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Impact of Proton Pump Inhibitor Use on 90-Day and 2-Year Postoperative Complications Following Intermedullary Nailing for Intertrochanteric Femur Fractures and ORIF for Proximal Humerus Fractures: A Retrospective Cohort Study

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Impact of Proton Pump Inhibitor Use on 90-Day and 2-Year Postoperative Complications Following Intermedullary Nailing for Intertrochanteric Femur Fractures and ORIF for Proximal Humerus Fractures: A Retrospective Cohort Study

Purpose: To evaluate the association between proton pump inhibitor (PPI) and postoperative outcomes following intermedullary nailing (IMN) of intertrochanteric femur fractures and open reduction internal fixation (ORIF) of proximal humerus fractures.

Methods: Two parallel retrospective cohort analyses were performed using the TriNetX Research Network. Adults (>18 y/o) undergoing IMN for intertrochanteric fractures (n=10,605 per cohort) or ORIF for proximal humerus fractures (n=3,114 per cohort) were grouped by PPI use within 90 days preoperatively. Propensity score matching balanced demographic and clinical characteristics. Outcomes were assessed within 90 days and 2 years postoperatively, reported as risk ratios (RR) with significance as $p<0.05$.

Results: After IMN, PPI use was associated with an increased risk of pulmonary embolism (RR:1.4, p=0.014), acute kidney injury (RR:1.3, p=0.001), and myocardial infarction (RR:1.3, p=0.033 at 90-days follow-up. At 2-years, PPI use was linked to higher rates of deep vein thrombosis (RR:1.1, p=0.031), acute kidney injury (RR:1.2, p=0.006), and pneumonia (RR:1.1, p=0.010). After ORIF, PPI use within 90 days postoperatively was associated with wound disruption (RR:1.7, p=0.05), infection (RR:1.8, p=0.002), deep vein thrombosis (RR:1.8, p=0.026), and pulmonary embolism (RR:2.8, p=0.003). At the 2-years, PPI users experienced increased risks of infection (RR:1.5, p=0.003), DVT (RR:1.8, p=0.002), PE (RR:1.8, p=0.019), UTI (RR:1.3, p=0.022), nonunion (RR:1.7, p=0.004), and malunion (RR:2.1, p=0.025).

Conclusion: PPI use is associated with adverse postoperative outcomes following IMN of intertrochanteric fractures and ORIF for proximal humerus fractures. Prospective studies are needed to clarify the causal relationships and isolate the effect of PPI use on postoperative outcomes.

Key Words: Proton pump inhibitors; intertrochanteric fractures; proximal humerus fractures; postoperative complications

Level of Evidence: Level III

Introduction

Intertrochanteric femur fractures are common injuries, particularly among older adults, and are associated with significant morbidity and mortality if not treated appropriately [1-4]. Surgical management, typically via intermedullary nailing, is indicated to restore hip stability, allow early weight-bearing, and prevent complications from prolonged immobility such as thromboembolic events or pneumonia [5-7]. The American Academy of Orthopaedic Surgeons (AAOS) clinical practice guidelines recommend prompt surgical fixation for these fractures to optimize functional recovery and minimize systemic complications [8]. Intertrochanteric fractures are extracapsular, often unstable, and biomechanically distinct from other proximal femur fractures, which makes intramedullary fixation particularly advantageous in providing load-sharing support and early mobilization [6,9,10]. Previous research has explored perioperative factors affecting outcomes such as infection, hardware failure, and thromboembolic risk, but few studies have specifically addressed the influence of commonly prescribed medications like proton pump inhibitors (PPIs) on postoperative outcomes in this population.

Proximal humerus fractures, in contrast, occur in the upper extremity and are typically managed surgically with open reduction and internal fixation (ORIF) when displaced or unstable, particularly in active patients or those with poor functional reserve [11,12]. Unlike intertrochanteric femur fractures, proximal humerus fractures do not directly bear weight, and their complications are often more localized, including malunion, nonunion, or hardware-related issues, rather than systemic sequelae [13-15]. Research on postoperative outcomes in this population has largely focused on functional recovery, infection, and need for revision surgery, with limited data on how medications such as PPIs may impact both systemic and local complications following surgery [11,13,16]. The differing biomechanics, loading characteristics, and complication profiles between these two fracture types make it important to evaluate the effect of PPI use separately in each surgical cohort.

Proton pump inhibitors (PPIs) are widely prescribed for gastroesophageal reflux disease, peptic ulcer disease, and other acid-related gastrointestinal conditions [17-19]. While generally considered safe, chronic PPI use has been associated with impaired calcium absorption, decreased bone mineral density, and increased risk of fractures, raising concern for postoperative outcomes in orthopedic patients [20-22]. Prior studies have linked PPI use to delayed fracture healing, higher infection risk, and increased systemic complications, but evidence remains limited and largely focused on hip fracture populations or general surgical cohorts [23,24]. Despite the widespread use of PPIs,

few studies have rigorously assessed their impact on postoperative complications following intermedullary nailing for intertrochanteric femur fractures or ORIF for proximal humerus fractures.

There remains a gap in the literature regarding the effect of PPI use on both short-term (90-day) and long-term (2-year) postoperative outcomes, including systemic complications, wound healing, thromboembolic events, and need for revision surgery in these specific fracture populations. Both intertrochanteric femur fractures and proximal humerus fractures occur predominantly in older adults, a demographic with heightened vulnerability to postoperative complications due to factors such as frailty, multimorbidity, and polypharmacy, further emphasizing the importance of understanding how medications like PPIs may influence outcomes in these high-risk patients. The purpose of this study is to evaluate the association between perioperative PPI use and postoperative complications following intertrochanteric femur and proximal humerus fracture fixation using a large, multicenter electronic health record database. We hypothesize that PPI use within 90 days of surgery is associated with an increased risk of both systemic and local postoperative complications compared to patients not taking PPIs.

Methods

Database

A retrospective cohort study was conducted using the TriNetX Research Network, a global federated database of de-identified electronic medical records (EMRs) from over 100 healthcare organizations, including academic medical centers, community hospitals, and specialty clinics. The database contains approximately 105 million patient records and provides real-time access to demographics, diagnoses, procedures, medications, and laboratory results. All data are de-identified in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and General Data Protection Regulation (GDPR), making this study exempt from institutional review board (IRB) oversight.

Patient Population

Adult patients aged 18 years or older who underwent either intermedullary nailing for intertrochanteric femur fractures (CPT: [27245]) or ORIF for proximal humerus fractures (CPT: [23615, 23616]) between January 1, 2000, and January 10, 2023, were identified. Patients were stratified into two cohorts based on documented PPI use within 90 days prior to surgery: (1) PPI users and (2) non-users. Patients with incomplete follow-up data, pathological

fractures, or prior surgeries at the affected site were excluded. Propensity score matching was employed to balance baseline characteristics, including age, sex, race, body mass index (BMI), and common comorbidities such as diabetes, hypertension, chronic kidney disease, and cardiovascular disease.

Demographics, Comorbidities, and Outcome Variables

Baseline demographics included age, sex, race/ethnicity, and BMI. Clinical comorbidities assessed prior to surgery were incorporated into propensity score matching to ensure comparable cohorts. Primary outcomes included postoperative complications within 90 days and 2 years, specifically infection, wound disruption, sepsis, thromboembolic events (DVT and PE), acute kidney injury, myocardial infarction, pneumonia, urinary tract infection, malunion, nonunion, and the need for revision surgery or hardware removal. Outcomes were identified using validated ICD-10 diagnosis and procedural codes available within the TriNetX platform.

Data Analysis

Descriptive statistics were used to summarize patient demographics, comorbidities, and outcome frequencies. Categorical variables were compared using chi-square tests, while continuous variables were compared using Student's t-tests, with statistical significance set at $p < 0.05$. Propensity score matching was performed using a 1:1 greedy nearest-neighbor algorithm without replacement to create balanced PPI user and non-user cohorts for each fracture type. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for all outcomes at 90 days and 2 years postoperatively. Pairwise comparisons were performed to evaluate differences between PPI users and non-users in both intertrochanteric femur and proximal humerus fracture cohorts. All statistical analyses were conducted using the TriNetX Analytics platform (TriNetX, LLC, Cambridge, MA), which utilizes SQL, R, and Python for data management and modeling.

Results

Demographics and Baseline Characteristics

For the proximal humerus fracture cohort, 3,800 PPI users and 9,361 non-users were identified prior to matching. Following 1:1 propensity score matching, 3,114 patients were included in each group. The mean age was 59.4 ± 14.2 years in the PPI group and 59.9 ± 14.0 years in the non-user group. Female patients represented 60.7% of PPI

users and 60.5% of controls. Mean BMI was 29.1 ± 7.3 kg/m² among PPI users and 29.0 ± 7.0 kg/m² in non-users. (Table 1)

For the intertrochanteric fracture cohort, 15,392 PPI users and 21,024 non-users were identified prior to matching. After 1:1 propensity score matching, each group included 10,605 patients. The mean age was 68.4 ± 14.6 years in the PPI cohort and 68.9 ± 14.9 years in the non-PPI cohort. Females comprised 54.4% of the PPI group and 54.5% of the non-user group. Mean BMI was 26.1 ± 6.6 kg/m² for PPI users and 26.0 ± 6.4 kg/m² for controls. (Table 2)

Proximal Humerus Fracture Outcomes

At 90 days postoperatively, PPI use was significantly associated with higher risks of wound disruption (RR 1.68, 95% CI 1.00–2.84, p=0.040), infection (RR 1.76, 95% CI 1.22–2.52, p=0.002), sepsis (RR 2.31, 95% CI 1.50–3.56, p<0.001), deep vein thrombosis (RR 1.79, 95% CI 1.07–3.02, p=0.026), pulmonary embolism (RR 2.81, 95% CI 1.37–5.78, p=0.003), and all-cause mortality (RR 2.00, 95% CI 1.33–3.01, p=0.001). (Table 3, Figure 1)

At 2 years postoperatively, PPI users demonstrated higher risks of malunion (RR 2.09, 95% CI 1.08–4.04, p=0.025) and nonunion (RR 1.69, 95% CI 1.17–2.42, p=0.004), while no significant differences were observed for mechanical complications (RR 1.15, 95% CI 0.88–1.52, p=0.305) or revision of proximal humerus fixation (RR 0.87, 95% CI 0.63–1.20, p=0.396). (Table 4, Figure 2)

Intertrochanteric Femur Fracture Outcomes

Within 90 days postoperatively, PPI use was associated with increased risk of infection (RR 1.60, 95% CI 1.30–1.98, p<0.001), sepsis (RR 1.91, 95% CI 1.66–2.19, p<0.001), deep vein thrombosis (RR 1.20, 95% CI 1.00–1.45, p=0.049), pulmonary embolism (RR 1.41, 95% CI 1.07–1.86, p=0.014), and all-cause mortality (RR 1.43, 95% CI 1.30–1.59, p<0.001). Wound disruption trended toward significance (RR 1.30, 95% CI 1.00–1.68, p=0.052). (Table 3, Figure 1)

At the 2-year follow-up, no statistically significant associations were observed between PPI use and mechanical complication (RR 1.18, 95% CI 0.99–1.41, p=0.063), malunion (RR 1.43, 95% CI 0.88–2.31, p=0.145), nonunion (RR 1.18, 95% CI 0.94–1.50, p=0.162), or revision of intramedullary fixation (RR 1.04, 95% CI 0.89–1.22, p=0.613). (Table 4, Figure 2)

Discussion

In this study, proton pump inhibitor (PPI) use within 90 days before surgery was associated with significantly higher risks of several postoperative complications in both intertrochanteric femur fractures managed with intramedullary nailing and proximal humerus fractures treated with ORIF. Specifically, PPI use correlated with increased short-term infection, sepsis, thromboembolic events, and mortality in the intertrochanteric fracture cohort, and with wound disruption, infection, sepsis, thromboembolic events, and mortality in the proximal humerus group. Longer-term outcomes revealed elevated risks of malunion and nonunion following humerus fracture fixation. These findings suggest that PPI exposure may contribute to systemic complications and impaired fracture healing postoperatively.

Prior orthopedic literature has suggested that PPI use may increase risk of infection, including prosthetic joint infection, potentially through alterations in gastrointestinal flora, hypochlorhydria, and micro aspiration leading to bacterial colonization [19,25]. For example, a recent case-cohort study of total hip arthroplasty patients found an association between PPI use and prosthetic joint infection [25]. In this study, PPI use was significantly associated with higher infection and sepsis rates after both intertrochanteric and proximal humerus fracture surgery, particularly in the 90-day postoperative period. This aligns with previous reports, although our data extend these findings to non-arthroplasty fracture fixation settings [26]. Biologically, acid suppression from PPIs can lead to changes in gastric pH that may promote bacterial overgrowth and reduce the barrier against pathogens, potentially increasing risk of postoperative infection [27-29]. Additionally, PPIs have been associated with impaired neutrophil function and reduced immune response, which could further compromise postoperative healing and infection resistance [30].

The observed increase in deep vein thrombosis (DVT) and pulmonary embolism (PE) among PPI users is less well-documented in the orthopedic trauma literature, though some studies suggest that PPI use may be associated with prothrombotic states or vascular events through mechanisms including elevated serum gastrin levels and hypomagnesemia.[31] In this intertrochanteric fracture cohort, PPI use was significantly associated with both DVT and PE in the short-term follow-up, while in the proximal humerus group, PPI use conferred even higher relative risks of DVT and especially PE. These findings diverge somewhat from the broader literature, which has focused more on fracture risk and less on postoperative thrombotic events. Mechanistically, PPIs can lead to magnesium depletion, which in turn may affect endothelial function and increase coagulation tendency [32-34]. Additionally, systemic

inflammation following surgery, combined with potential immune modulation by PPIs, could further increase thrombotic risk in vulnerable patients [35,36].

The association between PPI use and increased all-cause mortality in both fracture cohorts is consistent with some prior observational studies, particularly in hospitalized patients or those with serious comorbidity burden [37]. This study's findings reinforce the notion that PPI use may act as a marker for frailty or underlying illness severity; alternatively, PPIs themselves may contribute to adverse outcomes via mechanisms such as increased risk of infections, electrolyte disturbances (e.g., hypomagnesemia), or medication interactions [32-34]. Importantly, these risks were evident in the short-term postoperative period, underscoring the need for careful consideration of PPI use in patients undergoing fracture fixation.

In the proximal humerus cohort, but not the intertrochanteric group, PPI use was associated with higher rates of malunion and nonunion at 2-year follow-up. This aligns with preclinical and observational data suggesting that PPIs may impair fracture healing, even following surgical fixation [38,39,40,41]. A meta-analysis of observational studies demonstrated modestly increased fracture risk associated with chronic PPI use [38]. This study's results provide further clinical evidence that PPI use may negatively influence fracture healing in lower extremity surgical patients. Mechanistically, PPIs may reduce calcium solubility in the stomach, leading to hypocalcemia and subsequent secondary hyperparathyroidism, which could increase bone resorption [42,43]. Reduced magnesium absorption, vitamin B12 deficiency, and altered gut microbiota may also play secondary roles in impairing bone metabolism and healing [22,44].

Limitations and Strengths

This study has several important limitations. First, its retrospective cohort design introduces the possibility of residual confounding despite the use of propensity score matching. Although demographic and clinical factors such as age, sex, BMI, and comorbidities were balanced between cohorts, unmeasured variables—including socioeconomic status, frailty, nutritional status, and detailed perioperative management—may have influenced both PPI use and postoperative outcomes. Second, the TriNetX database relies on accurate coding, and miscoding or underreporting of exposures and outcomes could bias results. Third, the definition of PPI exposure as use within 90 days preoperatively does not fully capture duration, dosage, or adherence, limiting assessment of dose–response

effects. Similarly, our analysis could not differentiate between short-term versus chronic PPI users, which may carry different risks. Fourth, cause-and-effect relationships cannot be inferred, and PPI use may function as a surrogate marker of underlying disease severity or comorbidity rather than as a direct contributor to adverse outcomes.

Despite these limitations, the study has notable strengths. It leverages a large, multicenter, real-world dataset, allowing for adequate power to detect differences across two distinct orthopedic procedures. The use of propensity score matching minimized baseline imbalances and strengthened the validity of comparisons between PPI users and non-users. Additionally, the evaluation of both short-term (90-day) and long-term (2-year) outcomes provides a comprehensive view of the potential impact of PPI use on both systemic complications and fracture healing. By examining two fracture types with different biomechanical and biological healing environments, this study offers broader insights into the potential role of PPIs in orthopedic postoperative care.

Conclusion

Proton pump inhibitor use is associated with significantly higher risks of systemic complications- including infection, sepsis, thromboembolic events, and mortality- following both intertrochanteric femur fracture fixation and proximal humerus fracture fixation. Importantly, no increase in revision rates was observed, suggesting that PPI-related risks are driven primarily by systemic rather than local surgical factors. Given the widespread use and accessibility of PPIs, these findings highlight a modifiable perioperative risk factor that warrants careful consideration in orthopedic surgical candidates. Future prospective and randomized studies are needed to delineate the causal mechanisms, clarify the impact of dosage and duration, and guide evidence-based perioperative management of patients requiring acid suppression therapy.

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Tables

Table 1: Demographics of Preoperative PPI Use on Proximal Humerus ORIF Surgery: PPI Use vs No PPI Use

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Table 3: Ninety-Day Postoperative Outcomes of Proximal Humerus and Intertrochanteric Femur Fractures Comparing PPI use vs No PPI Use

Table 4: Two-Year Postoperative Outcomes of Proximal Humerus and Intertrochanteric Femur Fractures Comparing PPI use vs No PPI Use

Figure 1: Ninety-Day Postoperative Outcomes Associated With PPI Use

Figure 2: Two-Year Postoperative Outcomes Associated With PPI Use

Table 1: Demographics of Preoperative PPI Use on Proximal Humerus ORIF Surgery: PPI Use vs No PPI Use

Category	Variable	Before PPI (N=3,800)	Before No PPI (N=9,361)	p-value	After PPI (N=3,114)	After No PPI (N=3,114)	p-value
Demographics	Age at Index (mean ± SD)	60.3 ± 13.8 (n=3,787)	56.6 ± 15.3 (n=9,149)	<0.001	59.4 ± 14.2	59.9 ± 14.0	0.154
	White	3,019 (79.7%)	7,068 (77.3%)	0.002	2,474 (79.4%)	2,520 (80.9%)	0.144
	American Indian / Alaska Native	10 (0.3%)	24 (0.3%)	0.986	10 (0.3%)	10 (0.3%)	1.000

	Female	2,326 (61.4%)	5,506 (60.2%)	0.189	1,891 (60.7%)	1,885 (60.5%)	0.876
	Native Hawaiian / Pacific Islander	10 (0.3%)	19 (0.2%)	0.537	10 (0.3%)	10 (0.3%)	1.000
	Not Hispanic / Latino	2,567 (67.8%)	6,063 (66.3%)	0.096	2,110 (67.8%)	2,132 (68.5%)	0.550
	Hispanic / Latino	185 (4.9%)	498 (5.4%)	0.197	151 (4.8%)	162 (5.2%)	0.523
	Black	230 (6.1%)	572 (6.3%)	0.701	193 (6.2%)	185 (5.9%)	0.671
	Male	1,279 (33.8%)	3,116 (34.1%)	0.756	1,077 (34.6%)	1,104 (35.5%)	0.473
	Other Race	67 (1.8%)	236 (2.6%)	0.006	59 (1.9%)	57 (1.8%)	0.851
	Asian	52 (1.4%)	206 (2.3%)	0.001	46 (1.5%)	34 (1.1%)	0.177
Diagnoses	Asthma	412 (10.9%)	558 (6.1%)	<0.001	284 (9.1%)	295 (9.5%)	0.631
	COPD	498 (13.2%)	483 (5.3%)	<0.001	313 (10.1%)	316 (10.1%)	0.900
	CAD	554 (14.6%)	585 (6.4%)	<0.001	366 (11.8%)	368 (11.8%)	0.937
	History of nicotine dependence	534 (14.1%)	718 (7.8%)	<0.001	378 (12.1%)	386 (12.4%)	0.757
	Heart failure	367 (9.7%)	319 (3.5%)	<0.001	227 (7.3%)	213 (6.8%)	0.489

	Hypertension	2,127 (56.2%)	3,094 (33.8%)	<0.001	1,577 (50.6%)	1,595 (51.2%)	0.648
	CKD	400 (10.6%)	384 (4.2%)	<0.001	257 (8.3%)	261 (8.4%)	0.854
	Nicotine dependence	817 (21.6%)	1,363 (14.9%)	<0.001	616 (19.8%)	625 (20.1%)	0.775
	Alcohol-related disorders	526 (13.9%)	721 (7.9%)	<0.001	375 (12.0%)	381 (12.2%)	0.816
	GERD	1,452 (38.3%)	873 (9.5%)	<0.001	803 (25.8%)	792 (25.4%)	0.749
	Hyperlipidemia	1,261 (33.3%)	1,666 (18.2%)	<0.001	900 (28.9%)	903 (29.0%)	0.933
	Other anemias	815 (21.5%)	771 (8.4%)	<0.001	575 (18.5%)	430 (13.8%)	<0.001
	Type 2 diabetes	904 (23.9%)	1,224 (13.4%)	<0.001	651 (20.9%)	658 (21.1%)	0.828
	Vitamin D deficiency	429 (11.3%)	650 (7.1%)	<0.001	317 (10.2%)	312 (10.0%)	0.833
	Liver disease	452 (11.9%)	444 (4.9%)	<0.001	306 (9.8%)	301 (9.7%)	0.831
	Osteoporosis	491 (13.0%)	641 (7.0%)	<0.001	345 (11.1%)	348 (11.2%)	0.904
	Depressive episode	948 (25.0%)	1,097 (12.0%)	<0.001	640 (20.6%)	627 (20.1%)	0.682
	Major depressive disorder	175 (4.6%)	207 (2.3%)	<0.001	122 (3.9%)	117 (3.8%)	0.742

Medications	Opioids	3,383 (89.3%)	6,015 (65.7%)	<0.001	2,712 (87.1%)	2,698 (86.6%)	0.599
	Glucocorticoids	1,830 (48.3%)	2,383 (26.0%)	<0.001	1,337 (42.9%)	1,353 (43.4%)	0.682
Laboratory	BMI (mean ± SD)	29.2 ± 7.4 (n=2,540)	28.3 ± 6.9 (n=5,098)	<0.001	29.1 ± 7.3 (n=2,026)	29.0 ± 7.0 (n=1,980)	0.692
	BMI 0–20	309 (8.2%)	569 (6.2%)	<0.001	233 (7.5%)	220 (7.1%)	0.526
	BMI 20–25	867 (22.9%)	1,807 (19.8%)	<0.001	678 (21.8%)	655 (21.0%)	0.477
	BMI 25–30	1,129 (29.8%)	2,013 (22.0%)	<0.001	873 (28.0%)	892 (28.6%)	0.593
	BMI 30–35	833 (22.0%)	1,388 (15.2%)	<0.001	633 (20.3%)	643 (20.6%)	0.754
	BMI 35–40	493 (13.0%)	790 (8.6%)	<0.001	373 (12.0%)	380 (12.2%)	0.786
	BMI 40–100	315 (8.3%)	441 (4.8%)	<0.001	230 (7.4%)	229 (7.4%)	0.961

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Table 2: Demographics of Preoperative PPI Use on Intermedullary Nailing for Intertrochanteric Femur Fracture Surgery: PPI Use vs No PPI Use

Category	Variable	Before PPI (N=15,392)	Before No PPI (N=21,024)	p-value	After PPI (N=10,605)	After No PPI (N=10,605)	p-value	Std Diff
Demographics	Age at Index (mean ± SD)	69.4 ± 13.6	66.4 ± 16.7	<0.001	68.4 ± 14.6	68.9 ± 14.9	0.030	0.199 → 0.030

	White	12,054 (78.3%)	15,430 (74.3%)	<0.001	8,218 (77.5%)	8,302 (78.3%)	0.165	0.095 → 0.019
	American Indian / Alaska Native	32 (0.2%)	47 (0.2%)	0.711	25 (0.2%)	32 (0.3%)	0.353	0.004 → 0.013
	Female	8,511 (55.3%)	10,779 (51.9%)	<0.001	5,766 (54.4%)	5,775 (54.5%)	0.901	0.068 → 0.002
	Native Hawaiian / Pacific Islander	11 (0.1%)	27 (0.1%)	0.089	10 (0.1%)	10 (0.1%)	1.000	0.018 → <0.001
	Not Hispanic / Latino	11,146 (72.4%)	14,248 (68.6%)	<0.001	7,558 (71.3%)	7,643 (72.1%)	0.195	0.084 → 0.018
	Hispanic / Latino	736 (4.8%)	1,155 (5.6%)	0.001	582 (5.5%)	532 (5.0%)	0.124	0.035 → 0.021
	Black	1,115 (7.2%)	1,652 (8.0%)	0.012	817 (7.7%)	803 (7.6%)	0.717	0.027 → 0.005
	Male	5,823 (37.8%)	8,204 (39.5%)	0.001	4,179 (39.4%)	4,208 (39.7%)	0.684	0.034 → 0.006
	Other Race	244 (1.6%)	442 (2.1%)	<0.001	195 (1.8%)	178 (1.7%)	0.375	0.040 → 0.012
	Asian	268 (1.7%)	401 (1.9%)	0.186	204 (1.9%)	196 (1.8%)	0.686	0.014 → 0.006

Diagnoses	Asthma	1,391 (9.0%)	1,081 (5.2%)	<0.001	720 (6.8%)	755 (7.1%)	0.345	0.149 → 0.013
	COPD	3,789 (24.6%)	2,721 (13.1%)	<0.001	2,069 (19.5%)	2,017 (19.0%)	0.365	0.298 → 0.012
	CAD	4,667 (30.3%)	3,363 (16.2%)	<0.001	2,582 (24.3%)	2,590 (24.4%)	0.898	0.339 → 0.002
	History of nicotine dependence	3,632 (23.6%)	2,817 (13.6%)	<0.001	2,002 (18.9%)	2,005 (18.9%)	0.958	0.260 → 0.001
	Heart failure	3,810 (24.8%)	2,573 (12.4%)	<0.001	2,060 (19.4%)	2,010 (19.0%)	0.383	0.322 → 0.012
	Hypertension	11,004 (71.5%)	10,623 (51.2%)	<0.001	6,841 (64.5%)	6,884 (64.9%)	0.537	0.427 → 0.008
	CKD	3,867 (25.1%)	2,815 (13.6%)	<0.001	2,131 (20.1%)	2,108 (19.9%)	0.693	0.296 → 0.005
	Nicotine dependence	3,477 (22.6%)	3,765 (18.1%)	<0.001	2,242 (21.1%)	2,218 (20.9%)	0.686	0.111 → 0.006
	Alcohol-related disorders	1,671 (10.9%)	1,668 (8.0%)	<0.001	1,044 (9.8%)	1,026 (9.7%)	0.677	0.097 → 0.006
	GERD	6,971 (45.3%)	2,499 (12.0%)	<0.001	2,447 (23.1%)	2,445 (23.1%)	0.974	0.791 → <0.001

	Hyperlipidemia	7,320 (47.6%)	6,424 (30.9%)	<0.001	4,287 (40.4%)	4,262 (40.2%)	0.726	0.346 → 0.005
	Other anemias	5,801 (37.7%)	3,891 (18.7%)	<0.001	3,392 (32.0%)	2,663 (25.1%)	<0.001	0.431 → 0.153
	Type 2 diabetes	5,046 (32.8%)	4,301 (20.7%)	<0.001	2,999 (28.3%)	3,029 (28.6%)	0.648	0.275 → 0.006
	Vitamin D deficiency	2,462 (16.0%)	2,383 (11.5%)	<0.001	1,414 (13.3%)	1,445 (13.6%)	0.533	0.132 → 0.009
	Liver disease	2,078 (13.5%)	1,252 (6.0%)	<0.001	1,027 (9.7%)	1,012 (9.5%)	0.727	0.254 → 0.005
	Osteoporosis	3,567 (23.2%)	3,445 (16.6%)	<0.001	2,111 (19.9%)	2,095 (19.8%)	0.783	0.166 → 0.004
	Depressive episode	4,499 (29.2%)	3,556 (17.1%)	<0.001	2,470 (23.3%)	2,452 (23.1%)	0.770	0.290 → 0.004
	Major depressive disorder	762 (5.0%)	671 (3.2%)	<0.001	437 (4.1%)	397 (3.7%)	0.158	0.087 → 0.019
Medications	Opioids	14,005 (91.0%)	14,271 (68.7%)	<0.001	9,285 (87.6%)	9,269 (87.4%)	0.740	0.579 → 0.005
	Glucocorticoids	8,369 (54.4%)	6,131 (29.5%)	<0.001	4,956 (46.7%)	4,968 (46.8%)	0.869	0.521 → 0.002

Laboratory	BMI (mean ± SD)	26.3 ± 6.6	25.6 ± 6.2	<0.001	26.1 ± 6.6	26.0 ± 6.4	0.282	0.104 → 0.019
	BMI 0–20	2,409 (15.7%)	2,411 (11.6%)	<0.001	1,545 (14.6%)	1,475 (13.9%)	0.169	0.118 → 0.019
	BMI 20–25	4,986 (32.4%)	5,190 (25.0%)	<0.001	3,240 (30.6%)	3,199 (30.2%)	0.540	0.164 → 0.008
	BMI 25–30	5,007 (32.5%)	4,469 (21.5%)	<0.001	3,065 (28.9%)	3,109 (29.3%)	0.506	0.250 → 0.009
	BMI 30–35	2,837 (18.4%)	2,348 (11.3%)	<0.001	1,671 (15.8%)	1,613 (15.2%)	0.271	0.201 → 0.015
	BMI 35–40	1,308 (8.5%)	944 (4.5%)	<0.001	726 (6.8%)	714 (6.7%)	0.743	0.161 → 0.004
	BMI 40–100	741 (4.8%)	528 (2.5%)	<0.001	409 (3.9%)	409 (3.9%)	1.000	0.121 → <0.001

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Table 3: Ninety-Day Postoperative Outcomes of Proximal Humerus and Intertrochanteric Femur Fractures Comparing PPI use vs No PPI Use

	Proximal Humerus ORIF		**Intertrochanteric IMN**	
Outcome	**RR (95% CI)**	**p-value**	**RR (95% CI)**	**p-value**
Wound disruption	1.68 (1.00–2.84)	0.040	1.30 (1.00–1.68)	0.052
Infection	1.76 (1.22–2.52)	0.002	1.60 (1.30–1.98)	<0.001

Sepsis	2.31 (1.50–3.56)	<0.001	1.91 (1.66–2.19)	<0.001
Deep vein thrombosis	1.79 (1.07–3.02)	0.026	1.20 (1.00–1.45)	0.049
Pulmonary embolism	2.81 (1.37–5.78)	0.003	1.41 (1.07–1.86)	0.014
All-cause mortality	2.00 (1.33–3.01)	0.001	1.43 (1.30–1.59)	<0.001

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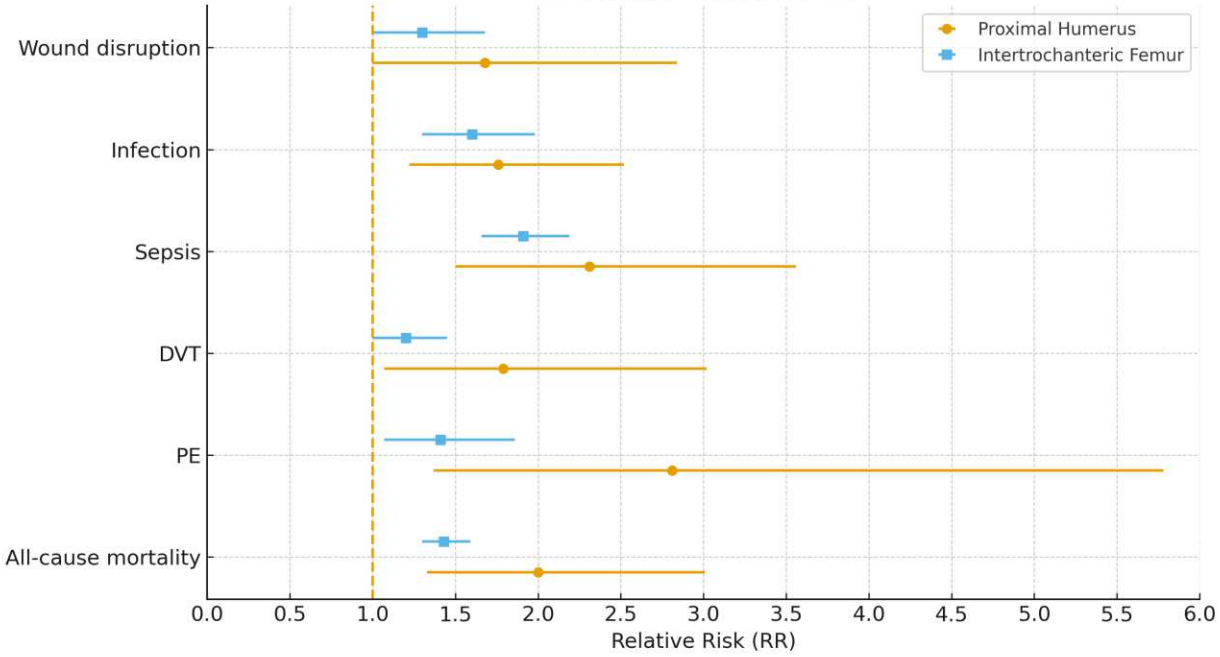
Table 4: Two-Year Postoperative Outcomes of Proximal Humerus and Intertrochanteric Femur Fractures Comparing PPI use vs No PPI Use

	Proximal Humerus ORIF		**Intertrochanteric IMN**	
Outcome	**RR (95% CI)**	**p-value**	**RR (95% CI)**	**p-value**
Malunion	2.09 (1.08–4.04)	0.025	1.43 (0.88–2.31)	0.145
Nonunion	1.69 (1.17–2.42)	0.004	1.18 (0.94–1.50)	0.162
Mechanical complication	1.15 (0.88–1.52)	0.305	1.18 (0.99–1.41)	0.063
Revision surgery	0.87 (0.63–1.20)	0.396	1.04 (0.89–1.22)	0.613

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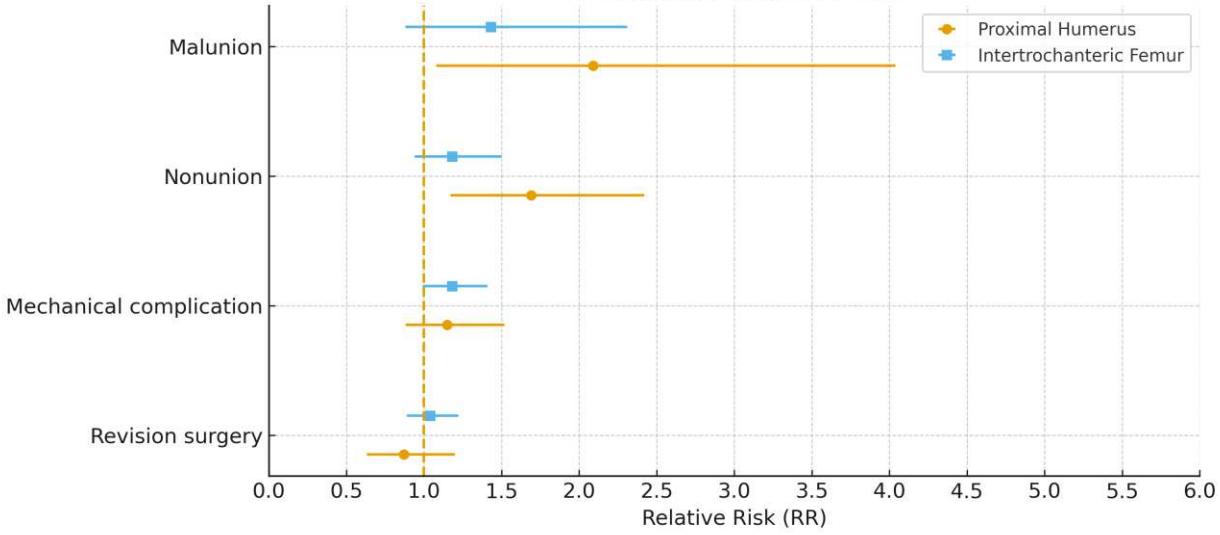
Figure 1. Ninety-Day Postoperative Outcomes Associated With PPI Use



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Figure 2. Two-Year Postoperative Outcomes Associated With PPI Use



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