Predictors of Medical Serious Adverse Events in Hip Fracture Patients Treated With Arthroplasty

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Aim: Patients with hip fractures are often frail with multiple comorbidities and at risk of medical serious adverse events (SAEs). We investigated the HEALTH trial patient population to ascertain predictors of SAEs.

Methods: We performed a multivariable Cox regression analysis. Occurrence of SAEs was included as the dependent variable with 31 potential prognostic factors being included as independent variables.

Results: One thousand four hundred forty-one patients were included in this analysis. Three hundred seventy (25.6%) patients suffered from an SAE. The most common events were cardiac (38.4%, n = 105), respiratory (20.8%, n = 77), and neurological (14.1%, n = 77). The majority of SAEs (50.8%, n = 188) occurred in the first 90 days after hip fracture with 35.4% occurring in the first 30 days (n = 131). Body mass index (BMI) between 18.5 and 24.9 compared with BMI between 25 and 29.9 [hazard ratio (HR) 1.32, $P = 0.03$] and receiving a total hip arthroplasty compared with a bipolar hemiarthroplasty (HR 1.36, $P = 0.03$) were associated with a higher risk of a medical SAE within 24 months of femoral neck fracture. Age ($P = 0.09$), use of femoral cement ($P = 0.59$), and use of canal pressurization ($P = 0.37$) were not associated with a medical SAE.

Conclusion: Total hip arthroplasty is associated with more SAEs in the immediate postoperative period, and care should be taken in selecting patients for this treatment compared with a hemiarthroplasty. A higher BMI may be protective in hip fracture patients while age alone does not predict SAEs and neither does the use of femoral cement and/or pressurization.

Key Words: serious adverse events, displaced femoral neck fracture, total hip arthroplasty, hemiarthroplasty

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

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INTRODUCTION

Elderly patients with hip fractures are often frail with multiple medical comorbidities and are at risk of suffering from medical serious adverse events (SAEs). Although the

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definitive treatment for hip fracture is surgical, medical comorbidities, as well as advancing age, have historically been reported to increase the risk of death after hip fracture.[1–3] The ability to more accurately predict medical SAEs in this patient group would be a useful tool for the surgeon to guide clinical decision making regarding the most appropriate surgical treatment for each individual.

The primary objective of this secondary analysis was to determine the factors predictive of medical SAEs in patients from the HEALTH trial aged 50 years or older who were treated with either hemiarthroplasty or total hip arthroplasty after a femoral neck fracture.[4,5] The secondary objectives were to determine the timing of the medical SAEs and to determine the proportion of medical SAEs that occurred after a fracture-related complication or revision surgery.

METHODS

Medical SAEs were diagnosed by physicians at the clinical sites and documented during the course of the HEALTH trial.[4,5] An SAE was defined as any adverse event that was fatal, life-threatening, required or prolonged hospital stay, resulted in persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event, symptom, sign, illness, or experience that developed or worsened in severity during the study. SAEs included neurological, respiratory, cardiac, renal, vascular, multiorgan failure, sepsis, anemia and other blood issues, dehydration, gastrointestinal (GI) bleed, ulcer, other GI problems, and prolonged hospitalization. Mortality itself was not considered an SAE. For the purposes of this secondary analysis, we did not consider any fracture-related complications as medical SAEs.

In this secondary analysis, we presented the overall incidence of medical SAEs that occurred in the HEALTH trial, the timing of the SAEs (0–30 days after fracture, 31–60 days after fracture, 61–90 days after fracture, and >90 days after fracture), the incidence of medical SAEs that occurred after a fracture-related complication, and the incidence of medical SAEs that occurred after a revision surgery.

Fracture-related complications were defined as complications related to the hip fracture and initial surgery as per the original HEALTH trial, such as periprosthetic fracture, hip instability or dislocation, implant failure (loosening/subsidence and breakage), wound-healing problems (including superficial/deep infection, wound necrosis), another soft-tissue procedure, clinically important heterotopic ossification, abductor failure, implant wear and corrosion, osteolysis, neurovascular injury, decreased function, and pain.

Revision surgery was defined as per the original HEALTH trial as any unplanned secondary procedure to treat a fracture-related complication, such as closed and open reductions of a hip dislocation, open reduction of a fracture, full or partial implant exchange, implant removal, implant adjustment, soft-tissue procedure, excision of heterotopic ossification, insertion of an antibiotic spacer, and other events as determined by an independent central adjudication committee.

We also performed a multivariable Cox regression to determine factors predictive of medical SAEs within 24 months of initial surgery in the HEALTH trial. Our outcome was a single composite measure which included any type of medical SAE within 24 months of initial surgery in the HEALTH trial. Thirty-one prognostic factors were included as the independent variables and were selected based on biological rationale, previous literature, and expert opinion. These factors included the variables used in the minimization allocation process for the HEALTH trial: age, prefracture living setting (institutionalized or not institutionalized), prefracture functional status (using assistive device for ambulation or able to ambulate without assistive device), and American Society of Anesthesiologists (ASA) class (class I/II or III/IV/V). For these covariates, we used values that were entered into the minimization system at the time of enrollment. Regression results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs), and *P* values. All tests were 2-tailed with alpha = 0.05. Statistical analysis was conducted using R (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In the HEALTH trial, 1441 patients were randomized to treatment. At 24 months, 1243 patients were living, and complete follow-up was achieved for 1058 (85.1%). In the 24 months after hemiarthroplasty and total hip arthroplasty treatment for femoral neck fracture, there was an overall 25.6% incidence of medical SAEs (n = 370). The incidence of the various SAEs are summarized in Table 1. The timing of medical SAEs is summarized in Table 2. The majority (50.8%, n = 188) occurred in the first 90 days after fracture. The most common events were cardiac (38.4%, n = 105), respiratory (20.8%, n = 77), and neurological (14.1%, n = 52).

For patients with fracture-related complications, respiratory and neurological were equally the most common SAE observed (53.8% n = 14). There were equal cases of cardiac, neurological, renal, vascular, sepsis, and other GI problem SAEs (81.8% n = 18) in patients undergoing revision surgery. The incidence of SAEs after fracture-related complications and revision surgery is summarized in Tables 3 and 4, respectively.

Body mass index (BMI) between 18.5 and 24.9 as compared to a BMI 25–29.9 (HR 1.32, 95% CI 1.03–1.70; $P = 0.03$), receiving a total hip arthroplasty as compared to receiving a bipolar hemiarthroplasty (HR 1.36, 95% CI 1.03–1.81; $P = 0.03$), not using preoperative traction (HR 1.89, 95% CI 1.18–3.03; $P < 0.01$), ASA classification class III/IV/V as compared to class I/II (HR 1.70, 95% CI 1.32–2.19; $P < 0.001$), receiving treatment for lung disease (HR 1.52, 95% CI 1.14–2.03; $P = 0.004$), receiving treatment for anemia or another blood disease (HR 1.95, 95% CI 1.30–2.95; $P = 0.001$), not receiving treatment for ulcers or stomach disease (HR 1.54, 95% CI 1.02–2.32; $P = 0.04$), receiving treatment for kidney disease (HR 1.58, 95% CI 1.0–2.42; $P = 0.04$), receiving treatment for heart disease (HR 1.30, 95% CI 1.03–1.65; $P = 0.03$), baseline use of steroids (HR 1.70, 95% CI 1.09–2.63; $P = 0.02$), preoperative thromboprophylaxis (HR 1.58, 95% CI 1.21–2.05; $P < 0.01$), anterolateral/lateral surgical approach as compared to posterior/

TABLE 1. Overall Incidence of Medical SAEs Within the 24 Months After Arthroplasty

Type of Serious Medical Event	Total Incidence, N = 1,441, n (%)	Incidence in the THA Group, N = 718, n (%)	Incidence in the HA Group, N = 723, n (%)
Cardiac	105 (7.3)	53 (7.4)	52 (7.2)
Respiratory	77 (5.3)	42 (5.9)	35 (4.8)
Neurological	52 (3.6)	27 (3.8)	25 (3.5)
Renal	43 (3.0)	23 (3.2)	20 (2.8)
Vascular	38 (2.6)	22 (3.1)	16 (2.2)
Sepsis	17 (1.2)	9 (1.3)	8 (1.1)
GI bleed	11 (0.8)	5 (0.7)	6 (0.8)
Other GI problem	10 (0.7)	6 (0.8)	4 (0.6)
Multiorgan failure	5 (0.3)	1 (0.1)	4 (0.6)
Dehydration	4 (0.3)	2 (0.3)	2 (0.3)
Anemia	3 (0.2)	1 (0.1)	2 (0.3)
Other blood issue	2 (0.1)	1 (0.1)	1 (0.1)
Ulcer	2 (0.1)	2 (0.3)	0 (0.0)
Prolonged hospitalization	1 (0.1)	0 (0.0)	1 (0.1)

GI, gastrointestinal; HA, hemiarthroplasty; THA, total hip arthroplasty.

posterolateral (HR 1.65, 95% CI 1.27–2.16; $P < 0.01$), and revision surgery (HR 9.89, 95% CI 5.96–16.4; $P < 0.01$) were associated with a higher risk of a medical SAE within 24 months of femoral neck fracture. Age ($P = 0.09$), use of femoral cement ($P = 0.59$), and use of canal pressurization ($P = 0.37$) were not associated with a medical SAE. Table 5 summarizes the predictors of SAEs in this patient group.

DISCUSSION

Our subanalysis of the HEALTH trial data has shown an overall incidence of medical SAE after hip fracture to be 25.6%. The most common type of medical SAE in this patient group was cardiac (38.4% n = 105), followed by respiratory (20.8% n = 77), and neurological (14.1% n = 52). For patients with fracture-related complications, respiratory and neurological SAEs were most commonly observed (each 26.3% n = 5). However, vascular SAE was the most common (20% n = 6) in patients undergoing revision surgery. Receiving a total hip arthroplasty was associated with an increased rate of SAEs compared with receiving a bipolar hemiarthroplasty. The patient groups for these interventions were randomized as per the HEALTH trial methodology, so we believe that this finding is accurate and could be used to guide practice. This could be attributed to the acetabular reaming and implantation or due to the longer operative time and larger physiological insult to the patient; however, we did not see any effect of length of surgery or intraoperative blood loss on postoperative SAEs when analyzed independently.

TABLE 2. Timing of Incidence of Medical SAEs After Arthroplasty

Type of Serious Medical Event	0–30 Days After Fracture, N = 131, n (%)	31–60 Days After Fracture, N = 35, n (%)	61–90 Days After Fracture, N = 22, n (%)	>90 Days After Fracture, N = 182, n (%)
Cardiac	44 (33.6)	7 (20.0)	4 (18.2)	50 (27.5)
Respiratory	24 (18.3)	9 (25.7)	6 (27.3)	38 (20.9)
Neurological	14 (10.7)	5 (14.3)	3 (13.6)	30 (16.5)
Vascular	17 (13.0)	6 (17.1)	3 (13.6)	12 (6.6)
Renal	13 (9.9)	4 (11.4)	3 (13.6)	23 (12.6)
GI bleed	7 (5.3)	0 (0.0)	0 (0.0)	4 (2.2)
Multiorgan failure	3 (2.3)	0 (0.0)	0 (0.0)	2 (1.1)
Sepsis	3 (2.3)	3 (8.6)	2 (9.1)	9 (5.0)
Anemia	2 (1.5)	0 (0.0)	0 (0.0)	1 (0.6)
Prolonged hospitalization	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Other blood issue	1 (0.8)	0 (0.0)	1 (4.5)	0 (0.0)
Ulcer	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.6)
Other GI problem	1 (0.8)	1 (2.9)	0 (0.0)	8 (4.4)
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.2)

GI, gastrointestinal.

TABLE 3. Incidence of Medical SAEs after Fracture-Related Complications

Type of Serious Medical Event	No Fracture-Related Complication, N = 339, n (%)	Fracture-Related Complication*, N = 26, n (%)
Cardiac	100 (29.5)	3 (11.5)
Respiratory	69 (20.4)	7 (26.9)
Neurological	44 (13.0)	7 (26.9)
Renal	42 (12.4)	1 (3.8)
Vascular	35 (10.3)	3 (11.5)
Sepsis	16 (3.4)	1 (3.8)
GI bleed	10 (3.0)	1 (3.8)
Other GI problem	10 (3.0)	0 (0.0)
Multiorgan failure	5 (1.5)	0 (0.0)
Dehydration	4 (1.2)	0 (0.0)
Ulcer	2 (0.6)	0 (0.0)
Anemia	1 (0.3)	1 (3.8)
Prolonged hospitalization	1 (0.3)	0 (0.0)
Other blood issue	0 (0.0)	2 (7.7)

*Total N is less than 370 because 5 participants experienced a medical SAE before their fracture-related complication.
GI, gastrointestinal.

There has been a recent trend in using total hip replacement over hemiarthroplasty for treatment of neck of femur fractures due to reported improved functional outcomes,[6] despite the reported higher dislocation rate.[7–9] Most studies of this nature record complications related to the operation such as hip dislocation or revision surgery,[10] but few large scale studies have recorded medical SAEs related to this patient group. Hansson et al[11] looked at 664 hip fracture patients and recorded pneumonia and additional falls as the most common complication but did not group the patients by operation.

The use of a laterally based approach was associated with an increased risk of SAEs compared with posterior approaches. This may have been due to selection bias because even hip fracture surgeons who favor the posterior approach will tend to use the anterolateral approach for hip fracture surgery in the frailer patient due to the reported lower dislocation rate. The National Institute for Clinical Excellence (NICE) UK guidelines for hip fracture management advise surgeons to consider the anterolateral approach in favor of the posterior approach for hemiarthroplasty[12]; however, a recent review of the literature found the evidence too heterogeneous to make a recommendation.[13] The draft NICE evidence review for approaches in total hip arthroplasty from October 2019 does not make any recommendations to favor one approach over the other, but the committee agreed that the surgeon undertaking the approach must have experience and competence in that particular approach to get consistently

TABLE 4. Incidence of Medical SAEs After Revision Surgery

Type of Serious Medical Event	No Revision Surgery, N = 314, n (%)	Revision Surgery, N = 22, n (%)
Cardiac	93 (29.6)	3 (13.6)
Respiratory	68 (21.7)	2 (9.1)
Neurological	46 (14.6)	3 (13.6)
Renal	37 (11.8)	3 (13.6)
Vascular	28 (8.9)	3 (13.6)
Sepsis	13 (4.1)	3 (13.6)
GI bleed	8 (2.5)	1 (4.3)
Other GI problem	7 (2.2)	3 (13.6)
Multiorgan failure	5 (1.6)	0 (0.0)
Dehydration	4 (1.3)	0 (0.0)
Anemia	2 (0.6)	0 (0.0)
Ulcer	2 (0.6)	0 (0.0)
Other blood issue	1 (0.3)	1 (4.3)
Prolonged hospitalization	0 (0.0)	0 (0.0)

Total N is less than 370 because 34 participants experienced a medical SAE before their revision surgery.
GI, gastrointestinal.

TABLE 5. Factors Associated With a Medical SAE (n = 1,244, 368 Events)

Variable	HR (95% CI)	P
BMI (kg/m²)		
<18.5 vs. 25–29.9	1.58 (0.99–2.52)	0.055
18.5–24.9 vs. 25–29.9	1.32 (1.03–1.70)	0.03
≥30 vs. 25–29.9	0.97 (0.67–1.42)	0.88
ASA classification		
Class III/IV/V vs. Class I/II	1.70 (1.32–2.19)	<0.001
Patient receiving treatment for lung disease		
Yes vs. no	1.52 (1.14–2.03)	0.004
Patient receiving treatment for anemia or another blood disease		
Yes vs. no	1.95 (1.30–2.95)	0.001
Patient receiving treatment for ulcers or stomach disease		
No vs. yes	1.54 (1.02–2.32)	0.04
Patient receiving treatment for kidney disease		
Yes vs. no	1.58 (1.03–2.42)	0.04
Patient receiving treatment for heart disease		
Yes vs. no	1.30 (1.03–1.65)	0.02
Baseline use of steroids		
Yes vs. no	1.70 (1.09–2.63)	0.02
Preoperative traction		
No vs. yes	1.89 (1.18–3.03)	0.02
Preoperative thromboprophylaxis		
Yes vs. no	1.58 (1.21–2.05)	<0.01
Type of surgical approach		
Direct anterior vs. posterior/posterolateral	1.42 (0.71–2.82)	0.31
Anterolateral/lateral vs. posterior/posterolateral	1.65 (1.27–2.16)	<0.01
Implant received		
Total hip arthroplasty vs. bipolar hemiarthroplasty	1.36 (1.03–1.81)	0.03
Total hip arthroplasty vs. monopolar hemiarthroplasty	1.34 (0.97–1.85)	0.08
Revision surgery before medical SAE		
Yes vs. no	9.89 (5.96–16.4)	<0.01
Age	1.01 (0.99–1.03)	0.09
Prefracture living setting		
Institutionalized vs. not institutionalized	1.42 (0.88–2.30)	0.15
Prefracture functional status		
Use of walking aid vs. independent ambulator	1.03 (0.80–1.31)	0.82
Patient receiving treatment for cancer		
Yes vs. no	1.19 (0.76–1.88)	0.45
Patient receiving treatment for rheumatoid arthritis		
Yes vs. no	0.50 (0.18–1.36)	0.17
Patient receiving treatment for diabetes		
Yes vs. no	1.30 (0.98–1.72)	0.07
Patient receiving treatment for depression		
Yes vs. no	0.81 (0.54–1.21)	0.31
Baseline use of opioid medications		
Yes vs. no	0.93 (0.61–1.40)	0.74
Time from injury to surgery (h)	0.998 (0.996–1.002)	0.07
Additional injuries		
Yes vs. no	0.94 (0.51–1.74)	0.86
Length of surgery (min)	1.001 (0.998–1.003)	0.50
Type of anesthesia		
Regional/other vs. general	1.23 (0.96–1.57)	0.10
Intraoperative blood loss (mL)	1.001 (0.999–1.002)	0.27
Use of femoral cement		
Yes vs. no	1.17 (0.64–2.14)	0.59
Use of canal pressurization as cementing technique	1.30 (0.72–2.34)	
Yes vs. no		0.37
Femoral canal prepared with pulsatile lavage	0.67 (0.45–1.003)	
Yes vs. no		0.051
Use of acetabular cement	0.77 (0.55–1.09)	
Yes vs. no		0.14
Fracture-related complication before medical SAE		
Yes vs. no	1.46 (0.45–4.70)	0.52

ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; HR, hazard ratio; SAE, serious adverse event.

good results.[14] However, there is a randomized controlled trial of 500 participants underway that is comparing the direct lateral versus posterolateral approach for hemiarthroplasty to answer this question.[15]

The use of bone cement in the treatment of hip fractures has created concerns[16] due to bone cement implantation syndrome.[17] This study adds to the existing weight of evidence[18] that the use of bone cement is safe in hip fracture surgery. Despite the higher risk patient population, pressurization of the canal and the use of femoral or acetabular cement was not associated with an increased rate of SAEs.

Interestingly, using preoperative skin traction seemed to lower the incidence of medical SAEs. This could be due to traction delivering better pain control for these patients and reducing the risk of fat embolism due to less movement at the fracture site. However, few institutions in the HEALTH trial used preoperative traction, so this finding could be attributable to sampling bias.

Treatment for existing medical conditions, such as lung disease, heart disease, diabetes, anemia, and the use of steroids, was all associated with an increased risk of SAEs. This correlates with clinical practice and existing studies.[19,20] A higher ASA grade was associated with an increased risk of SAEs. Smith et al conducted a meta-analysis of studies looking at preoperative indicators for mortality after hip fracture surgery. Four studies with a total of 1559 participants were included assessing risk of death based on ASA grade and found that patients with an ASA grade of 3 or 4 were at a 44% increased risk of death at 12 months compared to those with a grade of 1 or 2.[21] The Hailer et al[22] review using the Swedish joint register investigated 24,699 patients who had undergone total hip arthroplasty for neck of femur fracture and found that 90-day mortality was significantly higher in patients with ASA 3 compared with ASA 1 (HR = 9.5).

Another interesting finding of the subanalysis was that age alone does not predict medical SAEs and neither does prefracture functional or living status. Schnell et al[23] reported patient demographics and outcomes of 758 patients treated in their program over a 4-year period. They showed that 1-year mortality was highest for patients who were older than 90 years compared with those 70–79 or 80–89 years of age; however, they did not specifically report on the incidence of SAEs. Although it is logical that older hip fracture patients are less likely to survive at 1 year compared with younger patients, age does not seem to predict medical SAEs. This may be a result of the patients who are living to an older age before sustaining a hip fracture having less medical comorbidities, and in clinical practice, it is often the case that the older hip fracture patient is "fitter."

A higher BMI may be protective for medical SAEs in hip fracture patients. The CDC (Centers for Disease Control and Prevention) categorize BMI into 4 universal categories —<18.5 underweight, 18.5–24.9 normal weight, 25–29.9 overweight, and >30 obese.[24] Sherrif et al reviewed the National Surgical Quality Improvement Program database for hip fracture patients, and of the 15,108 patients, they found that patients with very low BMI had a higher mortality rate than patients with a very high BMI, but that those at the extreme ends of the BMI spectrum suffered the most complications. Transfusion rates were observed to decrease as BMI increased.[25]

The strength of our study is that the data used here are sourced from a large-scale trial which had broad inclusion criteria. Recruitment also occurred from a large number of hospitals in diverse health care systems, therefore, giving a more accurate view of SAEs in hip fracture patients encountered in day-to-day practice, as well as increasing the generalizability of the external validity of our findings.

A limitation of our subanalysis is the loss of patients over the 24 months of follow-up in the original study (14.9%). However, the loss to follow-up was consistent with or better than other trials including hip fracture patients.[25] The HEALTH trial had unavoidable variables across the patient group, such as patient positioning, surgical exposure, use of traction, type of anesthetic, and physiotherapy and rehabilitation protocols, which may have affected results. Finally, as the data used here were from subanalysis of another trial, there is not as detailed information collected on each SAE, than if it had been a trial designed with SAE as the primary outcome.

In conclusion, total hip arthroplasty is associated with more SAEs than hemiarthroplasty and care should be taken in selecting patients for this treatment. Cement does not increase the incidence of SAEs, and clinicians should remain confident to use this technique when appropriate. Age alone is not a predictor of medical SAEs; therefore, each hip fracture patient should receive individualized care. We hope that the findings of this subanalysis can aid the clinician when deciding the most appropriate surgical treatment for this vulnerable group.

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