

Association between Preoperative Waiting Times of Less Than 24 Hours versus 24 to 48 Hours and Clinical Outcomes in Elderly Patients Underwent Hip Fracture Surgery: A Single Center Randomized Controlled Trial

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Objective: Delayed surgical intervention following a hip fracture in the elderly patients may increase the risk of complications and mortality. The present study aimed to investigate the association between surgery within 24 hours versus 24 to 48 hours post-injury and clinical outcomes within the first month after surgery.

Materials and Methods: The present study was a randomized controlled trial (RCT) study conducted at Yasothon Hospital. Elderly patients diagnosed with hip fractures were randomized into two groups, the intervention group who underwent surgery within 24 hours and the control group who underwent surgery between 24 and 48 hours. Both groups were followed up for one month postoperatively. The outcomes were the postoperative oral morphine equivalent amount, mortality rate, length of hospital stays, and postoperative complications.

Results: Ninety-four patients were enrolled, with 47 patients in each group. Statistically significant differences were observed between the two groups in terms of hip fracture type ($p<0.001$), ASA classification ($p=0.032$), fixation method ($p<0.001$), operation time ($p=0.002$), and type of anesthesia used ($p=0.020$). Additionally, patients who underwent surgery within 24 hours had a significantly shorter length of hospital stay compared to those who underwent surgery between 24 and 48 hours ($p<0.001$). However, there were no statistically significant differences in postoperative oral morphine equivalent amount ($p=0.137$), one-month mortality rate ($p=0.153$), or postoperative complication rates ($p=1.000$) between the two groups.

Conclusion: Early hip fracture surgery within 24 hours for elderly patients can improve clinical outcomes, yet, surgery within the standard 48-hour period still yields similarly favorable outcomes. These findings could support more efficient hospital resource management while ensuring patient safety remains a priority.

Keywords: Hip fracture; Surgical waiting time; Elderly; Clinical outcomes

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Hip fractures are a severe consequence of high-impact trauma to the proximal femur and particularly prevalent among older adults with osteoporosis, a condition that weakens bone structure and increases fracture susceptibility. The global incidence of hip fractures has been steadily rising. Currently, the incidence of hip fractures in Asia remains lower than in Western countries, primarily due to genetic and

different lifestyles. However, demographic shifts, particularly the rapid aging of the population, are expected to significantly increase the burden of hip fractures in Asia by 2050. Projections indicate that Asia will become the most affected region in the future⁽¹⁾.

According to the National Health Examination Survey of Thailand, one in three elderly individuals experiences a fall each year, with approximately 20% sustaining injuries. Annually, over 10,000 older adults suffer hip and proximal femur injuries, and around 20% of those with hip fractures die within one year of the event⁽²⁾. Additionally, a significant proportion of hip fracture patients experience long-term disabilities, which impact on their quality of life and impose a substantial economic burden on the healthcare systems⁽³⁾.

Hip fractures not only have direct consequences for affected individuals but also pose a significant

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challenge for healthcare systems worldwide. Managing these patients requires substantial medical resources and often results in prolonged hospitalization. In countries with limited healthcare infrastructure, treating hip fracture cases present critical challenges. Moreover, delays in accessing surgical intervention have been shown to significantly affect mortality rates and postoperative outcomes^(4,5). Complications such as deep vein thrombosis (DVT), pneumonia, infections, and heart failure are common in patients who experience prolonged preoperative waiting times. Inadequate treatment can lead to permanent loss of mobility, increased dependence on caregivers, and poorer functional outcomes. The severity of hip fractures is closely linked to the duration of the preoperative delay^(6,7).

Studies have shown that performing surgery within the first 24 to 48 hours after injury can reduce mortality rates and improve recovery. Delaying surgery beyond 48 hours is associated with higher mortality and increased risk of complications. Timely surgical intervention shortens hospital stays, lowers overall healthcare costs, and speeds up rehabilitation, especially in elderly patients who are particularly vulnerable to postoperative complications⁽⁴⁻⁷⁾. The mortality rate among elderly patients with hip fractures is notably high, with 5% to 10% dying within one month of the fracture. Within one year, approximately one-third of hip fractured patients succumb to complications, a rate significantly higher than the general mortality rate of elderly individuals in the same age group, which averages around 10% per year. These findings highlight the significant impact of hip fractures on mortality risk in the elderly population^(8,9).

Given the existing evidence, preoperative waiting time has been identified as a critical determinant of postoperative complications, recovery, and mortality in elderly hip fracture patients. While current treatment guidelines recommend surgery within 48 hours to reduce these risks, questions remain whether performing surgery even earlier could further improve clinical outcomes. Therefore, it is essential to investigate the association between surgical timing, specifically, surgery within 24 hours versus 24 to 48 hours post-injury, and clinical outcomes within the first month after surgery among elderly patients admitted to a secondary care public hospital. The findings from the present study would provide valuable evidence to refine treatment strategies and optimize healthcare delivery in regional hospital settings.

Materials and Methods

Trial design

The present study was a randomized controlled trial conducted in the Orthopedic Surgery Department of Yasothon Hospital, Yasothon Province, Thailand, between June 2024 and January 2025. The participants were randomly assigned into two groups, the intervention group, including those underwent hip fracture surgery within 24 hours, and the control group with surgery between 24 and 48 hours. At Yasothon Hospital, Thailand, surgical techniques were selected based on fracture type. Non-displaced femoral neck fractures were primarily treated with multiple screws fixation. Displaced femoral neck fractures were typically managed using cementless bipolar hemiarthroplasty, Austin Moore hemiarthroplasty for limited activity levels, and total hip replacement for preexisting hip pathologies, such as osteonecrosis or severe osteoarthritis of the hip. Intertrochanteric fractures were typically managed using proximal femoral nailing (PFN) for unstable fractures or dynamic hip screw fixation for stable fractures. Subtrochanteric fractures were treated using long PFN. The attending orthopedic surgeon chose the technique according to standard orthopedic management. Both groups were followed up immediately after surgery and monitored for mortality and clinical outcomes for one month postoperatively.

Eligibility criteria

The patient's inclusion criteria were aged 60 years or older, diagnosed with hip fracture based on radiographic imaging such as X-ray or CT scan, determined to require surgical intervention, and capable of providing informed consent, or have a legal representative to provide consent on their behalf. Patients were excluded on meeting any conditions such as history of prior hip surgery such as periprosthetic fracture, multiple fractures involving other skeletal regions, concurrent head injury, high-energy trauma mechanism, pathologic fracture due to pre-existing bone disease, presence of severe medical conditions that contraindicate surgery such as hemodynamic instability, severe cardiac conditions, severe respiratory insufficiency, neurological impairment with confusion or altered mental status, uncontrolled coagulopathy, or uncontrolled infection, refusal of surgical treatment, and decline to participate in the study.

These exclusion criteria were applied to ensure the homogeneity of the study population, reduce confounding factors, and enhance the internal validity

of the findings. Patients with multiple injuries or severe systemic diseases often experience different clinical trajectories, which may obscure the effect of surgical timing on outcomes. Therefore, excluding these patients allowed for a more focused and accurate assessment of the relationship between surgical delay and postoperative outcomes in elderly patients with fragility hip fractures.

Sample size

The sample size was determined based on a randomized controlled trial with a continuous outcome, guided by the findings of Allahabadi et al.⁽¹⁰⁾, which assessed the impact of early hip fracture surgery on postoperative opioid consumption. In the treatment group, the mean was 81.3 with a standard deviation (SD) of 174.9, while in the control group, the mean was 213.3 with an SD of 271.3. The ratio of control to treatment was 1.00. Using an alpha (α) level of 0.01 with $Z(0.975)=1.96$, and a beta of 0.20 with $Z(0.80)$, the estimated sample size for each group was calculated to be 47 patients, leading to a total of 94 patients. An alpha level of 0.01 was selected instead of the conventional 0.05 to minimize the probability of a Type I error, considering the small sample size and multiple comparisons of clinical outcomes.

Intervention

In the present study, the intervention group consisted of patients undergoing surgery within 24 hours after hospital admission, while the control group included patients undergoing surgery between 24 and 48 hours after admission. Both groups received identical standard perioperative care, including preoperative antibiotic administration, fluid management, and preoperative and postoperative rehabilitation following standard clinical guidelines.

Outcomes

The primary outcome was total postoperative opioid consumption, expressed in oral morphine equivalents (OME), calculated based on standardized equianalgesic conversion ratios such as 10 mg of intravenous morphine equal to 30 mg of oral morphine, 100 mg of tramadol equal to 10 mg of oral morphine. OME was recorded cumulatively during the entire inpatient stay.

Secondary outcomes included:

Length of hospital stay, defined as the time interval in hours between official hospital admission and discharge as documented in the hospital information system.

Mortality, defined as all-cause mortality occurring within 30 days postoperatively, regardless of the cause or location of death, and verified through hospital records or follow-up contact.

Postoperative complications included anemia, delirium, urinary tract infection (UTI), and Sepsis.

Randomization, allocation concealment, and blinding

Block randomization with a fixed block size of four was used to ensure balanced allocation between the intervention and control groups. The allocation sequence was computer-generated and concealed using sequentially numbered, sealed opaque envelopes, which were opened only after obtaining informed consent from participants. Although blinding of patients and surgeons was not feasible due to the nature of the surgical intervention, detection bias was minimized by employing trained outcome assessors who were blinded to group allocation. These assessors were independent of the surgical team and used standardized forms to collect postoperative clinical data during the follow-up period. The CONSORT flow diagram of the study is illustrated in Figure 1.

Ethical approval

The present study was approved by the Human Research Ethics Committee of Yasothon Hospital (YST 2024-19) and registered in the Thai Clinical Trials Registry (thaiclinicaltrials.org) under the identifier TCTR20240626001. All the patients provided signed informed consents before being enrolled in the study.

Statistical analysis

The comparison between the intervention and the control groups was conducted as follows: categorical variables were analyzed using the chi-square test or Fisher's exact test, depending on data distribution and expected cell counts. For continuous variables, the Shapiro-Wilk test was used to assess the normality of data. If the data were normally distributed, the independent t-test was employed, otherwise, the Mann-Whitney U test was applied for non-normally distributed variables. The significance difference was set at p-value less than 0.05. There were no missing data or loss to follow-up during the study period. All 94 participants completed the 30-day postoperative evaluation. The flow of participant enrollment, allocation, follow-up, and analysis are illustrated in Figure 1 (CONSORT diagram).

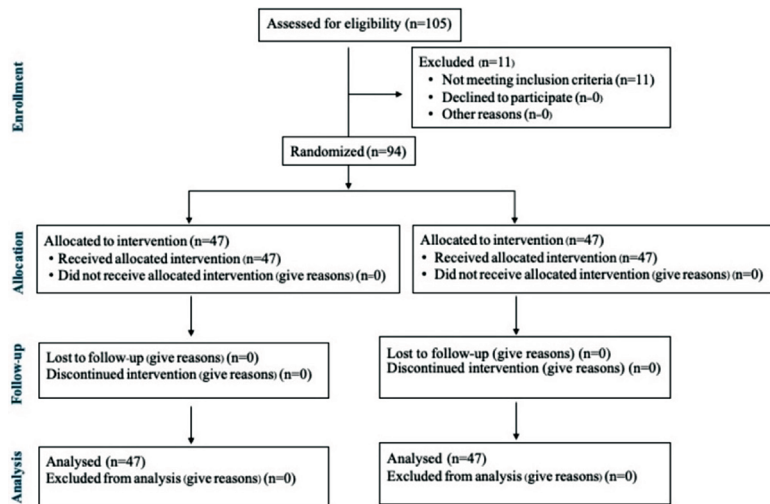


Figure 1. The CONSORT flow diagram of the study.

Table 1. Baseline characteristics of the patients

Variables	Surgical duration			p-value
	Surgery within 24 hours (n=47)	Surgery between 24 to 48 hours (n=47)	Total (n=94)	
Sex; n (%)				0.192
Male	19 (40.4)	13 (27.7)	32 (34.0)	
Female	28 (59.6)	34 (72.3)	62 (66.0)	
Age (years); mean±SD	75.91±6.27	75.91±5.88	75.91±6.04	1.000
BMI (kg/m ²); mean±SD	21.75±3.44	21.78±3.59	21.77±3.50	0.975
Underweight (<18.50)	6 (12.8)	11 (23.4)	17 (18.1)	0.136
Normal (18.50 to 22.99)	24 (51.1)	15 (31.9)	39 (41.5)	
Overweight (≥23.00)	17 (36.2)	21 (44.7)	38 (40.4)	
Fracture type; n (%)				<0.001
Neck of femur	10 (21.3)	28 (59.6)	38 (40.4)	
Intertrochanteric fracture	37 (78.7)	19 (40.4)	56 (59.6)	
ASA classification; n (%)				0.032
2	17 (36.2)	7 (14.9)	24 (25.5)	
3	29 (61.7)	39 (83.0)	68 (72.3)	
4	1 (2.1)	1 (2.1)	2 (2.1)	
Preoperative opioid use; n (%)				0.404
No	29 (61.7)	25 (53.2)	54 (57.4)	
Yes	18 (38.3)	22 (46.8)	40 (42.6)	
Surgical fixation/treatment; n (%)				<0.001
Bipolar hemiarthroplasty	10 (21.3)	28 (59.6)	38 (40.4)	
Proximal femoral nailing	37 (78.7)	19 (40.4)	56 (59.6)	
Operative time (minutes); mean±SD	44.72±17.12	56.21±18.51	50.47±18.65	0.002
Estimate blood loss; mean±SD	70.00±50.30	81.70±47.88	75.85±49.20	0.108
Anesthesia type; n (%)				0.020
Spinal block	36 (76.6)	44 (93.6)	80 (85.1)	
General anesthesia	11 (23.4)	3 (6.4)	14 (14.9)	
Morphine (mg); mean±SD	15.60±15.15	19.36±17.68	17.48±16.48	0.287
Tramol (mg); mean±SD	17.02±95.14	8.51±21.67	12.77±68.76	0.353
Fentanyl (mcg); mean±SD	0.00±0.00	23.19±109.43	11.60±77.84	0.080

SD=standard deviation; BMI=body mass index; ASA=American Society of Anesthesiologists

Table 2. Total length of hospital stays and outcomes after 30-days of hip fracture surgery

Variables	Surgical duration			p-value
	Surgery within 24 hours (n=47)	Surgery between 24 to 48 hours (n=47)	Mean difference (95% CI)	
Total length of hospital stay (hours)	142.28±63.56	203.98±90.30	-61.70 (-93.26 to -30.14)	<0.001
Postoperative pain score; n (%)				0.332
0	7 (14.9)	11 (23.4)		
1	21 (44.7)	14 (29.8)		
2	19 (40.4)	21 (44.7)		
3	0 (0.0)	1 (2.1)		
Total oral morphine equivalents; mean±SD	51.89±54.30	67.43±61.85	-15.54 (-39.08 to 8.00)	0.155
Cumulative post-operative OME; mean±SD	42.83±53.56	56.74±55.50	-13.91 (-35.96 to 9.14)	0.137
Average OME per hospital day; mean±SD	9.29±9.89	8.61±8.44	0.68 (-3.02 to 4.40)	0.961
Mortality; n (%)	0 (0.0)	2 (4.3)		0.153
Complication; n (%)				1.000
No	25 (53.2)	25 (53.2)		
Yes	22 (46.8)	22 (46.8)		
• Anemia	19 (40.4)	17 (36.2)		0.671
• Delirium	4 (8.5)	7 (14.9)		0.336
• Urinary tract infection	2 (4.3)	1 (2.1)		0.557
• Sepsis	0 (0.0)	1 (2.1)		0.315

SD=standard deviation; OME=oral morphine equivalent; CI=confidence interval

Results

Table 1 presents the baseline characteristics of elderly patients who underwent hip fracture surgery, categorized by surgery time as within 24 hours versus between 24 and 48 hours. No significant differences were observed in terms of age ($p=1.000$), body mass index (BMI) ($p=0.975$), and preoperative opioid use ($p=0.404$). However, there were statistically significant differences in fracture type ($p<0.001$), the American Society of Anesthesiologists (ASA) classification ($p=0.032$), surgical fixation method ($p<0.001$), operative time ($p=0.002$), and type of anesthesia used ($p=0.020$). Patients who underwent surgery within 24 hours had a significantly shorter operative time, with a mean of 44.72 ± 17.12 minutes compared to 56.21 ± 18.51 minutes in the delayed surgery group ($p=0.002$). Although estimated blood loss tended to be higher in the 24 to 48-hour group, this difference was not statistically significant ($p=0.108$).

Table 2 presents the clinical outcomes of elderly patients undergoing hip fracture surgery and categorized by surgical waiting time as within 24 hours versus between 24 and 48 hours. Patients who underwent surgery within 24 hours had a significantly shorter total length of hospital stay compared to those who underwent surgery between 24 and 48 hours with 142.28 ± 63.56 hours versus 203.98 ± 90.30 hours ($p<0.001$). However, there were no statistically

significant differences in postoperative pain scores with the pain scores assessed using a numeric rating scale (NRS) ($p=0.332$), total OME ($p=0.155$), or cumulative postoperative opioid consumption ($p=0.137$). Mortality was observed in two patients, or 4.3%, in the delayed surgery group, while no deaths were reported in the early surgery group, though this difference was not statistically significant ($p=0.153$). The overall complication rate was identical between the two groups at 46.8%, with anemia being the most common complication at 38.3%. No significant differences were found in the incidence of delirium ($p=0.336$), UTI ($p=0.557$), or sepsis ($p=0.315$) between the groups.

To account for baseline imbalances in fracture type, ASA classification, fixation method, anesthesia type, and operative time, adjusted analyses were conducted using multivariable regression models (Table 3). After adjustment, patients who underwent surgery within 24 hours had a significantly shorter hospital stay compared to those who underwent surgery between 24 and 48 hours, with a mean difference (MD) of 60.29 hours (95% CI 21.18 to 99.35, $p=0.030$).

There were no statistically significant differences between the two groups in terms of postoperative pain scores (adjusted MD -0.16, 95% CI -0.55 to 0.22, $p=0.400$), total morphine consumption (adjusted

Table 3. Unadjusted and adjusted effect estimates comparing clinical outcomes between surgery within 24 hours and 24 to 48 hours

Variables	Unadjusted			Adjusted effect estimate*		
	24 hours	24 to 48 hours	p-value	Adjusted	95% CI	p-value
Length of stay (hours); mean±SD	142.3±63.6	204.0±90.3	<0.001	60.29	21.18 to 99.35	0.03
Postoperative pain; mean±SD	1.25±0.70	1.25±0.84	1.00	-0.16	-0.55 to 0.22	0.40
Total morphine; mean±SD	51.89±54.30	67.43±61.85	0.155	-2.73	-31.36 to 25.90	0.85
Cumulative opioid; mean±SD	42.8 ± 53.6	56.7±55.5	0.137	-4.58	-31.20 to 22.03	0.73
Mortality; n (%)	0 (0.0)	2 (4.3)	0.153	Adj. OR 7.00	0.32 to 152.79	0.21
Complications; n (%)	22 (46.8)	22 (46.8)	1.000	Adj. OR 0.62	0.22 to 1.72	0.36

SD=standard deviation; Adj. OR=adjusted odds ratio; CI=confidence interval

* Adjusted effect estimates were obtained from linear regression (for continuous variables) and logistic regression (for binary outcomes), controlling for fracture type, ASA classification, fixation method, anesthesia type, and operative time.

MD -2.73 mg, 95% CI -31.36 to 25.90, $p=0.850$), or cumulative postoperative opioid use (adjusted MD -4.58 mg, 95% CI -31.20 to 22.03, $p=0.730$). The adjusted odds ratio (adj. OR) for 30-day mortality in the delayed surgery group was 7.00 (95% CI 0.32 to 152.79, $p=0.210$), although this was not statistically significant. Similarly, there was no significant difference in the overall complication rate, with an adjusted odds ratio of 0.62 (95% CI 0.22 to 1.72, $p=0.360$) between the two groups.

Discussion

The present study investigated the association between surgery within 24 hours versus 24 to 48 hours post-injury among elderly patients with hip fractures and clinical outcomes within the first month after surgery. No statistically significant differences in postoperative pain levels ($p=0.332$), total oral morphine consumption ($p=0.155$), or cumulative opioid use ($p=0.137$) between the early and the delayed hip surgery groups were revealed. These findings are aligned with the previous studies, which have shown that earlier surgery does not significantly reduce opioid analgesic consumption or postoperative pain levels. Garlich et al. (2020)⁽¹¹⁾ reported that although early administration of regional analgesia reduced preoperative pain and opioid use, there were no significant differences in postoperative pain levels or cumulative opioid use between patients receiving early versus delayed regional analgesia. Similarly, Cunningham et al. (2022)⁽¹²⁾ found no significant differences in opioid consumption between patients who received regional analgesia and those who did not, despite initial expectations that regional anesthesia would reduce opioid requirements. Other factors, such as anesthetic techniques, postoperative care, and early rehabilitation protocols, may have a greater impact on pain management and opioid use than surgical timing alone.

Next, the current study found that surgery within 24 hours was significantly associated with a shorter hospital stay compared to surgery between 24 and 48 hours ($p<0.001$). This finding is consistent with a study by Unnanuntana et al. (2024)⁽¹³⁾, which retrospectively analyzed hip fracture patients in a tertiary private hospital in Thailand and found that patients who underwent surgery within 24 hours had a median hospital stay of six days (IQR 4 to 9) compared to eight days (IQR 7 to 13) in those who underwent delayed surgery ($p<0.001$). This also aligns with a meta-analysis by Zhu et al. (2023)⁽¹⁴⁾, which examined the effects of Enhanced Recovery After Surgery (ERAS) in hip fracture patients and found that ERAS-based care was associated with a 2-day reduction in hospital stay (MD -2.00, 95% CI -2.87 to -1.14, $p<0.0001$). It is possible that longer surgical delays increase the risk of hospital-acquired complications, such as DVT, pneumonia, and hospital-acquired infections, leading to prolonged hospitalization⁽¹⁴⁾.

The present study found no significant difference in the overall complication rate between the two groups, with both at 46.8%, with anemia being the most common postoperative complication at 38.3%. No significant differences were observed in the incidence of delirium ($p=0.336$), UTI ($p=0.557$), or bloodstream infection ($p=0.315$) between the two groups. These findings agree with Unnanuntana et al. (2024)⁽¹³⁾, which reported no significant reduction in overall complications ($p=0.410$) in patients undergoing early hip surgery. Furthermore, Cai et al. (2023)⁽¹⁵⁾ investigated the effects of surgical delay beyond 48 hours in elderly hip fracture patients and found no statistically significant difference in complication rates between early and delayed surgery groups. This suggests that surgical delay alone may not be the primary factor influencing complication rates. Other factors, such as pre-existing

comorbidities such as anemia, cardiac disease, chronic kidney disease, or malnutrition, may play a more critical role in determining postoperative outcomes, regardless of surgical timing⁽¹⁵⁾.

The one-month mortality rate in the delayed surgery group was 4.3%, whereas no deaths occurred in the early surgery group, though this difference was not statistically significant ($p=0.153$). These results align with the previous studies, which suggest that earlier surgery may reduce mortality risk, but the difference does not always reach statistical significance. The mortality rate observed in the present study was lower than that reported by Ghosh et al. (2023)⁽¹⁶⁾, which examined 30-day and 6-month mortality rates in elderly hip fracture patients and found a 30-day mortality rate of 19.2%, which was associated with factors such as pre-existing comorbidities and time to hospital admission rather than surgical timing alone. Similarly, Kristan et al. (2021)⁽¹⁷⁾ investigated the impact of surgical delays on 30-day and one-year mortality rate and found that the 30-day mortality rate was 5.1%, and the one-year mortality rate was 18.4%, but there was no clear association between surgical delays beyond 48 hours and mortality risk.

Although theoretical evidence suggests that early surgery within 24 hours may improve survival rates, the present study does not confirm a statistically significant impact. The low mortality rate in the present study may be attributed to patient selection criteria, including the exclusion of patients with severe comorbid conditions, as well as high-quality perioperative care and postoperative rehabilitation measures, which may have played a more significant role in survival outcomes than surgical timing alone.

Although this clinical topic has been widely investigated internationally, the present study findings offer context-specific insight for regional hospitals in Thailand, where surgical scheduling and resource limitations often influence care delivery. These results could support revisions to the National Clinical Guidelines, encouraging early surgery when feasible, while balancing it with safe patient optimization.

Limitation

The present study has limitations. First, it was conducted at a single secondary-care hospital in Thailand, which may limit the generalizability of the findings to other healthcare settings with different resources or systems of care. Second, the study focused only on short-term outcomes within

30 days after surgery, without evaluating long-term functional recovery or mortality. Third, despite randomization, baseline imbalances in fracture type, ASA classification, fixation method were present, which may have influenced the outcomes. Although adjusted analyses were performed, the limited sample size restricted statistical power, limiting the ability to conduct subgroup analyses. Lastly, the study lacked a pre-specified protocol, which may affect transparency, introduce analytical bias.

Conclusion

The present study demonstrates that hip fracture surgery within 24 hours significantly reduces hospital length of stay but does not impact the one-month mortality or complication rates. However, individual patient risk factors should be carefully considered when determining the optimal timing for surgery. Treatment guidelines should prioritize minimizing surgical delays while ensuring patient safety remains the primary concern.

What is already known about this topic?

Existing evidence supports that the optimal timing for hip fracture surgery is within 48 hours, as this window has been shown to significantly reduce morbidity and mortality in patients. Timely intervention within this period helps to minimize complications, accelerate recovery, and improve overall outcomes.

What does this study add?

This study adds valuable insight into the timing of hip fracture surgery, showing that performing the procedure within 24 hours in elderly patients significantly reduces hospital length of stay, which can enhance resource management and expedite patient recovery. However, it also highlights that earlier surgery does not impact on the one-month mortality rates or reduce the incidence of postoperative complications. The findings emphasize that while early surgery is beneficial, rushing into surgery without proper preoperative optimization is not advised, as thorough preparation may lead to better overall outcomes, especially in elderly patients with comorbidities.

Conflicts of interest

The author declares no conflicts of interest.

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