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Original article

Unplanned emergency department visits within 90 days of hip hemiarthroplasty for osteoporotic femoral neck fractures: Reasons, risks, and mortalities

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1 . A B S T R A C T

Objectives: Bipolar hemiarthroplasty is commonly performed to treat displaced femoral neck fractures in osteoporotic patients. This study aimed to assess the occurrence and outcomes of unplanned return visits to the emergency department (ED) within 90 days following bipolar hemiarthroplasty for displaced femoral neck fractures.

Methods: The clinical data of 1322 consecutive patients who underwent bipolar hemiarthroplasty for osteoporotic femoral neck fractures at a tertiary medical center were analyzed. Data from the patients' electronic medical records, including demographic information, comorbidities, and operative details, were collected. The risk factors and mortality rates were analyzed.

Results: Within 90 days after surgery, 19.9% of patients returned to the ED. Surgery-related reasons accounted for 20.2% of the patient's returns. Older age, a high Charlson comorbidity index score, chronic kidney disease, and a history of cancer were identified as significant risk factors for unplanned ED visits. Patients with uncemented implants had a significantly greater risk of returning to the ED due to periprosthetic fractures than did those with cemented implants (P = 0.04). Patients who returned to the ED within 90 days had an almost fivefold greater 1-year mortality rate (15.2% vs 3.1%, P < 0.001) and a greater overall mortality rate (26.2% vs 10.5%, P < 0.001). *Conclusions*: This study highlights the importance of identifying risk factors for unplanned ED visits after bipolar hemiarthroplasty, which may contribute to a better prognosis. Consideration should be given to the use of cemented implants for hemiarthroplasty, as uncemented implants are associated with a greater risk of periprosthetic fractures.

1. Introduction

Osteoporotic hip fractures represent a significant and escalating public health issue, with an estimated annual incidence of 6.26 million cases projected by 2050 [1,2]. Femoral neck fractures, a common type of hip fracture, can have a 1-year mortality rate of up to 24% [3,4]. In the

treatment of displaced femoral neck fractures, our study specifically focused on the use of bipolar hemiarthroplasty, which is generally preferred in such cases [5].

Although the results of bipolar hemiarthroplasty are generally acceptable, there are still potential complications associated with this surgery, including prosthesis-related issues, unstable hemodynamics,

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infections, and local pain disorders [6-8]. These complications can cause patients to return to the emergency department (ED), which can significantly impact their prognosis. Therefore, measuring the rate of unplanned returns to the ED after surgery is a common way to assess the quality of orthopedic care. Reducing the unplanned return rate could help to lower costs and improve the efficiency of the healthcare system [9].

Despite the significant increase in the number of bipolar hemiarthroplasties performed in recent years, insufficient attention has been given to the number of postoperative ED visits. Hence, the aim of this study was to identify the incidence and prognosis of and the reasons for and risk factors for unplanned return to the ED within 90 days after bipolar hemiarthroplasty.

2. Methods

2.1. Study population

This study exclusively involved a total of 1353 consecutive patients who underwent bipolar hemiarthroplasties, with no instances of unipolar procedures, for the treatment of femoral neck fractures at a tertiary medical center between January 1, 2013, and December 31, 2021. All bipolar hemiarthroplasties were performed with an anterolateral approach.

The exclusion criteria were patients without at least 90 days of follow-up information, patients with incomplete medical records, and patients who underwent elective total hip arthroplasty or bilateral operations. Additionally, pathological fractures were also excluded because of potential increased complications and mortality rates. In total, 1322 patients were ultimately included in this study. This study was approved by the Institutional Review Board of the study center.

2.2. Data collection and outcome measures

Patient data, including demographic information, comorbidities, Charlson Comorbidity Index (CCI) [10,11], laboratory data, and smoking status, as well as operative details, including operative time, cemented or uncemented type, and American Society of Anesthesiologists scores, were obtained from the patients' electronic medical records. The presence of preoperative and postoperative anemia (defined as <12 g/dL for males and < 11 g/dL for females) was included in the analysis.

We collected ED visit information from the electronic medical records of all the patients and identified patients who visited the ED within 90 days. Reasons for ED visits after hemiarthroplasty were categorized as either surgery-related or non-surgery-related. Surgery-related reasons included postoperative dislocation, periprosthetic fracture, superficial infection (defined as an infection at the surgical site not requiring additional operation), deep infection (defined as an infection at the surgical site requiring additional operation), postoperative pain and swelling. Nonsurgery-related reasons included gastrointestinal, cardiovascular, pulmonary, urinary, and neurological problems; soft tissue infection; traumatic injury; endocrine diseases; fever of unknown origin; and other issues.

2.3. Statistical analysis

Categorical variables are expressed as counts and proportions and were assessed using the chi-square test. Continuous variables were analyzed using Student's t-test. To determine the risk, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) by using multivariate logistic regression. The cumulative incidence and survival rate of ED visits for both groups were analyzed using Kaplan-Meier survival curves and log-rank tests. A P-value < 0.05 was considered to indicate statistical significance. All the statistical analyses were performed using Statistical Product and Service Solutions (SPSS) 26.0 (IBM, NY, USA).

2.4. Postoperative protocol

Our postoperative protocol included an average hospital stay of approximately 6.7 days. Physical therapists provided daily instructions on the proper use of four-legged walkers to prevent falls after surgery. Additionally, physicians and nurses educate patients about fall prevention strategies. After discharge from our hospital, patients are scheduled for a follow-up appointment approximately 2 weeks, 1, 3 and 6 months after surgery.

3. Results

3.1. Basic characteristics of the study cohort

Our study included a total of 1322 patients, with an average age of 75.7 ± 10.7 years. Of these patients, 67.7% were women. The average CCI score was 4.61 points. There were 378 patients (28.5%) with preoperative anemia and 889 patients (67.2%) with postoperative anemia. The average follow-up duration was 2.8 \pm 2.5 years (2.4 \pm 2.2 years for patients with unplanned ED visits and 2.9 \pm 2.4 years for those who did not return to the ED. P = 0.002).

We found 263 patients (19.9%) who visited the ED within 90 days after their hemiarthroplasties. Of those patients, 71 patients (27.0%) returned within the first 15 days, 72 patients (27.4%) returned within 16-30 days, and 77 patients (29.3%) returned within 31-60 days. The remaining 43 patients (16.3%) returned after 61-90 days (Fig. 1).

The patients in the ED visit group were older (77.6 \pm 10.0 vs 75.3 \pm 10.7, P = 0.02) and had higher CCI scores (5.3 \pm 2.0 vs 4.4 \pm 1.9, P = 0.001). The unplanned ED visit group also had more patients with postoperative anemia (73.4% vs 65.7%, P = 0.018), congestive heart failure (7.2% vs 3.7%, P = 0.012) and chronic kidney disease (18.6% vs 11.7%, P = 0.003) and a greater proportion of patients with a history of cancer (20.2% vs 13.6%, P = 0.013). The 1-year mortality rate was significantly greater in the unplanned ED visit group (40 of 263 (15.2%) vs 33 of 1059 (3.1%), P < 0.001). The overall mortality rate during the follow-up period was also greater in the unplanned ED visit group (26.2% vs 10.5%, P < 0.001) (Table 1).

3.2. Risk factors for ED visits

Multivariate logistic regression analysis revealed that a CCI score ≥ 6 (OR: 1.88, 95% CI: 1.40–2.51, P < 0.001), the presence of chronic

Cumulative Incidence of **Unplanned Emergency Department Visits**

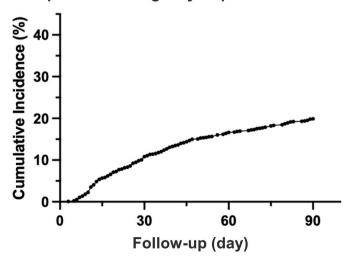


Fig. 1. Cumulative incidence of unplanned emergency department visits.

Table 1

Characteristics of patients who did/did not return to the emergency department (ED) within 90 days after hip hemiarthroplasty.

	ED visit (Yes) (N = 263)	ED visit (No) (N = 1059)	Total (N = 1322)	P-value
Sex (male, female)	98, 165	329, 730	427, 895	0.05
Age, yrs	77.6 ±	75.3 ±		0.002 ^a
2	10.0	10.7		
BMI, kg/m ²	22.2 ± 4.6	22.4 ± 5.5		0.17
CCI score	5.3 ± 2.0	4.4 ± 1.9		< 0.001 ^a
CCI score ≥ 6	105	260	365	$< 0.001^{a}$
	(39.9%)	(24.6%)	(27.6%)	
ASA classification ≥ 3	134 (51%)	537	671	0.94
		(50.7%)	(50.8%)	
Tobacco use history	19 (7.2%)	52 (4.9%)	71 (5.4%)	0.136
Waiting time before	49.7	46.5	48.3	0.83
surgery, hrs				
Stem of hemiarthroplasty				
Cemented stem	94 (35.7%)	323	417	0.10
		(30.5%)	(31.5%)	
Uncemented stem	169	736	905	
	(64.3%)	(69.5%)	(68.5%)	
Postoperative anemia	193	696	889	0.018 ^a
	(73.4%)	(65.7%)	(67.2%)	
Operation time, minute	96.3 \pm	98.4 ±		0.13
	35.1	38.8		
Medical history				
Myocardial infarction	25 (9.5%)	65 (6.1%)	90 (6.8%)	0.05
Congestive heart failure	19 (7.2%)	39 (3.7%)	58 (4.4%)	0.012 ^a
Cerebral vascular event	38 (14.5%)	129	167	0.32
		(12.2%)	(12.6%)	
Chronic kidney disease	49 (18.6%)	124	173 (13.1	0.003 ^a
		(11.7%)	%)	
Diabetes mellitus	88 (33.5%)	307	395	0.16
		(29.0%)	(29.9%)	
Dementia	32 (12.2%)	88 (8.3%)	120 (9.1%)	0.05
Cancer	53 (20.2%)	144	197	0.013 ^a
		(13.6%)	(14.9%)	
One-year mortality	40 (15.2%)	33 (3.1%)	73 (5.5%)	$< 0.001^{a}$
Overall mortality	69 (26.2%)	111	180	$< 0.001^{a}$
		(10.5%)	(13.6%)	
Follow-up duration, yrs	$\textbf{2.4} \pm \textbf{2.2}$	$\textbf{2.9} \pm \textbf{2.4}$		0.002 ^a

Age, body mass index (BMI), Charlson Comorbidity Index (CCI) score, operation time, and follow-up duration are shown as the mean \pm standard deviation. ASA classification, American Society of Anesthesiologists physical status classification.

^a P < 0.05.

kidney disease (OR: 1.59, 95% CI: 1.09–2.32, P = 0.016) and having a cancer history (OR: 1.62, 95% CI: 1.14–2.31, P = 0.008) significantly increased the risk of presenting to the ED within 90 days after hemiarthroplasty. Congestive heart failure was associated with an increased risk of an unplanned ED visit in the univariate analysis, but the risk was not significant in the multivariate analysis (Table 2).

3.3. Reasons for ED visits

Among the 263 patients who revisited the emergency department within 90 days, 53 patients (20.2%) presented with surgery-related complications. While certain issues, such as postoperative pain (5.3%), dislocation (4.2%), and superficial infections (4.9%), were effectively managed in the ED, leading to the subsequent discharge of these patients, it is important to recognize that these conditions, though manageable in an ED setting. Among the 11 patients who experienced dislocation, the average time to return to the emergency department was 23.9 days. Five patients described injuries resulting from twisting their leg while walking, while the remaining six patients described falls as the cause. Nine patients (3.4%) had periprosthetic fractures, and all of them had undergone uncemented hemiarthroplasties. The patients underwent Table 2

ORs of unplanned ED visits within 90 days after hip hemiart	hroplasty.

	Univariate analysis OR (95% CI)	P-value	Multivariate analysis OR (95% CI)	P-value
Age	1.02 (1.01–1.04)	0.002 ^a	1.01 (1-1.03)	0.18
Sex	1.32 (0.99–1.75)	0.06	1.28 (0.96–1.71)	0.10
CCI score ≥ 6	2.04 (1.54-2.71)	$< 0.001^{a}$	1.88 (1.4–2.51)	$< 0.001^{a}$
Diabetes mellitus	1.23 (0.92–1.64)	0.157	1.19 (0.88–1.60)	0.3
Congestive heart failure	2.04 (1.16–3.59)	0.01 ^a	1.80 (0.99–3.19)	0.056
Chronic kidney disease	1.73 (1.2–2.48)	0.003	1.59 (1.09–2.32)	0.016 ^a
Cancer history	1.55 (1.1–2.2)	0.01 ^a	1.62 (1.14-2.31)	0.008 ^a
Uncemented stem	1.27 (0.95–1.68)	0.1	1.31 (0.85–1.51)	0.41
Postoperative anemia	1.44 (1.06–1.94)	0.02 ^a	1.2 (0.88–1.64)	0.25

OR, odds ratio; ED, emergency department; CI, confidence interval; CCI, Charlson Comorbidity Index.

^a P < 0.05.

surgical fixation or revision surgery after the ED visit. None of the patients in our series who received cemented implants had periprosthetic fractures. Among the 9 patients with periprosthetic fractures, the average time to return to the emergency department was 26.7 days, with all injuries resulting from falls at home. Three of these patients had a history of diabetes mellitus, and the falls were attributed to sudden hypoglycemic dizziness. Six patients (2.3%) with acute deep infection required further surgical debridement or Girdlestone procedures.

The other patients (79.8%) returned to the ED for nonsurgical reasons. The most common reasons included gastrointestinal (18.6%), cardiovascular (14.1%), chest (13.7%), and urinary (11.4%) issues. In the group of patients who returned to the ED within 30 days, surgery-related pain and swelling were significantly more prevalent within 30 days postoperatively (P = 0.02). Additionally, those who returned between 31 and 90 days after surgery showed a notable increase in non-surgery-related soft tissue infections (P = 0.04) (Table 3).

3.4. Surgery-related issues in cemented or uncemented hip hemiarthroplasty

Among the 53 patients who returned to the ED for surgery-related reasons, the uncemented group exhibited a significant tendency toward periprosthetic fracture (9 patients, 1%, P = 0.04), while the cemented group showed a significant tendency toward superficial infection (8 patients, 1.9%, P = 0.02). There were no significant differences in other reasons, such as dislocation, deep infection, pain, or swelling (Table 4).

3.5. ED returns and mortality

Mortality is an important outcome measure after hip fractures. Compared with patients who did not return to the ED within 90 days after the index surgery, patients who returned to the ED within 90 days after the index surgery had a significantly greater mortality rate during the follow-up period. (log-rank test, P < 0.005) (Fig. 2)

4. Discussion

The most important findings of this study were that a high CCI score, chronic kidney disease, and cancer history significantly increased the risk of unplanned ED visits within 90 days after hemiarthroplasties for osteoporotic patients with displaced femoral neck fractures. The use of uncemented femoral stems was associated with more periprosthetic fractures than the use of cemented implants. Patients who had an

Table 3

Chief complaints or problems among patients who presented to the emergency
department (ED) within 90 days after hip hemiarthroplasty.

	Patients (N = 263)	ED visit within postoperative 30 days (N = 143)	ED visit during postoperative 31–90 days (N = 120)	P- value
Surgery-related	53			
	(20.2%)			
Dislocation	11	8	3	0.21
	(4.2%)			
Periprosthetic	9 (3.4%)	5	4	0.94
fracture				
Superficial	13	10	3	0.09
infection	(4.9%)			
Deep infection	6 (2.3%)	4	2	0.54
Pain and	14	12	2	0.02^{a}
swelling	(5.3%)			
Nonsurgery-	210			
related	(79.8%)			
Gastrointestinal	49	28	21	0.67
	(18.6%)			
Cardiovascular	37	18	19	0.45
	(14.1%)			
Pulmonary	36	23	13	0.31
	(13.7%)			
Urinary	30	16	14	0.9
	(11.4%)			
Soft tissue	19	6	13	0.04 ^a
infection	(7.2%)			
Trauma	13	6	7	0.54
	(4.9%)			
Neurological	12	5	7	0.34
	(4.6%)			
Endocrine/	6 (2.3%)	1	5	0.06
Rheumatology				
Fever of	2 (0.8%)	1	1	0.9
unknown				
Others	6 (2.3%)	2	4	0.3

^a P < 0.05.

Table 4

Surgery-related problems among patients who presented to the emergency department within 90 days after cemented or uncemented hip hemiarthroplasty.

	Cemented (N = 417)	Uncemented (N = 905)	P- value
Dislocation	3 (0.7%)	8 (0.9%)	0.76
Periprosthetic fracture	0 (0%)	9 (1%)	0.04 ^a
Superficial infection	8 (1.9%)	5 (0.6%)	0.02 ^a
Deep infection	1 (0.2%)	5 (0.6%)	0.43
Pain and swelling	5 (1.2%)	9 (1%)	0.74

 $^{\rm a}\,$ P < 0.05, chi-square test.

unplanned return visit to the ED had an almost 5-fold greater 1-year mortality rate.

Our study revealed that 19.9% of patients visited the ED within 90 days. A large cohort study with 200,645 patients revealed that the incidence of unplanned ED return after total knee arthroplasty (TKA) and total hip arthroplasty (THA) within 90 days was 5.2% and 4.6%, respectively [12]. Another systematic review showed that the average ED visit rate within 90 days after total joint arthroplasty (TJA) was 10.3% (0–33%), with 10.8% for TKA and 9.7% for THA [13]. The incidence of ED visits following hemiarthroplasty was much greater than that following TKA and THA. This may be because of the patients' conditions and different outcomes after surgical procedures. Compared with patients who underwent primary TKA or THA, patients who experienced hip fracture tended to be older and have more comorbidities. Even for hip fractures, some previous studies have shown that THA is better than hemiarthroplasty in terms of pain and functional scores

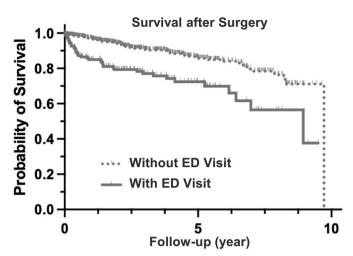


Fig. 2. Kaplan–Meier survival curve of patients who did/did not present to the emergency department (ED) within 90 days after bipolar hemiarthroplasty for femoral neck fractures.

[14]. While the optimal treatment between total hip arthroplasty (THA) and hemiarthroplasty for hip fractures remains a subject of debate, previous studies have indicated comparable mortality rates between these two procedures [15–19].

Several studies have demonstrated that older age is an independent risk factor for readmission and complications following total joint arthroplasty. Older age has been associated with some preexisting medical conditions or comorbidities that can lead to complications and mortality [20–23]. In our study, we found that age was also an independent predictor of unplanned ED visits within 90 days after hemiarthroplasty.

A high CCI score and multiple comorbidities have a significantly negative impact on surgical outcomes [24–26]. We found that a CCI score ≥ 6 might be the cutoff score associated with an increased risk of unexpected return to the ED after hip hemiarthroplasties. Both chronic kidney disease and a history of cancer increase the likelihood of unplanned ED returns. Cancer history profoundly influences overall health status. In addition to direct cancer-related effects such as metastasis and decreased activity and stress tolerance, it can induce cachexia, potentially leading to muscle wasting. This complication can hinder rehabilitation endeavors and negatively impact survival rates. For patients with multiple comorbidities, we recommend discussing the associated risks with their families before surgery. Proper management of comorbidities is mandatory to reduce the risk of complications and unplanned ED visits.

Postoperative anemia is commonly observed after hemiarthroplasty for femoral neck fracture. Both chronic and acute anemia are associated with an increased risk of injury to major organs such as the brain, heart, and kidney [27]. Although blood transfusion may treat anemia and improve the oxygen supply, it is associated with increased mortality and morbidity, neuroinflammation, and cognitive impairment [28–31]. We found that the unplanned ED return group had more patients with postoperative anemia. However, it was not a significant risk factor for ED return in the multivariate analysis.

Previous studies have shown that female sex is an independent risk factor for readmission, revision surgery, and wound infection after hip arthroplasty [32]. A retrospective study showed that female patients had a 75% increased risk of requiring transfusion [33]. Another retrospective cohort study of primary hip arthroplasty patients showed that female patients had almost double the risk of periprosthetic femur fracture [34]. However, in our study, we did not find any sex differences in the incidence of complications or the risk of returning to the ED after hemiarthroplasty.

Most of the complaints of patients who presented to the ED were not

surgery related. We observed a high incidence of gastrointestinal complaints (18.6%), which was consistent with the outcomes typically observed in elective TJA [35]. Based on our investigation, most patients with gastrointestinal complaints returned to the ED because of abdominal pain and gastrointestinal bleeding, which were related to nonsteroidal anti-inflammatory drugs (NSAIDs), liver diseases, or cancer. NSAIDs may induce mucosal injury in the upper, middle, and lower gastrointestinal tract. The coadministration of nonselective NSAIDs and proton pump inhibitors (PPIs) or the transition to selective cyclooxygenase-2 (COX-2) inhibitors may alleviate symptoms and reduce the risk of peptic ulcers among individuals at increased risk [36]. Therefore, postoperative medication should be prescribed with caution regarding gastrointestinal issues, particularly in terms of NSAID usage.

Although the incidence of infection is low, surgical site infections also remain a significant concern, thus highlighting the importance of peri-operative infection control.

We found that there was no difference in the overall ED return rate between patients who underwent cemented and uncemented hemiarthroplasties. However, patients with uncemented implants had a significantly greater risk of periprosthetic fracture. The debate between cemented and uncemented femoral stems has continued for decades. Our findings favored cemented stems for hemiarthroplasty and confirmed the findings of some current studies [7]. A previous retrospective cohort study reported that uncemented hemiarthroplasty led to more aseptic loosening [5]. Cemented hemiarthroplasty was associated with a significantly lower incidence of implant-related complications, better short-term outcomes, and significantly fewer periprosthetic fractures [37–39].

A recent meta-analysis also revealed that elderly people with osteoporosis who had uncemented stems are more prone to fractures [40]. This might be attributed to repeated hammering during surgery to achieve stability between the implant and bone for uncemented press-fit fixation. This repetitive action could cause intraoperatively, visually subtle fracture lines, thus increasing the risk of postoperative periprosthetic fractures.

However, we found that the cemented group had a longer surgical time and a greater incidence of superficial infection, which may be attributed to the older age of the patients in the cemented group and the longer surgical time.

Hip fractures present a considerable burden to public health owing to their high incidence and severity. These catastrophic events are associated with high 1-year mortality rates, up to 20% [3,41]. We further found that patients who returned to the ED within 90 days after hemiarthroplasty had significantly greater 1-year and overall mortality than patients who did not return to the ED. In a recent study focusing solely on hemiarthroplasty for femoral neck fracture, the 1-year postoperative mortality rate among older adults was reported to be 18.5%. This rate appears to be slightly greater than that of our group of patients who returned to the ED, where the 1-year mortality rate was 15.2% [42].

To minimize these risks, clinicians should regularly monitor and follow patients with the most common risk factors. Postoperative ED visits are often associated with various factors, such as postoperative complications and issues related to the planning and release of patients. For instance, issues with the discharge planning process can lead to significant visits. Ensuring that patients receive the necessary postoperative care, such as proper discharge planning and rehabilitation, can help reduce the number of visits to the ED. In addition, education programs about when and how to seek medical attention can help prevent unnecessary visits. These interventions, which are customized to the individual's risk profile, can help improve the outcome and reduce the strain placed on emergency medical services.

This study has several limitations. First, it was a retrospective analysis. However, it was difficult to design a randomized controlled trial to observe the incidence of returning to the ED for hip fractures. The data were collected from the electronic medical records of consecutive patients who were treated in a tertiary medical center, and all parameters were carefully verified. Second, the surgeries were performed by multiple orthopedic surgeons at the hospital, which might have introduced bias in the outcomes. With strict adherence to the clinical pathway for bipolar hemiarthroplasty, we offered standard postoperative care for all patients to minimize the risk for complications. Third, although we followed all patients for at least 90 days, the overall mortality rate after 90 days might be underestimated if patients do not return to our hospital because of fatal events. However, as our medical center is the primary healthcare facility in the region, it is common and reasonable for patients with serious postoperative complications to return to the same institute for follow-up. The complication and mortality rates we reported in this study might be underestimated, but we believe that the actual rate would be low.

5. Conclusions

In this study, we found that approximately 20% of osteoporotic patients who underwent hemiarthroplasty for hip fracture returned to the ED within 90 days after surgery. A high CCI score (\geq 6), chronic kidney disease, and cancer history were identified as significant risk factors for ED visits. Patients with uncemented implants were also more likely to visit the ED postoperatively because of periprosthetic fractures. For the specific population, it is recommended to consider the use of cemented fixation directly, especially for the elderly population or individuals with notable osteoporosis. Patients who returned to the ED within 90 days after their index surgery had significantly greater 1-year and overall mortality rates. Clinicians should be aware of these risk factors and consider closer monitoring and follow-up for patients with these characteristics.

CRediT author statement

Yang-Yi Wang: Writing – Original draft. Yi-Chuan Chou: Conceptualization, Writing – Original draft. Yuan-Hsin Tsai: Investigation. Chih-Wei Chang: Analysis data. Yi-Chen Chen: Analysis data. Ta-Wei Tai: Conceptualization, Writing – Review & editing.

Data availability statement

All data generated or analyzed during this study are included in this article, but some personal information are confidential.

Conflicts of interest

Ta-Wei Tai received honoraria for lectures, meetings, and/or travel from Amgen and Alvogen/Lotus. **The other authors** reported that they have nothing to declare for potential conflicts of interest.

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