

Adverse Events following Intramedullary Nailing in Metastatic Pathological versus Non-Pathological Femoral Shaft Fractures: A Retrospective Comparative Study

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Abstract

Background: Antegrade intramedullary nailing is indicated for treating metastatic pathological femoral shaft fractures. Although good functional outcomes could be obtained from internal fixation, postoperative adverse events have been reported in patients with pathological fractures and non-pathological fractures. Not only adverse events but also their consequences including, readmission and reoperation, need to be considered. Few studies have assessed the risk of postoperative adverse events, reoperation, and readmission without comparison. Therefore, this study aimed to compare the risk of in-hospital adverse events and consequences after discharge between patients with metastatic pathological and non-pathological femoral fractures undergoing intramedullary nailing.

Methods: We conducted a retrospective study by extracting records from the Hospital Information System database. We accessed patients with pathological metastatic pathological and non-pathological femoral shaft fractures undergoing intramedullary nailing by the International Classification of Diseases code; from June 2006 to 2020. We then tracked the in-hospital medical and surgical adverse events postoperatively, along with the consequences after discharge. The in-hospital adverse events risk between the two groups of patients were analyzed and compared by multivariate logistic regression analysis.

Results: Included patients consisted of 48 in pathological groups and 185 in non-pathological groups. Significantly higher rates of surgical and medical adverse events in patients with pathological fractures compared to patients with non-pathological fractures were observed. After adjusting for potential confounding factors in multivariate regression analysis, patients with pathological fractures had higher odds of both adverse surgical (adjusted OR 2.43, 95% CI 1.15 - 5.13) and medical adverse events (adjusted OR 2.81, 95% CI 1.13 - 7.03).

Conclusions: Patients with metastatic pathological femoral shaft fractures undergoing intramedullary nailing were more likely to experience postoperative adverse events than patients with non-pathological fractures.

Introduction

Femoral shaft fractures are common trauma injuries with high global incidence rates [1]. These fractures usually result from either high or low energy injuries; the latter frequently occur in patients with bones weakened through some pathology [2–4]. Pathological femoral fractures can result from various underlying diseases, such as infection, metabolic bone diseases, or bone tumors. Among bone tumors, metastatic disease is the most frequent malignant neoplasm of the bone, ranging from 25–85%, and usually originating from the prostate, breast, lung, kidney, or thyroid [5–8]. The femur is the second most common metastasis site following the vertebra [9, 10], with high susceptibility of progression to pathological fractures because the femur is a long, high load-bearing bone [11, 12]. Pathological fractures of the femur are associated with severe pain, immobilization, and diminished quality of life [7, 13].

Therefore, these patients require prompt surgical intervention to restore their function and relief pain [14–17].

Surgical fixation of metastatic bone disease is principally indicated for pathological femoral fractures [14, 16]. Durable implants and mechanically stable internal fixation need to be considered due to the poor bony union of pathological fractures [11, 18]. Antegrade intramedullary nailing is an option for treating pathological femoral shaft fractures, since several studies have reported that patients treated with this method had good functional outcomes [19–23]. Although the benefits of internal fixation after a pathological fracture of the femur are known, patients who incurred adverse events following this surgical procedure have been reported [14, 24–27].

Postoperative adverse events reported in patients with femoral fractures showed relatively higher rates of adverse events in pathological fractures than those in non-pathological fractures; even non-pathological fractures have been associated with severe soft tissue injuries and multiple surgical procedures [7, 15, 28]. However, these studies included patients with different characteristics and various surgical procedures, for which the adverse events were not comparable. Hence, not only adverse events but also their consequences; including, readmission, reoperation, and mortality, need to be taking into consideration. These adverse events have been reported to increase mortality in patients with pathological fractures after an operation [7, 29]. Nonetheless, few studies have assessed the risk of reoperation and readmission, which are essential for further treatment planning [27]. Therefore, this study aimed to compare the risk of in-hospital adverse events and consequences after discharge, between patients with metastatic pathological and non-pathological femoral fractures undergoing intramedullary nailing. We hypothesized that patients with pathological femoral fractures had both more adverse events following surgical fixation as well as more undesired consequences.

Materials And Methods

Study design and sample

A retrospective study was conducted from October 2020 to February 2021 at Songklanagarind hospital, a tertiary hospital in Thailand. We retrieved the records of patients with femoral fractures undergoing intramedullary nailing, by using the International Classification of Diseases 9 Procedure (ICD-9): code 79.15, indicating a closed reduction of fractures with internal fixation of the femur from the Hospital Information System database; from June 1st, 2006 to June 30th, 2020. Patients aged 20–65 years and diagnosed with femoral shaft fractures were included. We only selected patients who underwent surgical fixation with a long intramedullary nail. Those who had a pathological fracture from a primary bone tumor, had metabolic bone disease, or had inadequate or missing information were excluded. The sample size was calculated based on the rates of adverse events in patients with pathological and non-pathological fractures of 23% and 7%, respectively. According to a 95% confidence interval, type II error of 20%, and the ratio of 1:4; at least 50 and 200 patients with pathological and non-pathological fractures were required.

Exposure and control

Patients, who had pathological fractures of the femoral shaft using the ICD-10: code M84.4x, undergoing intramedullary nailing and confirmed as pathological fractures from metastatic bone disease by medical record review, were assigned to be the pathological group as an exposure group. Those who had traumatic femoral shaft fractures using the ICD-10: code S72.x and were treated by intramedullary nailing called were assigned to be the non-pathological group as a control group.

Outcome measurement and independent variables

Outcomes measured in our study were in-hospital postoperative adverse events, which were classified as surgical and medical adverse events and their consequences, consisting of reoperation and readmission. Surgical adverse events were defined as surgical site infection that required debridement or prolonged antibiotics, wound dehiscence requiring resuture, hematoma surrounding the surgical wound, nerve injury or arterial injury presenting after surgery, or acute anemia having received blood transfusions within one day postoperatively. Medical adverse events were defined as sepsis or septic shock, unplanned intubation postoperatively, acute renal failure, pneumonia, urinary tract infection, cerebrovascular disorder, myocardial infarction, venous thromboembolism, or gastrointestinal bleeding. Readmission within one year due to the progression of their underlying metastatic cancer or problems resulting from any adverse event was also recorded. Reoperation was defined as an operation performed on a previously operated femur.

Patients' characteristics, including age, gender, body mass index (BMI), and comorbidities (hypertension, diabetes mellitus, thyroid disease, heart disease, lungs disease, renal disease, liver disease, cerebrovascular disease, rheumatic disorders, hematologic disorders, osteoporosis, and immunodeficiency syndrome) were reviewed and recorded in the data recording form. Preoperative (duration before surgery, preoperative hematocrit, and platelet), intraoperative (total blood loss, intraoperative blood transfusion, operative time), and postoperative information (volume of drainage, duration of admission) were also recorded.

Analysis

The data were entered in EpiData version 3.1 and analyzed using the R software version 4.0.3 (The R Foundation for Statistical Computing, 2020, Vienna, Austria). Patients' characteristics and surgical information between the exposure and control groups were analyzed using unpaired t-test, Wilcoxon rank-sum test, or Chi-square test as appropriate. We compared adverse events, reoperation, and readmission using univariate analysis and multiple logistic regression. Potential variables associated with adverse events, with a p-value less than 0.2 on univariate analysis, were included in the multiple logistic regression models for each outcome using backward stepwise selection. The associations of exposure to all outcomes were measured by the adjusted odds ratios (adjusted OR), with a 95% confidence interval (CI). Statistical significance was considered as a p-value less than 0.05.

Ethical consideration

This study was approved by Institutional Review Board, Faculty of Medicine, Songklanagarind Hospital, Prince of Songkla University (IRB number REC 63-426-11-1).

Results

Patients with pathological and non-pathological femoral shaft fractures operated on during the 14 years of the study period, accounting for 56 and 249, consecutively, were identified. The data of 48 patients with pathological femoral fractures and 185 patients with non-pathological fractures were analyzed for adverse events. Figure 1 shows the flow chart of patient inclusion in this retrospective study. Patient characteristics compared between the two groups are shown in Table 1. Patients with pathological femoral fractures from metastatic bone disease were more likely to be female, had no comorbidity, and were fractured at the proximal location. The mechanism of injury was significantly different when compared between the two groups ($p < 0.001$). Primary cancers that caused pathological fractures were the breast (33.3%) and lung (33.3%); which were predominately frequent, followed by thyroid (6.25%), kidney (6.25%), prostate (6.25%), and the others were nasopharynx, esophagus, liver, or colon. Table 2 shows preoperative, intraoperative, and postoperative parameters. Preoperative hematocrit in patients with pathological fractures were significantly lower than in those with non-pathological fractures ($p = 0.031$). Duration of operative time of fewer than 325 minutes ($p < 0.001$), and volume of drainage ($p = 0.003$) in patients with pathological fractures were significantly higher than those with non-pathological fractures.

Table 1
Patient characteristics compared between the two groups

| Type of Fracture | | | |
|---------------------------------------|---|--|---------|
| | Non-pathological fracture (n = 185) number (%) | Pathological fracture (n = 48) number (%) | p value |
| Age (years)* | | | < 0.001 |
| Median (IQR) | 28 (23,45) | 60.5 (49,67.2) | |
| Gender* | | | < 0.001 |
| Male | 142 (76.8) | 19 (39.6) | |
| Female | 43 (23.2) | 29 (60.4) | |
| Body mass index (kg/m ²)* | | | 0.003 |
| Median (IQR) | 22.6 (20.4,25.7) | 20.1 (19.1,21.8) | |
| Comorbidities | | | 0.128 |
| At least 1 comorbidity | 50 (27) | 19 (39.6) | |
| No comorbidity | 135 (73) | 29 (60.4) | |
| Location of fracture* | | | < 0.001 |
| Proximal shaft | 48 (25.9) | 31 (64.6) | |
| Midshaft | 128 (69.2) | 13 (27.1) | |
| Distal shaft | 9 (4.9) | 4 (8.3) | |
| Mechanism of injury* | | | < 0.001 |
| High injury | 165 (89.2) | 1 (2.1) | |
| Low injury | 20 (10.8) | 13 (27.1) | |
| No injury | 0 | 34 (70.8) | |
| <i>IQR</i> interquartile range | | | |
| *Statistical significance at p < 0.05 | | | |

Table 2

Preoperative, intraoperative, and postoperative parameters compared between the two groups

| Type of Fracture | | | |
|--|---------------------------|-----------------------|---------|
| | Non-pathological fracture | Pathological fracture | p value |
| Preoperative parameters | | | |
| Duration before surgery (days) | | | 0.52 |
| Median (IQR) | 8 (6,11) | 8 (5,15.5) | |
| Preoperative Hematocrit (%)* | | | 0.031 |
| Median (IQR) | 33.3 (30.1,38.2) | 32.3 (28.7,34.4) | |
| Preoperative Platelet (10 ⁹ /L) | | | 0.131 |
| Median (IQR) | 270 (202,366) | 311 (250.5,382) | |
| Intraoperative parameters | | | |
| Operative time (minutes)* | | | < 0.001 |
| Median (IQR) | 355 (267,435) | 247.5 (195,310) | |
| Total blood loss (ml) | | | 0.468 |
| Median (IQR) | 350 (200,500) | 400 (200,725) | |
| Blood transfusion (ml) | | | 0.06 |
| Median (IQR) | 0 (0,198) | 0 (0,249) | |
| Postoperative parameters | | | |
| Volume of drainage (ml)* | | | 0.003 |
| Median (IQR) | 80 (30,140) | 120 (51.5,250) | |
| Duration of admission (days) | | | 0.875 |
| Median (IQR) | 16 (12,21) | 15.5 (11.8,22.8) | |
| <i>IQR</i> interquartile range | | | |
| *Statistical significance at p < 0.05 | | | |

Rate of overall adverse events was 43.7% (102/233), of which were in pathological fractures (n = 32, 66.7%) and non-pathological fractures (n = 70, 37.8%). The rates of surgical and medical adverse events in both groups were 36.9% (n = 86) and 13.7% (n = 32), respectively (Table 3). There were significantly higher rates of surgical and medical adverse events in patients with pathological fractures compared with patients with non-pathological fractures (33% versus 52.1% and 8.1% versus 35.4%). Acute anemia was the most common adverse surgical event; accounting for 47.9% in pathological fractures and 29.2% in

non-pathological fractures. Septic shock and urinary tract infections in patients with pathological fractures were more common than in the other group. However, there was no incidence of vascular injury, wound dehiscence, or cerebrovascular disorder in either group. Factors associated with adverse events in the final model of multivariate regression analysis are presented in Fig. 2. After adjusting for all potential confounding factors in multivariate regression analysis, patients with pathological fractures had higher odds of overall adverse events (adjusted OR 3.98, 95% CI 1.85–8.56), adverse surgical events (adjusted OR 2.43, 95% CI 1.15–5.13), and adverse medical events (adjusted OR 2.81, 95% CI 1.13–7.03) than in those with the non-pathological fractures. In regard to consequences after discharge, there was an increased risk of readmission in the pathological group (adjusted OR 2.61, 95% CI 1.00–6.79). On the other hand, the risk of reoperation was not different (adjusted OR 0.23, 95% CI 0.02–2.14).

Table 3
Surgical and medical adverse events compared between the two groups

| | Type of Fracture | | Total | p value |
|---------------------------------------|---|-------------------------------------|--------------|-------------|
| | Non-pathological fracture number (%) | Pathological fracture number (%) | | |
| Surgical adverse event | 61 (33) | 25 (52.1) | 86 (36.9) | 0.023* |
| Surgical site infection | 1 (0.5) | 1 (2.1) | | 0.370 |
| Hematoma | 4 (2.2) | 2 (4.2) | | 0.606 |
| Acute anemia | 54 (29.2) | 23 (47.9) | | 0.022* |
| Nerve injury | 6 (3.2) | 0 | | 0.350 |
| Medical adverse event | 15 (8.1) | 17 (35.4) | 32 (13.7) | < 0.001* |
| Septic shock | 3 (1.6) | 4 (8.3) | | 0.030* |
| Acute renal failure | 3 (1.6) | 2 (4.2) | | 0.274 |
| Pneumonia | 4 (2.2) | 4 (8.3) | | 0.059 |
| Urinary tract infection | 2 (1.1) | 4 (8.3) | | 0.017* |
| Myocardial infarction | 0 | 1 (2.1) | | 0.206 |
| Gastrointestinal bleeding | 1 (0.5) | 1 (2.1) | | 0.370 |
| Unplanned intubation | 2 (1.1) | 1 (2.1) | | 0.501 |
| Venous thromboembolism | 3 (1.6) | 3 (6.2) | | 0.104 |
| *Statistical significance at p < 0.05 | | | | |

Discussion

Rates of any adverse events in patients with metastatic pathological femoral fractures were greater than those with non-pathological femoral fractures after adjusting with other potential factors. The risk of adverse surgical and medical events in the pathological group was around twofold to threefold higher than the other group. Patients with pathological fractures were more likely to be readmitted, but less likely to be re-operated on.

Rates of overall adverse events, regardless of the fracture type, in our study were markedly high compared to findings in previous studies, which had different fracture locations and outcome measurements [3, 7, 27, 29]. Regarding outcome measurements, other studies did not define acute postoperative anemia as an adverse event, whereas this was the most common adverse event in our study, leading to higher overall adverse event rates [3, 27]. However, if anemia was dismissed, the overall adverse event rates were similar to the study of Ristevski et al. [29] As to fracture locations, Behnke et al. [7] also included fractures at the spine, upper, or lower extremities, not only femur fractures, as in our study. Due to the wide range of fracture locations, the rates of adverse events were probably attenuated.

Acute postoperative anemia was the most frequent adverse surgical event following intramedullary nailing, which was consistent with a previous study that assumed that performing intramedullary nailing was susceptible to bleeding during canal reaming. This resulted in postoperative anemia, which in turn required postoperative blood transfusions [30]. Significantly higher acute anemia rates in patients with pathological fractures have been found. A possible explanation was that the ongoing bleeding effects and coagulopathic state from multiple traumas in the non-pathological group might lower than the chance of excessive bleeding from passing the long intramedullary nail through the tumor and type of primary cancer; particularly in highly vascularized tumor; including thyroid, prostate, and renal cancer [31–33]. Although intraoperative total blood loss and blood transfusions in our study were not different between both groups, the blood loss measured by the volume of drainage was higher in the pathological group, which supported the results of postoperative anemia. We could not establish any significance of surgical site infection, hematoma, or nerve injuries, because these event rates were low in both groups.

In line with adverse surgical events, risks of adverse medical events were greater in the pathological group. Septic shock and urinary tract infection were common adverse medical events that were higher in the pathological group than that of the non-pathological group. There was inconsistency with the findings of a previous study that included impending fractures undergoing prophylactic stabilization as a control group [27], while our study selected non-pathological fractures. High infection rates in pathological fractures could be explained through old age, low immunity, and the poor baseline status of patients with metastatic bone disease [34]. In addition, patients with pathological fractures required more time for ambulation, which increased the risk of urinary tract infection [35]. Even with slowly progressed ambulation, the incidences of venous thromboembolism events were not significantly increased in patients with pathological fractures because of medical and mechanical prophylaxis given during admission.

In our study, the readmission risk within one year was more than twice and approached significance, which was different from a previous study measuring readmission at only 30 postoperative days [27]. Due to the longer period of data collection in our study, it tended to include more readmission events from adverse events, added with disease progression in the pathological group. Although the previous study did not report on reoperation rates, we attempted to explore this issue, and found similar reoperation rates between the pathological and non-pathological groups. These findings may result from the hypothesis that the pathological group had lower survival rates, particularly in patients experiencing postoperative

complications [15, 27]. Additionally, the surgery goal for pathological fractures was only to improve quality of life; therefore, a second operation was rarely required, with the exception for postoperative complications [14, 16]. However, the goal of surgical fixation in both traumatic or non-pathological fractures is to provide stability and restore length, alignment, and rotation of the femur to achieve proper bony union. Some patients with this type of fracture were exposed to delayed union or nonunion risk factors; including, smoking history, open fractures, and severe enveloped soft tissue injury [36]. Consequently, they experienced a second surgery to assist in bone healing or to correct malalignment of the femur [37].

To our knowledge, no study has compared adverse events between patients with pathological and non-pathological femoral shaft fractures following surgical fixation. We followed the patients one year after discharge to observe the consequences of their surgical procedure. This study does have some limitations. First, this was a single-center study, which may limit the generalizability of its findings. Second, the sample size calculation considered the rates of any adverse events between the two groups that may have led to a small sample for specific adverse events. Third, we did not calculate the sample size based on multivariate analysis to identify other associated factors. Finally, this was a retrospective study in which some important data were not be recorded.

Recognizing the probability of postoperative adverse events in patients undergoing intramedullary nailing will assist clinicians in providing pertinent information to both patients and their families. Moreover, as a consequence of high adverse surgical and medical events rates, preoperative patient preparation should be heeded, especially reserved blood components. During the postoperative period, hematocrit and vital sign monitoring are suggested, due to the high risks of postoperative anemia and infection, along with promptly solving problems in case of any adverse events occurring. A further multi-center, prospective study with large sample size is suggested.

Conclusion

The risks of in-hospital postoperative adverse events were significantly greater in patients with metastatic pathological femoral shaft fractures than patients with non-pathological fractures undergoing intramedullary nailing after adjusting for potential confounders. Exploring through one-year follow-up, the risks of readmission in patients with pathological fractures seem higher; however, reoperation rates were not different. Counseling patients about the risk of adverse events along with well-prepared preoperatively patient care should be undertaken.

Abbreviations

ICD: International Classification of Diseases; BMI: body mass index; OR: odds ratio; CI: confidence interval; IQR: interquartile range

Declarations

Ethics approval and consent to participate

This systematic review was approved by Institutional Review Board, Faculty of Medicine, Songklanagarind Hospital, Prince of Songkla University (IRB number 64-159-11-1). Requirement for written informed consent by individual participants was waived.

Consent for publication

Not applicable

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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Authors' contribution

All authors were involved in study conceptualization and study design. CA: data collection, investigation, formal analysis, and writing - original draft. KI: visualization and validation. PT: Resources. BT: supervision and writing - editing manuscript. TL: formal analysis, result interpretation, and writing – review and editing manuscript. All authors read and approved the final manuscript for submission.

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Figures

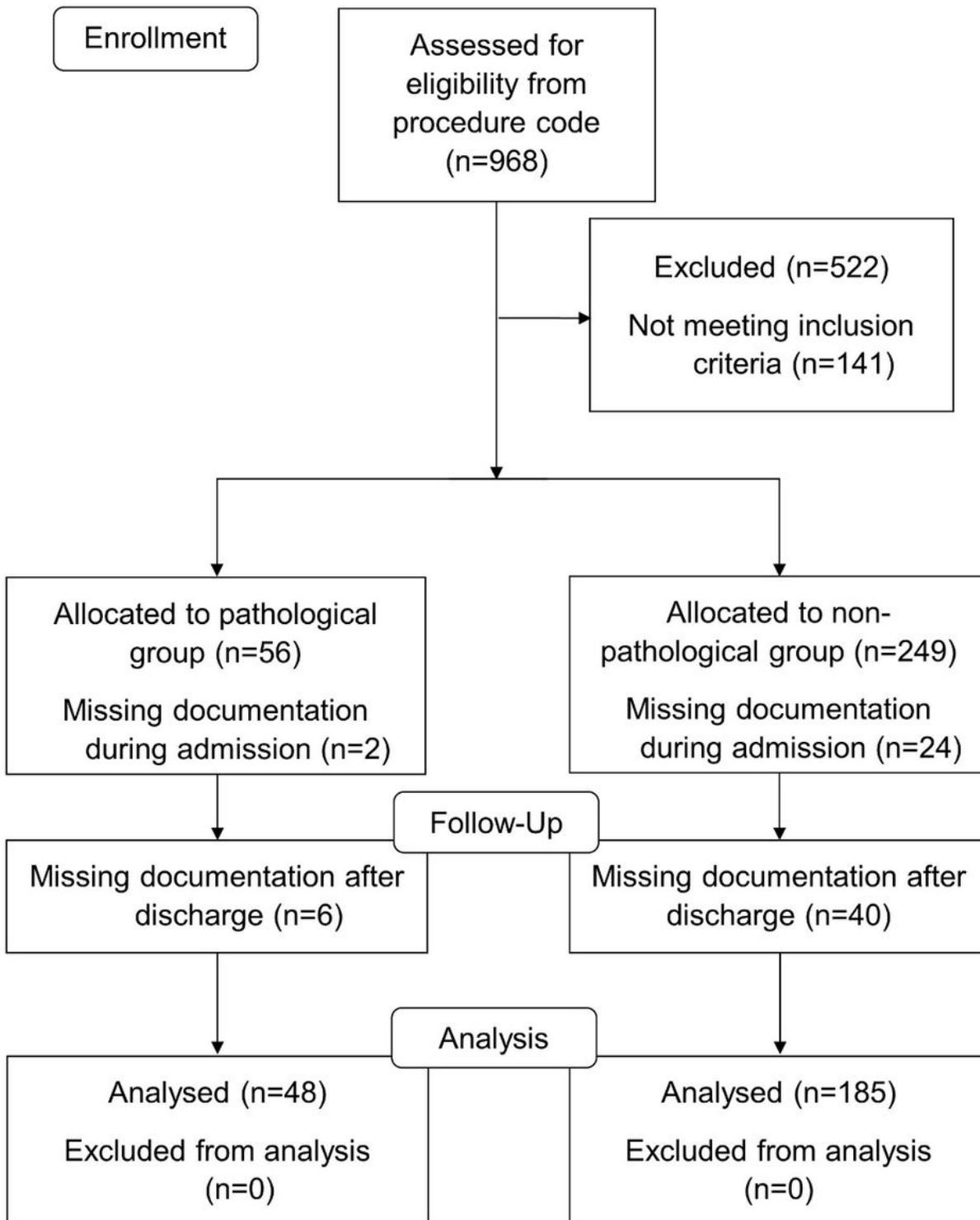
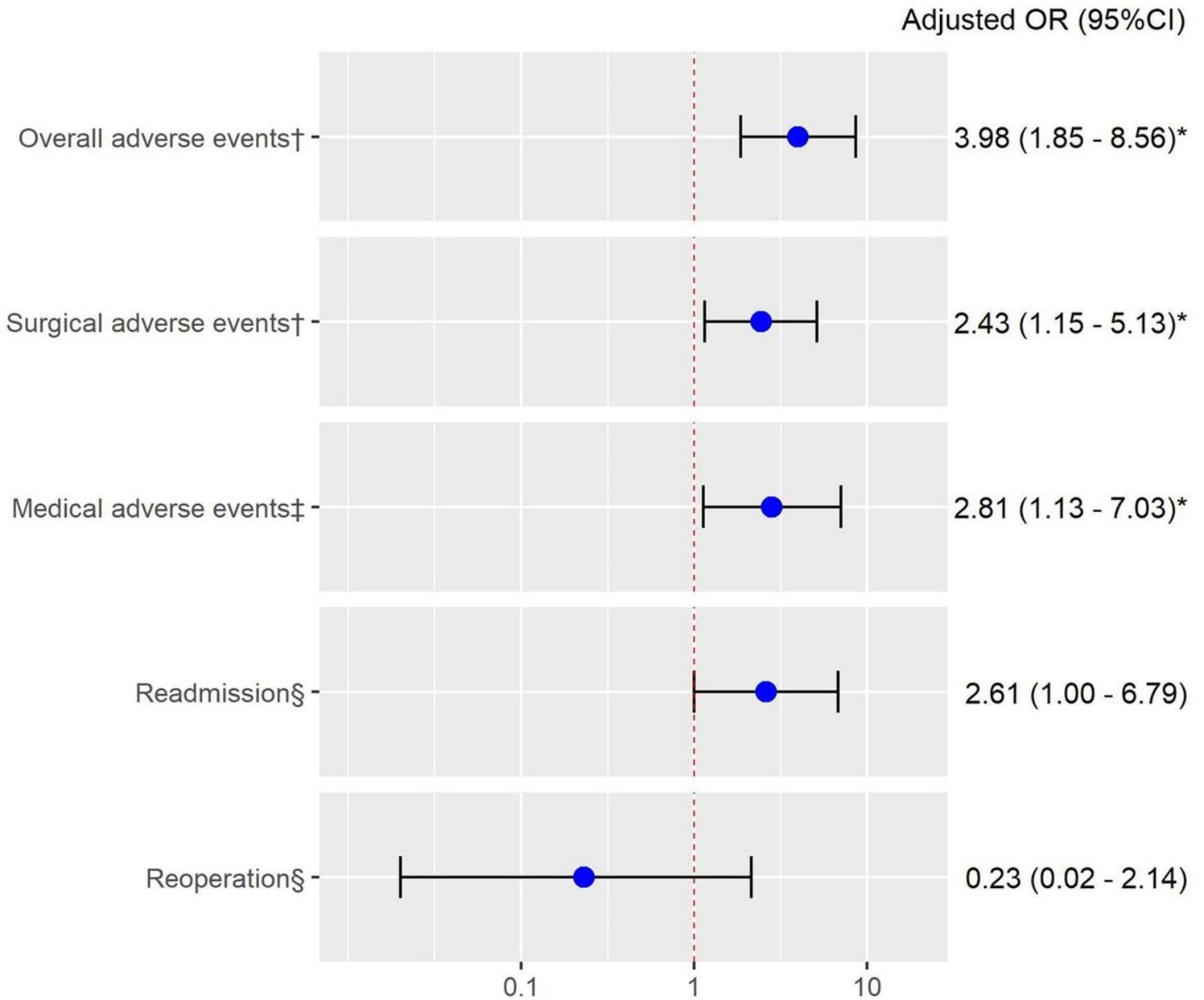


Figure 1

Patient enrollment flow chart



† Adjusting for operative time and postoperative drainage
 ‡ Adjusting for age and duration of admission
 § Adjusting for gender, medical, and adverse surgical events
 * Statistical significance at $p < 0.05$

Figure 2

Postoperative adverse events, reoperation, and readmission in pathological fractures compared to non-pathological fractures.