

Assessment of opioid administration patterns following lower extremity fracture among opioid-naïve inpatients: retrospective multicenter cohort study

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BACKGROUND: Prescribing habits during admission have largely contributed to the opioid epidemic. Orthopedic surgeons represent the third-highest opioid-prescribing specialty. Since more than half of body fractures in Saudi Arabia have been lower extremity fractures, it is imperative to understand opioid administration patterns and correlates among opioid-naïve inpatients.

OBJECTIVES: Assess opioid administration patterns and correlates among opioid-naïve inpatients with lower extremity fractures.

DESIGN AND SETTINGS: Retrospective cohort

PATIENTS AND METHODS: Opioid naïve individuals aged 18 to 64 years, admitted due to lower extremity fracture from 2016 to 2020 were included. Data was collected from health records of the Ministry of National Guard Health Affairs (MNG-HA) at five different medical centers. The high-dose (≥ 50 MME) patients were compared with low dose (< 50 MME) patients. Any association between inpatient factors and high-dose opioid use was analyzed by multiple logistic regression.

MAIN OUTCOME MEASURES: Opioids taken during inpatient admission as measured by milligram morphine equivalents (MME)/per day.

SAMPLE SIZE: 1520 patients

RESULTS: Most of the 1520 patients (88.5%) received an opioid medication, while (20.3%) received high-dose opioids at a median daily dose of 33.7 MME/per day. The proportion of patients received naloxone (20.7%) was double among high-dose opioid inpatients. High-dose opioid patients during admission were two times more likely to receive an opioid prescription after discharge (odds ratio, 2.32; 95% confidence interval, 1.53, 3.51), and three more times likely to receive ketamine during admission (odds ratio, 3.02; 95% confidence interval, 1.64, 5.54).

CONCLUSION: Notable variabilities exist in opioid administration patterns that were not explained by patient factors. Evidence-based opioid prescribing practices should be developed for orthopedic patients to prevent opioid overprescribing and potential opioid overdose among orthopedic patients.

LIMITATIONS: Retrospective, unmeasurable confounders might have biased our results. Since based on National Guard employees, results may not be generalizable.

CONFLICT OF INTEREST: None.

Globally, the overall consumption of opioid analgesics more than doubled between 2009 and 2019 according to The International Narcotics Control Board (INCB) recent report; however, there has been a notable variation in consumed doses across countries.^{1,2} In some countries such as the United States and Canada this increase in quantity and doses has led to epidemics of opioid misuse and abuse over this period, which was largely attributed to inappropriate opioid prescriptions.³ Thus, prescribing habits during admission have largely contributed to the opioid epidemic.⁴ In the last decade, opioid overprescribing whether during admission or after discharge, is considered to have a major role in shaping the modern opioid use disorder crisis in the United States and other parts of the world.^{5,6} More than half of patients hospitalized annually receive an opioid during their hospitalization, which might be a first opioid exposure.⁷ As a result of high opioid utilization, overdose deaths from prescription opioid and illicit opioids are responsible for the highest drug overdose mortality rates ever recorded, accounting for more than 63 thousand deaths in 2016 alone.⁸

In Saudi Arabia, the initial opioid exposure usually occurs after admission following a road injury, which has been a public health challenge for years. The 2018 World Health Organization global status report on road safety estimated that there were more than nine thousand motor vehicle crashes (MVC) fatalities in Saudi Arabia.⁹ The estimated mortality was 28.8 deaths per 100 000 population, which is a relatively high mortality rate compared to other high-income countries. Large numbers of individuals involved in motor vehicle injuries often require long-term trauma rehabilitation due to different types of trauma. Lower extremity fracture is among the highest trauma classification for those involved with MVC.^{10,11} Thus, it is very likely for individuals involved in MVC to be seen and admitted by an orthopedic surgeon where the first opioid prescription might be given. Therefore, in Saudi Arabia, the lower extremity fracture population is at risk of long-term opioid utilization during admission.

Orthopedic surgeons represent the third-highest opioid-prescribing specialty compared to other specialties.¹² Approximately, one out of each ten opioid-naïve patients undergoing orthopedic surgery is at risk for chronic opioid dependence and overdose.¹³ Naïve patients are defined as those with no prescribed opioid medication in the 30 days before admission.¹⁴ Inpatient opioid exposure may result in an increased proportion of inpatient complications and subsequent opioid abuse or dependence.¹⁵ Therefore, further

attention to patterns of inpatient opioid exposure is crucial. In Saudi Arabia, according to The International Narcotics Control Board in 2020, the consumption of opioid products has increased dramatically from 2009 to 2019 but is still at low doses compared to the United States.¹⁶ However, little is known about the inpatient setting of opioid administration and factors associated with it as previous Western and Middle Eastern studies were heavily focused on outpatient opioid prescription patterns.^{2,17,18} Hence, assessing and understanding the opioid administration patterns among opioid-naïve inpatients for pain due to lower extremity fracture is necessary to inform clinical decisions on pain treatment and its correlation with opioid prescription after discharge.¹² To our knowledge, no previous multicenter study has evaluated inpatient opioid consumption among lower extremity fracture inpatients. This is relevant in Saudi Arabia because the incidence of lower extremity fracture represents approximately 6 out of 10 body fractures.¹⁹ Moreover, we shine some light on the situation in a country with no opioid epidemic and how it differs from a country facing an opioid epidemic crisis. In Saudi Arabia the number of MVCs has continued to rise, resulting in a large number of lower extremity fracture injuries that require hospital admissions. It is imperative to examine this population with susceptibility to high-risk first-time exposure to an opioid prescription. To fill these knowledge gaps, we used inpatient and outpatient electronic health record data from a large health system between 2016 and 2020 to examine inpatient opioid administration among opioid-naïve patients.

PATIENTS AND METHODS

The current study is a retrospective cohort (chart review) study using data from the Ministry of National Guard Health Affairs' (MNG-HA). Data was extracted from the administrative electronic health records system BESTCare at MNG-HA. MNG-HA includes five medical cities in five different regions (Riyadh, Jeddah, Madinah, Alhassa, and Dammam) in Saudi Arabia with more than 2800 overall total beds. MNG-HA in Riyadh serves the central region, while MNG-HA in Jeddah and Madinah serve Western and Southern regions of Saudi Arabia. MNG-HA in Alhassa, and Dammam serve the Eastern and Northern regions. Due to the high prevalence of MVCs in both urban and rural cities in Saudi Arabia, all five medical cities provide orthopedic services. MNG-HA provides all types of care to all National Guard soldiers, their dependents, and individuals residing in Saudi Arabia, starting from primary health care up to tertiary specialized care. The

ethics committee approved this study (RYD-20-419812-161716). No informed consent was needed because of the retrospective, observational design nature of this study.

All individuals eligible for analysis were patients aged 18 to 64 years old, and were primarily admitted due to lower extremity fracture (pelvis, hip, thigh, knee, leg, ankle, foot, and toes) from 1 January 2016, to 31 December 2020, based on ICD10 code, the expanded version of the World Health Organization, Australian Modification. We excluded patients who were diagnosed with malignancy, sickle cell anemia, thalassemia, multiple orthopedics admissions, no outpatient clinic visits (**Figure 1**). In terms of opioid medications, medical records were abstracted for all prescriptions written in the 90 days before the patient admission date and up to 365 days after discharge. Opioid medications as specified by the patient on intake were also identified during the pre-admission period. Post-discharge prescription was defined as an opioid prescription up to one year after discharge. Naïve patients were defined as those with no prescribed opioid medication in the 30 days before admission, and with no documented history of opioid use and who had not received prescriptions for opioids in this time period.¹⁴

The primary outcome of interest was opioids taken during inpatient admission following lower extremity fracture. We used milligram morphine equivalent (MME) per day as a value assigned to

opioids to represent their relative potencies.¹⁷ We stratified patients into three groups: those who did not receive an opioid during admission, and those who received a high dose of opioids per day, or a low dose per day using The Centers for Disease Control and Prevention (CDC) guidelines for prescribing opioids. We calculated MMEs/per day by adding the total daily amount of each opioid product that the patient took and then using the CDC conversion reference based on morphine. Then we calculated the average day rate for opioid consumption relative to morphine. We calculated the MMEs per day for each prescription as the product of the medication strength, number of units, number of refills, and the relevant conversion factor using CDC conversion reference table.²⁰ Accordingly, we defined opioid strength of administration into those who received dosages ≥ 50 MME per day as a high-dose opioid and those who received dosages < 50 MME per day as a low-dose opioid as this is the lowest high-dose threshold that guidelines recommend clinicians to avoid.²⁰

On the basis of prior studies, we included information on patient, clinical and hospital characteristics, calendar year and geographic location as covariates in our multivariable regression models. Patient demographic factors included gender, age (in categories: 18–30, and 31–64 years old); calendar year admission, body mass index, body region fracture, the Charlson Comorbidity Index (CCI) as mild for scores of 1–2, moderate for 3–4 and severe for ≥ 5 .^{19–21} We further included hospitalization-related factors such as surgery performed, type of anesthesia, intensive care unit (ICU) admission, days of ICU admission, days of hospital admission, and patients admitted through the Emergency Department. We included naloxone prescription during admission, which is commonly used for opioid overdose reversal,^{22,23} and other sedative and pain medications given during and before admission such as lorazepam during admission, ketamine during admission, lorazepam before admission, and morphine before admission at least a month prior to admission.

We first examined the descriptive statistics to compare patient demographics, clinical and inpatient-related factors across different levels of MMEs/per day. We used a univariate analysis, to compare patient characteristics across different levels of MME/per day. Bivariate associations were assessed using chi-square, the Fisher exact test for categorical variables, the non-parametric Spearman correlation test for continuous variables that violated normality, and the ANOVA test for class category variables with more than

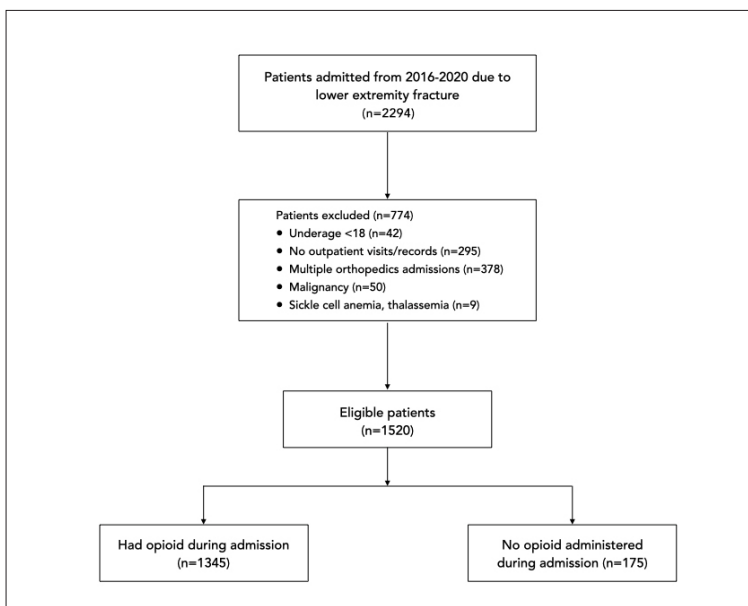


Figure 1. Flow diagram of patient selection.

two levels. The aim of the study was to understand and assess the rate of opioid use among inpatients diagnosed with lower extremity fractures, and to estimate predictors for high-risk opioid overdose. We used a maximum likelihood logistic regression model to examine the association between inpatient-related factors, demographics and clinical characteristics and high-dose opioid use. We first obtained univariable unadjusted estimates of the observed associations and then did a multivariable analysis that adjusted for significant confounders. We conducted ordinal regression analysis to estimate predictors of high-risk opioid overdose. We assessed the model of fit using the Akaike Information Criterion. Box-Tidwell method used to examine collinearity, indicated no significant interaction between the continuous variables and the log of the continuous variable ($P=.14$). We also conducted an assessment for multicollinearity between exposures with no high polychoric correlation observed. All test assumptions were met. We further used purposeful variable selection for model building.²³ Demographic, clinical and inpatient-related variables retained for analysis were used in the final multivariable logistic regression model. All analyses were performed using SAS 9.4 with two-sided P value ($\alpha=0.05$).

RESULTS

From 2016 to 2020, 1520 individuals were admitted for a traumatic lower extremity fractures injury and were included in the final analysis after applying exclusion criteria. More than eight out of each ten lower extremity fractures received an opioid medication (88.5%). At admission, 309 (20.3%) patients received high-dose opioids at a median daily MME of 70.0, 1036 (68.2%) received low-dose opioids, and 175 (11.6%) did not receive an opioid during admission (**Table 1**). The mean age for inpatients receiving high-dose opioids was slightly lower than low-dose opioid patients and those not receiving an opioid during admission. The cohort was predominantly, male across all groups. About one-fourth of the cohort were obese, while only 8% of those did not receive opioid medication were obese. Body region fracture differed significantly across inpatients with and without opioid administration ($P<.0001$). The hip and thigh were the body regions fractured the most among high-dose inpatients (35.6%). Conversely, a severe CCI score was highest among low-dose opioid inpatients (5.4%).

The majority of hospitalized patients underwent surgery (94.5% to 93.3%), while 76.6% of inpatients without an opioid prescription had surgery (**Table 1**).

Two-thirds of the high-dose patients were admitted in the Riyadh region (77.7%). There were no determined patterns of frequency of opioid administration across the period of study, but the year 2020 was the lowest year of opioid consumption overall (12.3%). The proportion of ICU admissions was double among high-dose opioid patients compared to low-dose patients (**Table 2**). More than half of both high- and low-dose opioid recipients were admitted through the emergency department. Compared to low-dose patients, high-dose opioid patients had more discharge prescriptions (**Table 2**). The proportion of patients receiving naloxone (opioid overdose reversal) (20.7%) was more than double among high-dose opioid inpatients compared to low-dose opioid inpatients (8.0%). The same patterns were observed for sedative medications, ketamine during admission where the highest proportion was among high-dose opioid patients (**Table 2**). The proportion of patients with history of opioid use was double among patients with low-dose opioid recipients compared to high-dose recipients.

The adjusted multiple regression model showed that patients with high-dose opioid during admission were more likely to be obese, less likely to be admitted for more than 7 days, and more likely to have multiple body region fractures than those who were not given opioids during admission (**Table 3**). Patients with high-dose opioid during admission were three times more likely to be admitted to the intensive care unit (ICU) and two times more likely to undergo surgery compared to those who did not receive opioid. Patients with high-dose opioid during admission were two times more likely to receive an opioid prescription post discharge, and three times more likely to receive naloxone during admission than those who did not receive an opioid during admission. Similarly, high-dose opioid patients were three times more likely to receive sedatives during admission.

DISCUSSION

In this retrospective multicenter cohort study, we present four key findings. First, eight out of ten inpatients with lower extremity fractures were given opioid medication during hospitalization. In addition, two in ten traumatic lower extremity fractures inpatients received high-dose opioids with the largest proportion in the high-dose group who underwent surgery, and some who needed ICU admission. Likewise, opioid use was common even for medical admissions with fewer days of hospital stay and younger ages. Conversely, high-dose MME/per day

Table 1. Demographic and clinical characteristics for inpatients diagnosed with lower extremity fracture by opioid dose (n=1520).

	High- dose opioid per day (≥ 50 MME)	Low- dose opioid per day (< 50 MME)	No opioid during admission	P value
Total	309 (20.3)	1036 (68.2)	175 (11.5)	
Milligram morphine equivalent (median, IQR)	70.0 (58.0, 96.9)	26.0 (14.3, 37.8)	NA	<.0001
Age (years), (median, IQR)	34.0 (25.0, 51.0)	34.0 (25.0, 51.0)	30.0 (23.0, 43.0)	.05
Gender				.05
Male	227 (73.5)	703 (67.9)	131 (74.9)	
Female	82 (26.5)	333 (32.1)	44 (25.1)	
Body mass index				
Underweight	11 (3.6)	39 (3.8)	4 (2.3)	
Normal	61 (19.7)	226 (21.8)	12 (6.9)	<.0001
Overweight	75 (24.2)	223 (21.5)	20 (11.4)	
Obese	89 (28.8)	284 (27.4)	14 (8.0)	
Unknown	73 (23.6)	264 (25.5)	125 (71.4)	
Body region fracture				
Ankle and foot	37 (12.0)	206 (19.9)	58 (33.1)	
Hip and thigh	110 (35.6)	283 (27.3)	38 (21.7)	
Knee and lower leg	59 (19.1)	222 (21.4)	38 (21.7)	<.0001
Lower limb (various or unspecified regions)	31 (10.0)	145 (14.0)	30 (17.1)	
Pelvis	40 (10.4)	119 (11.5)	9 (5.1)	
Multiple body regions	32 (12.9)	61 (5.9)	2 (1.1)	
Charlson comorbidity index				
Mild	48 (15.5)	151 (14.6)	25 (14.3)	
Moderate	15 (4.8)	45 (4.3)	10 (5.7)	.83
Severe	11 (3.6)	56 (5.4)	7 (4.0)	
No comorbidity	235 (76.0)	784 (75.7)	133 (76.0)	
Performed surgery				
Yes	292 (94.5)	967 (93.3)	134 (76.6)	<.0001
No	17 (5.5)	69 (6.7)	41 (23.4)	
Type of anesthesia				
General	260 (84.1)	821 (79.2)	110 (62.9)	
Spine/ Epidural	14 (4.5)	36 (3.5)	1 (0.6)	<.0001
Other (Nerve Block/ Topical/MAC/local)	35 (11.3)	179 (17.9)	64 (36.6)	

Table 1 (cont.). Demographic and clinical characteristics for inpatients diagnosed with lower extremity fracture by opioid dose (n=1520).

	High-dose opioid per day (≥ 50 MME)	Low-dose opioid per day (< 50 MME)	No opioid during admission	P value
Regions				
Riyadh	240 (77.7)	624 (60.2)	84 (48.0)	<.0001
Jeddah	26 (8.4)	220 (21.2)	64 (36.6)	
Madinah	11 (3.6)	53 (5.0)	6 (3.4)	
Dammam	12 (3.9)	70 (6.8)	15 (8.6)	
Alhassa	20 (6.5)	70 (6.8)	6 (3.4)	
Year				
2016	63 (20.4)	166 (26.2)	12 (6.9)	<.0001
2017	81 (24.6)	218 (21.0)	61 (34.9)	
2018	56 (18.1)	260 (25.1)	47 (26.9)	
2019	74 (21.0)	224 (21.6)	31 (17.7)	
2020	35 (12.3)	168 (16.2)	24 (13.7)	

Data are n (%) unless noted otherwise. ANOVA test for more than two categories per variable, chi-square test and Fisher exact test for less than five observations per cell. MME: Milligram morphine equivalent (MME).

was not common among older patients, females,²⁴ and patients with lower leg fractures, and high CCI score as those patients usually demanded a higher daily MME/per day than their counterparts due to their pain severity levels.²⁵ The variations of opioid use among lower extremity fracture inpatients could be attributed to discordance in pain intensity, and ability to manage pain among orthopedic inpatients.^{26,27} Orthopedic surgeries are some of the most traumatic, often involving reconstruction of the bone, tendon, and muscle.²⁸ Consequently, orthopedic surgeons often prescribe opioids to help manage the severity of pain. In usual orthopedic practice, several considerations are taken to provide the safest decision in how to manage pain such as patient opioid history of use, and standardized amount of opioid based on type of fracture or procedure.²⁹ Heterogeneous patient populations and procedure types complicate the surgeon's decision-making processes for prescribing opioids.

On the other hand, there are various studies that have reported inappropriate and overprescribing of opioids by orthopedic surgeons for both inpatients and at discharge.^{3,30} Orthopedic trauma patients may be at higher risk for preoperative opioid use and non-medical opioid use due to higher dose of opioid medication received during admission.^{28,31} Fracture patients admitted at trauma centers were

significantly more likely to use opioids preoperatively than in the general population. Also, preoperative opioid use is associated not only with longer opioid use but also with frequent postoperative doctor visits after discharge.^{31,32} The potential consequences of receiving high-dose opioid during admission include the risk of overdose. Dunn and colleagues found that recent opioid use was associated with an increased risk for any overdose events and serious overdose events compared to no-opioid using patients.³⁰ In our finding, the median daily MME/per day per patient among high-dose opioid recipients was 70.0 and the risk of overdose was 3.5 times higher than patients who did not receive an opioid, which means 20% of all lower extremity fracture inpatients were at potential risk of overdose due to high opioid consumption during admission. Thus, there is concern for in-hospital opioid use in the orthopedic trauma population at MNG-HA medical centers.

Our finding that one fifth of our inpatient population received a high dose of opioid explains our second finding that the proportion of inpatients receiving naloxone (opioid overdose reversal) was double among high-dose opioid inpatients compared to low-dose opioid inpatients. It is well known that naloxone is considered the best practice for reducing patient death associated with opioid overdose if administered in time.^{21,33,34} In our study, approximately two out of

Table 2. Admission characteristics hospital and medication related characteristics for patients diagnosed with lower extremity fracture by opioid dose (n=1520).

	High- dose opioid per day (≥50 MME)	Low- dose opioid per day (<50 MME)	No opioid during admission	P value
Total	309 (20.3)	1036 (68.2)	175 (11.5)	
Admitted to ICU				
Yes	18 (5.8)	26 (2.5)	-----	.0005
No	291 (94.2)	1010 (97.5)	175 (100.0)	
Days in ICU (median, IQR) (n=44)	8 (4.2, 14.2)	7 (2.0, 16.0)		.83
Patients admitted through Emergency Department				<.0001
Yes	189 (61.4)	532 (51.3)	41 (23.4)	
No	119 (38.6)	504 (48.6)	134 (76.6)	
Days in hospital, mean (median)	8 (4.0, 13.0)	7 (2, 14)		<.0001
Post-discharge opioid prescription				
Yes	40 (12.9)	78 (7.5)	4 (2.3)	.0001
No	269 (87.1)	958 (92.5)	171 (97.7)	
Naloxone prescription during admission				<.0001
Yes	64 (20.7)	83 (8.0)	-----	
No	245 (79.3)	953 (92.0)	175 (100.0)	
Sedative medication use during admission				<.0001
Yes	32 (10.4)	56 (5.4)	2 (1.1)	
No	277 (89.6)	980 (94.6)	173 (98.9)	
Ketamine used during admission				.003
Yes	19 (6.1)	16 (1.5)	-----	
No	290 (93.8)	1020 (98.5)	175 (100.0)	
History of sedative use				.14
Yes	9 (2.9)	56 (5.4)	11 (6.3)	
No	300 (97.1)	980 (94.6)	164 (93.7)	
History of opioid use				.006
Yes	19 (6.1)	131 (12.6)	20 (11.4)	
No	290 (93.8)	905 (87.4)	155 (88.6)	

Data are n (%) unless noted otherwise. ANOVA test for more than two categories per variable, chi-square test and Fisher exact test for less than five observations per cell. MME: Milligram morphine equivalent (MME). (n=44 for days in ICU).

Table 3. Predictors of high-dose opioid (≥ 50 MME) per day vs no opioid during admission among inpatients diagnosed with lower extremity fractures (n=1520).

	Odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
Body mass index				
Underweight	0.59 (0.32, 1.08)	.36	0.88 (0.45, 1.71)	.92
Normal	Reference		Reference	
Overweight	1.24 (1.16, 2.41)	.001	1.14 (1.07, 1.62)	.02
Obese	1.54 (1.01, 2.54)	<.0001	1.23 (1.08, 1.73)	.002
Unknown	0.45 (1.3, 2.61)	<.0001	0.38 (0.27, 0.45)	<.0001
Days in hospital				
1-7 days	Reference		Reference	Reference
More than 7 days	0.79 (0.87, 0.59)	<.0001	0.34 (0.26, 0.45)	<.0001
Body region fracture				
Ankle and foot	0.43 (0.31, 0.58)	<.0001	0.38 (0.27, 0.54)	<.0001
Hip and thigh	Reference		Reference	
Knee and lower leg	0.71 (0.53, 0.95)	.71	0.36 (0.27, 0.47)	.02
Lower limb (various or unspecified regions)	0.74 (0.38, 0.75)	.01	0.55 (0.38, 0.81)	.001
Pelvis	3.84 (0.59, 1.21)	.35	1.42 (1.39, 2.16)	.003
Multiple body regions	3.2 (1.77, 2.86)	.006	2.28 (1.38, 3.75)	<.0001
Admitted to ICU				
Yes	2.08 (1.15, 3.75)	.01	3.09 (1.54, 6.17)	.001
No	Reference		Reference	
Performed surgery				
Yes	2.11 (1.44, 3.09)	.0001	2.93 (1.68, 5.09)	.0001
No	Reference		Reference	
Post discharge opioid prescriptions				
Yes	3.62 (2.8, 4.69)	<.0001	2.32 (1.53, 3.51)	<.0001
No	Reference		Reference	
Naloxone prescription during admission				
Yes	3.04 (2.17, 4.27)	<.0001	3.48 (3.26, 5.12)	<.0001
No	Reference		Reference	
Ketamine used during admission				
Yes	5.47 (2.01, 5.99)	<.0001	4.11 (1.96, 8.62)	.0002
No	Reference		Reference	

Table 3 (cont.). Predictors of high-dose opioid (≥ 50 MME) per day vs no opioid during admission among inpatients diagnosed with lower extremity fractures (n=1520).

	Odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
Sedative used during admission				
Yes	0.84 (1.89, 2.91)	.00002	0.61 (1.01, 1.82)	.0004
No	Reference		Reference	
History of opioid use				
Yes	0.89 (0.76, 0.98)	.05	0.74 (0.51, 1.12)	.14
No	Reference	Reference	Reference	

Model summary measures: Hosmer and Lemeshow goodness of fit ($P=.09$), Cox-Snell $R^2=0.64$, Nagelkerke $R^2=0.71$.

ten high-dose lower extremity fracture inpatients were given naloxone, which seems to indicate that many patients were at risk of overdose. On the other hand, there are no specific guidelines for opioid administration at NGHHA hospitals. This indicates a need to implement clinical decision support tools to avoid inappropriate and overprescribing prescribing of naloxone.

The third key finding indicates that high-dose opioid inpatients were two times more likely to receive an opioid prescription at discharge compared to those who did not receive opioids during hospitalization. Similarly, the fourth key finding indicates that high-dose opioid patients were four times more likely to receive ketamine during admission. It is well documented in the literature that high consumption of different types of sedatives or opioids during or before admission is significantly associated with a discharge opioid prescription compared to no-opioid or low-dose opioid use during admission.^{15,35,36} We observed that high-dose opioid recipient inpatients were more likely to use ketamine during admission as it is commonly used for the management of postoperative pain due to one of its interactions being at binding sites of opioid receptors.³⁷ Thus, ketamine might be a potential predictor of at discharge opioid prescription. In one of the few studies that have explored the potential impact of ketamine on at discharge opioid prescription, Brandal and colleagues did not observe an impact of ketamine prescription on discharge opioid prescribing practices.³⁸ However, their study focused on enhanced recovery after under the hypothesis that ketamine might decrease the need of opioid prescriptions after surgery as both medications are used for pain management.³⁸ Further studies should examine opioid orders at discharge from the hospital

on opioid prescription practices and prolonged opioid use. This is important as determining which is the most significant factor that predicts the frequency of at discharge prescription; it would help in identifying the population at risk of overdose. More research is needed to fill in this critical gap.

The study has several strengths. First, we used clinical administrative data with a clinical diagnosis confirmed by a health practitioner or physician. Second, the study is a multicenter study that included hospital data from the major cities or most populated cities in Saudi Arabia and had a large sample size. To our knowledge, no previous multicenter study has examined opioid inpatient consumption in MNG-HA medical centers. Our findings should also be viewed in light of several limitations. First, given the retrospective nature of the analysis, there may be unmeasurable confounders that might have biased our results. Second, the information used was based on National Guard employees and their dependents, therefore, these results may not be generalizable. Third, it is possible that some patients required increased opioid administration for a different diagnosis that was not accounted for in this study. However, this potential confounder was minimized by excluding cancer patients and non-orthopedic surgery.

In conclusion, our analysis of 1520 inpatients with traumatic lower extremity fractures across five institutions found that there are notable variabilities in opioid administration patterns that were not explained by patient factors. Furthermore, high average MME/day administration among lower extremity fractures high-dose inpatients was observed. One fifth of extremity fractures inpatients received high-dose opioids, and had a high naloxone administration rate. Accordingly, there was a high overdose rate among high-dose

opioid inpatients. It is imperative that evidence-based opioid prescribing practices for orthopedic patients are developed to prevent opioid overprescribing, and potential opioid overdose among orthopedic patients admitted in MNG-HA hospitals. Additional studies that examine other inpatient populations with frequent opioid prescriptions are recommended. More importantly, follow up of outpatients who received opioid prescriptions is highly recommended.

Availability of data and materials

For further assistance please contact the corresponding author.

Authors' contributions

All authors contributed equally to this manuscript. All authors read and approved the final manuscript.

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