 (4.88)	8 (10.96)	.493
Cardiac complications	48 (10.48)	7 (17.07)	12 (16.44)	.184
Sepsis	7 (1.53)	0 (0)	3 (4.11)	.199
Deep venous thrombosis	5 (1.09)	1 (2.44)	1 (1.37)	.748
Pneumonia	54 (11.79)	4 (9.76)	6 (8.22)	.638
Urinary tract infection	45 (9.83)	2 (4.88)	10 (13.70)	.312
Surgical site infection	11 (2.40)	1 (2.44)	5 (6.85)	.113
Pressure ulcers	40 (8.73)	2 (4.88)	9 (12.33)	.389
Acute kidney injury	20 (4.37)	0 (0)	6 (8.22)	.119
Delirium	49 (10.70)	4 (9.76)	5 (6.85)	.597

and an anticoagulation group with surgery delayed beyond 48 hours (n=73). Cardiac complications were more common in both anticoagulation therapy groups (surgery <48 h-17.07%; surgery >48 h-16.44%) compared to the control group (10.48%). However, these differences were not statistically significant ( $P=.184$ ). Similarly, no statistically significant differences were observed in other postoperative complications among the 3 groups ( $P>.05$ ). Detailed information about complication rates and statistical comparisons is summarized in Table 2. Percent changes in hemoglobin were similar across all 3 groups ( $P>.05$ ), with mean values ( $\pm$  SD) of  $16.7 \pm 10.1\%$  (95% confidence interval [CI]: 15.8-17.7) in the no anticoagulation group,  $16.6 \pm 10.0\%$  (95% CI: 13.3-19.8) in the anticoagulation therapy group that underwent surgery within 48 hours, and  $14.1 \pm 10.3\%$  (95% CI: 11.7-16.6) in the anticoagulation therapy group that waited more than 48 hours for surgery.

Multivariate logistic regression analyses were performed to determine whether age, sex, anticoagulation therapy, time to surgery, and length of hospital stay (LOS) are independent predictors of 30-day postoperative complications and mortality. Age and LOS were significantly associated with increased mortality risk ( $P<.05$ ), with odds ratios of 1.10 (95% CI: 1.04-1.15) and 1.09 (95% CI: 1.01-1.18), respectively. Anticoagulant therapy, sex, and time to surgery did not demonstrate significant associations with mortality (Table 3). Regarding 30-day postoperative complications, age (odds ratio [OR]=1.06, 95% CI: 1.04-1.09), time to surgery (OR=1.60, 95%

CI: 1.03-1.31), and length of stay (OR=1.15, 95% CI: 1.07-1.24) were identified as independent risk factors ( $P<.05$ ). Anticoagulant therapy and sex were not significantly associated with complication rates (Table 4).

## Discussion

This study demonstrated that patients receiving anticoagulation therapy experienced significantly longer times to surgical intervention and prolonged hospital stays compared to controls. Specifically, 64.04% (n=73) of patients on anticoagulation experienced a delay of more than 48 hours before undergoing surgery, with a median time to surgery of 3 days, compared to 2 days in the control group. These findings are clinically meaningful given current international guidelines, including those from the Fragility Fracture Network, which advocate for surgical intervention within 48 hours—preferably within 36 hours in some regions—to minimize morbidity and mortality.<sup>10</sup> The study confirms that both age and LOS are significant risk factors for mortality and the occurrence of 30-day postoperative complications. Moreover, time to surgery was identified as an independent risk factor for 30-day postoperative complications, highlighting the clinical importance of minimizing surgical delays. Although anticoagulation therapy was not an independent risk factor for 30-day postoperative complications or mortality, it was significantly associated with longer hospital stays and delayed surgery, which may indirectly contribute to poorer outcomes.

**Table 3.** Multivariate logistic regression analysis identifying predictors of 30-day mortality

Independent variables	Coefficient B	Standard error	Z	P	Odds ratio	95% confidence interval
Age	0.09	0.02	3.7	<.001**	1.1	1.04-1.15
Sex	0.37	0.38	0.98	.329	1.45	0.69-3.05
Anticoagulative therapy	-0.04	0.39	0.12	.908	0.96	0.45-2.04
Time to surgery	0.04	0.07	0.55	.579	1.04	0.91-1.19
Length of stay	0.09	0.04	2.26	.024*	1.09	1.01-1.18

R squared for model=0.11,  $P<.001$ .

\*Indicates  $P<.05$ .

\*\*Indicates  $P<.01$ .

**Table 4.** Multivariate logistic regression analysis identifying predictors of 30-day postoperative complications

Independent variables	Coefficient B	Standard error	Z	P	Odds ratio	95% confidence interval
Age	0.06	0.01	4.28	<.001**	1.06	1.04-1.09
Sex	0.04	0.24	0.15	.879	1.04	0.65-1.65
Anticoagulative therapy	0.06	0.23	0.27	.79	1.06	0.68-1.67
Time to surgery	0.15	0.06	2.38	0.017*	1.6	1.03-1.31
Length of stay	0.14	0.04	3.7	<.001**	1.15	1.07-1.24

R squared for model=0.2,  $P<.001$ .

\*Indicates  $P<.05$ .

\*\*Indicates  $P<.01$ .

These results are consistent with existing literature. A recent systematic review reported that anticoagulated patients undergoing hip fracture surgery experienced a mean surgical delay of 13.7 hours and had approximately a 3-fold higher likelihood of surgical delay beyond 48 hours compared to non-anticoagulated individuals.<sup>11</sup> Importantly, the current findings reinforce these observations, with over 60% of patients on anticoagulation exceeding this threshold.

The current study also contributes to the growing evidence base assessing whether DOAC-related surgical delays translate into increased perioperative risk. While a delay beyond 48 hours has previously been linked to higher mortality and complication rates, the current data did not reveal statistically significant differences in 30-day mortality or major complications between anticoagulated and non-anticoagulated patients.<sup>8,12</sup> These findings align with prior retrospective studies indicating no significant differences in hemoglobin drop, transfusion requirement, reoperation, or 30-day mortality among patients undergoing early hip fracture surgery while on DOAC therapy.<sup>13,14</sup> This study demonstrated similar hemoglobin changes between the anticoagulation and control groups, suggesting that anticoagulation status did not significantly influence perioperative blood loss.

The findings of this study are partially consistent with those reported by Kavak et al,<sup>15</sup> who evaluated 596 geriatric hip fracture patients and identified a mean surgical delay of 3.21 days (range: 1-9 days) as a significant predictor of 30-day mortality ( $P < .001$ , OR: 2.006). Their study found that patients who died within 30 days postoperatively had a median surgical delay of 5 days, compared to 3 days among survivors. Similarly, in the anticoagulated cohort, the median surgical delay was 3 days, a duration in line with the threshold described by Kavak et al<sup>15</sup> as potentially acceptable for medical optimization without excessive risk. However, the absence of a significant difference in 30-day mortality in the population suggests that in carefully selected patients—particularly those with well-controlled comorbidities—a 3-day delay may not independently increase early mortality risk. Notably, both studies underscore that delays beyond 3 days should prompt clinical reassessment, particularly in the presence of additional risk factors such as a high ASA score or significant perioperative complications.<sup>15</sup>

Notably, both this study and others underscore that delays should prompt reassessment, particularly in the presence of additional risk factors. For instance, Bombacı et al<sup>16</sup> found that a high ASA score (ASA 4), abnormal preoperative creatinine levels, and the presence of cognitive dysfunction such as dementia were all significant preoperative indicators of postoperative mortality. That study also highlighted that the majority of deaths (57.14%) occurred within the first 3 months, emphasizing the vulnerability of this early recovery period.<sup>16</sup> Similarly, Zehir et al<sup>17</sup> identified delayed surgical intervention as a critical factor influencing 30-day mortality in patients receiving clopidogrel therapy. Their findings indicate that patients who underwent surgery more than 48 hours after clopidogrel administration experienced significantly prolonged hospitalizations ( $P < .01$ ) and a higher incidence of postoperative complications.<sup>17</sup>

In terms of LOS, patients receiving anticoagulant therapy had a significantly longer LOS (median: 9 days) compared to controls (median: 7 days). Despite the increased LOS, no statistically significant differences were observed between groups regarding rates of mortality, cardiac events, infections, sepsis, deep vein thrombosis, or

other postoperative complications ( $P > .05$ ). This aligns with findings from studies on preoperative cardiac evaluations, where extensive testing was shown to significantly delay surgery and prolong hospital stays, also without a corresponding reduction in perioperative mortality.<sup>18</sup> This phenomenon is consistent with previous analyses demonstrating a weak correlation between complication rates and extended LOS (Spearman's  $\rho = 0.56$ ,  $P < .01$ ), suggesting that other factors—including preoperative delay, social discharge barriers, or institutional practices—contribute to prolonged hospitalization.<sup>19</sup> In contrast, other studies have identified medical complications such as urinary tract infections (15.4%), pneumonia (9.0%), and constipation (6.8%) as primary drivers of extended LOS.<sup>20</sup> The discrepancy between findings reinforces the multifactorial nature of hospital stay duration in this patient population, in which age, frailty, comorbid burden, and postoperative recovery dynamics interplay.

Finally, these findings reaffirm that current surgical timing guidelines should not be rigidly deferred based solely on anticoagulation status, particularly with DOACs. As emerging evidence shows limited association between DOAC use and increased perioperative bleeding risk, the rationale for delayed surgical intervention must be patient-specific and guided by renal function, drug pharmacokinetics, and overall clinical stability. Blanket delays may unnecessarily expose patients to complications associated with prolonged immobility and hospitalization.

Limitations of this prospective study using secondary data include the inability to directly quantify blood loss, necessitating the use of indirect estimates based on pre- and postoperative hemoglobin levels. Complete data regarding the timing of the last DOAC dose administration were not available for all patients, precluding a comprehensive analysis of the time from the last anticoagulant dose to surgical intervention. Information regarding the use and timing of platelet aggregation inhibitor administration was not recorded, limiting the ability to assess the impact of ongoing antiplatelet therapy on perioperative bleeding risk. In addition, this study did not include possible predictors of mortality and complications: patients' pre-fracture activity levels, ambulatory status, c-reactive protein-to-albumin ratio, and the modified 5-item frailty index. Finally, the single-center design may limit the extent to which these findings are applicable to other institutions or patient populations.

This study concludes that the administration of anticoagulation therapy was not associated with an elevated incidence of postoperative complications compared to the control group, and no statistically significant difference in percent change of hemoglobin levels was observed between the 2 groups. Age and LOS were found to be significant risk factors for 30-day postoperative complications and mortality. Time to surgery also emerged as an independent predictor of 30-day complications. While anticoagulation therapy itself was not an independent risk factor for 30-day postoperative complications or mortality, it was significantly associated with both extended hospital length of stay and a prolonged time to surgical intervention, which can indirectly increase the risk of poor outcomes.

**Data Availability Statement:** The data that support the findings of this study are available on request from the corresponding author.

**Ethics Committee Approval:** Ethical committee approval was received from the Lithuanian Bioethics Research Ethics Committee (Approval No.: 2022/11-1473-941; Date: 22.11.2022).

**Informed Consent:** Written informed consent was obtained from the patients who agreed to take part in the study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – P.M., I.Š.; Design – P.M., I.Š.; Supervision – I.Š.; Resources – I.Š.; Materials – P.M., I.Š.; Data Collection and/or Processing – E.F.B., D.D., R.B.; Analysis and/or Interpretation – E.F.B., D.D., R.B., P.M.; Literature Search – P.M., E.F.B., D.D.; Writing – E.F.B., D.D.; Critical Review – P.M., I.Š.

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