Title: Outcomes following lower limb fracture surgery in South Africa: A prospective cohort study of 495 patients

Abstract

Background

Musculoskeletal injuries are more common in Sub-Saharan Africa than anywhere else in the world, yet there is limited evidence to guide the management of these injuries in low- and middle-income countries. We aimed to evaluate the outcomes of lower limb intramedullary nailing (IM) for long bone fractures in South Africa and identify predictors of these outcomes.

Methods

Adults who sustained tibia and femur shaft fractures and were treated with IM at two tertiary hospitals in South Africa from September 2017 to December 2018 were followed for at least 12 months. We compared fracture characteristics and outcomes between open and closed fractures. We employed multivariable logistic regression models to investigate the associations between union status at 6 months, infection and quality of life (EuroQol EQ-5D-5L) in open and closed fractures.

Results

In total, 495 patients with tibia and femur fractures underwent IM nailing. 240 patients had open fractures and 255 patients presented with closed fractures. Gunshot wound fractures comprised 52% (124/240) of the open fractures.

The overall delayed and non-union rate reported in our study was 18% and 5.8% across the study population. The rate of deep surgical site infection, superficial site infection and late infection in the study population was 6%, 2% and 2% respectively.

Open fractures had a higher odd of delayed union (aOR: 1.97, 95%CI: 1.03 – 3.75), non-union (aOR: 3.01, 95%CI: 1.20 – 7.53), and early surgical site infections (aOR: 3.46, 95%CI: 1.39 – 8.62) when compared to closed injuries. The overall health-related quality of life outcomes was comparable between open and closed fractures at the 9-month follow-up.

Conclusions

Our study demonstrates comparable outcomes of infection and fracture healing rates in patients who undergo internal fixation for lower limb fractures in a resource-limited setting, when compared to study populations in a high-income country.

Level of evidence: Level II

Key Words: bone healing, delayed union, fracture, human immunodeficiency virus, gunshot, intramedullary nailing, nonunion, union

Introduction

Injuries are the leading cause of death among people aged between 10-49 years and up to 50 people sustain temporary or permanent disabilities for every fatality (1). Injuries occur at disproportionately higher rates in low and middle-income countries (LMIC) (2-4), and approximately one billion people each year seek healthcare services for the treatment of traumatic injuries in these countries (2). Musculoskeletal injuries constitute the majority (78%) of cases and sub-Saharan Africa (SSA) has a higher incidence of musculoskeletal injuries than any other world region (2, 5). Moreover, in the majority of LMIC, musculoskeletal injury-related death and disability have been steadily rising (6). However, there is limited evidence to guide the management of these injuries in LMIC (7).

Lower limb long bone fractures (femur and tibia) rank among the top three anatomical sites of global injury in terms of prevalence (8). They can be treated effectively, with good clinical outcomes, within health systems that include timely prehospital care, safe definitive surgery, and rehabilitation (9, 10). Due to numerous barriers to care in low-resourced settings, surgical treatment of these fractures can be limited, resulting in poor outcomes and long-term disability (11-13). This has a significant economic impact on the individual, their dependants and the country as a whole since the majority of injuries occur in young adult males, who are commonly the main source of income within these communities (14).

There is a clear opportunity for cost-effective improvement of musculoskeletal injury care and outcomes across all LMIC. However, there is currently limited available evidence on the outcomes of lower limb long bone fractures in resource-limited settings (15).

We aimed to evaluate the outcomes of lower limb IM for long bone fracture in two tertiary hospitals in South Africa. We explored results following surgery for open and closed lower limb fractures, evaluating treatment and recovery outcomes, as well as the subsequent impact of their injury on quality of life.

Methods

Study design and participants

This study is part of the HIV in Orthopaedic Skeletal Trauma (HOST) Study, a multicentre prospective case-cohort study in Cape Town, South Africa (16). Participants who underwent surgery for a lower-limb fracture (femur or tibial shaft fracture) between September 2017 and December 2018 at X Hospital or Y Hospital were included. These two hospitals are the only public tertiary trauma centres in the Western Cape, serving over 7 million people and providing care that is representative of tertiary referral hospitals across the whole of South Africa (17).

All patients older than 18 years who underwent intramedullary (IM) nailing for open or closed fracture fixation within 2 weeks of tibia and femur fractures were eligible for inclusion. At both study sites, all low velocity gunshot wound fractures had their bullet entry and exit wounds left to heal by secondary intention. Across both study sites, all gunshot wound fractures are then given antibiotics prophylaxis at presentation and surgery. However, this information was not collected as part of this study protocol.

Patients were excluded from the study if they had a major head injury, a pre-surgical infection at the fracture site, an open fracture that waited over 48 hours before the initial debridement, severe burns, a pathological fracture, or if they were unable or unwilling to comply with the study procedures, questionnaire completion, or follow-up attendance.

The HIV in Orthopaedic Skeletal Trauma (HOST) study obtained ethical approval from the ethics committees of the study sites: the University of Cape Town, Faculty of Health Sciences (ref: 590/2016) and the University of Stellenbosch (ref: N17/05/052).

Baseline

Two local research nurses conducted all data collection using a database hosted on REDCap for every patient recruited (18). Baseline data was collected upon recruitment, and all participants were followed up for at least 12 months. Individuals not taking anti-retroviral therapy (ART) were offered testing to confirm their HIV status, with new diagnoses referred to HIV community clinics. Outpatient assessments and x-rays were undertaken at 2 and 6 weeks and at 3, 6, 9 and 12 months to assess bone union. All participants attended a face-to-face outpatient clinic six months post-operatively. If participants' fractures were confirmed to have united at 6 months, participants were followed up by telephone at 9 and 12 months. Participants were reimbursed for all travel expenses related to face-to-face follow-up appointments. A nonunion was confirmed if fracture union had not occurred at 9 months after injury. Participants with confirmed nonunions were offered further management, according to local protocols for treatment of nonunion. If, at any time, the responsible consultant surgeon felt that there was a need for further surgery to achieve union before 9 months, it was offered after a joint discussion with at least 2 consultant orthopaedic surgeons (ML, SMG, SMQ).

Definitions and outcomes

The primary outcome for the study was the proportion of participants with delayed bone union at 6 months follow-up. The secondary study outcomes were non-union, infection, and self-reported health-related quality of life.

Bone healing was evaluated using the validated radiological union scoring system for the tibia (RUST) (19, 20). Fracture union was defined as radiological union on RUST score [score of 3 on at least 3 of the 4 cortices (anterior, lateral, medial, or posterior cortex)—a total RUST score of 9 or more] within 6 months of surgery (20-22). Delayed bone union was defined as impaired bone healing at 6 months on RUST score < 9 (20-22). Nonunion was defined as either impaired bone healing at 9 months on RUST score < 9 or the need for further surgery to achieve union (RUST score 9) before 9 months (decision made by 2 orthopaedic surgeons).

Two blinded independent reviewers (both orthopaedic surgeons) assessed radiological fracture union on radiographs. In case of discrepancies in RUST scoring between the reviewers, a third reviewer (orthopaedic surgeon) independently undertook a review of the radiograph to determine the final outcome.

Infection was diagnosed using the United States Centers for Disease Control and Prevention criteria for "superficial surgical site infection (SSI)" and "deep surgical site infection (DSI)." A diagnosis of early infection was determined by combining the number of SSIs and DSIs. Late infection was diagnosed as any late-wound breakdown (>30 days for closed reduction of fractures or >90 days for openly reduced fractures) or sinus formation or unexplained late pain with associated radiological changes consistent with preimplant infection (23).

Self-reported health-related quality of life was assessed using the EuroQol EQ-5D-5L (24-26) and Disability Rated Index (DRI). (27) The index utility scores for EQ-5D-5L were cross walked to EQ-5D-3L (28) before applying the EQ-5D-3L value set for the Zimbabwe population since there is no country validated EQ-5D-5L value set for South Africa (29).

Finally, the crowding index, calculated as the number of co-residents per room, or household density, is an indicator of socioeconomic status. (30)

Statistical methods

Baseline characteristics were summarised using percentages and comparison between open and closed fractures was conducted using $\chi 2$ tests. A non-parametric Wilcoxon rank-sum (Mann-Whitney) test was used to compare the distribution of EQ-5D-3L index scores between the 2 groups. Patients were included in the outcome analysis at each time point only if both baseline and corresponding follow-up data were available. multivariable logistic regression model was developed to estimate the odds ratio (OR) and a 95% confidence interval (CI) for the primary outcome (delayed union), comparing open and closed fractures and adjusted for confounders identified *a priori* through causal diagrams, such as age, sex, HIV status, and BMI status. A multivariable logistic regression model was used to estimate the OR and 95% CI for secondary outcomes of non-union, infection, comparing open and closed fractures and adjusted for age, sex, HIV status and BMI status. A random effects model was used to account for participants with multiple tibia or femur fractures, which are correlated within the same participant. In the linear regression model estimating the EQ-5D-3L index score at 6 months, adjustments were made for the same covariates as in the logistic regression model, namely age, sex, HIV status, and BMI status

Data were managed and analysed using Stata 18, StataCorp 4905, Lakeway Drive College Station, Texas 77845, USA.

We followed STROBE guidelines for reporting results (31).

Results

Demographics and injury characteristics

Between September 2017 and March 2021, 495 patients presented with 542 open and closed tibia and femur fractures, all of which were treated with IM nailing. In total, there were 240 patients (260 IM nailings) who suffered from an open fracture and 255 (282 IM nailing) with a closed injury. The overall prevalence of HIV in the study population was 20.7% (85/409), which is slightly higher than the national prevalence of HIV within a similar age group (17.1%).(32) It is common for study cohorts focused on trauma to report higher rates of HIV, when compared to the national prevalence.(23) Several demographic differences between patients with open fractures and closed fractures are highlighted (Table 1). Notably, a higher proportion of males had open fractures compared to closed fractures (85% vs. 74%, p = 0.002), and the HIV-positive status was more prevalent in the closed fracture group (12% vs. 22%, p = 0.003). A higher proportion of patients with open fractures were within the "normal" BMI range compared to those with closed fractures (60% vs 48%, p=0.042).

Over one quarter of patients (131/495, 26%) were seen at a district level hospital, prior to transfer to one of the specialist hospitals for surgery, with a similar proportion of open and closed injuries transferred (closed 24% (61/255) vs open 29% 70/240). Nearly all participants reported excellent pre-injury quality of life and had a similar pre-injury level of socioeconomic status (crowding index). (Table 1)

Patients with closed fractures were more prone to injuries resulting from high-energy incidents, such as motor vehicle accidents (MVA) involving drivers or passengers (14% in open fractures vs. 31% in closed fractures) and pedestrians (24% in open fractures vs. 46% in closed fractures). Gunshot wound fractures comprised 52% (124/240) of the open fractures. If these fractures were removed, high-energy mechanisms resulted in similar rates of open and closed fractures (MVA driver/passenger 30% (34/116) open vs 31% (80/255) closed, MVA pedestrian 49% (57/116) open vs 46% (117/255) closed (Table 2).

Regarding the site and injury severity score, there was a higher number of open tibial fractures (57%) compared to closed fractures (49%), though the difference is not statistically significant (p = 0.075).

Closed injuries had a higher injury severity score than open fractures (p = 0.019) (Table 3). However, when gunshot wound fractures are removed, there was no evidence of a difference in injury severity between open and closed injuries (p = 0.073).

Over half of open fractures were Gustilo Anderson (GA) type I injuries (52%, 136/260), and almost all gunshot wound fractures were GA type I (81%, 109/134). The majority (97%, 252/260) of participants who sustained an open fracture had their antibiotics within 24 hours of their injury and all the participants were given antibiotics according to hospital guidelines prior and following their surgical procedure (Table 4).

Outcomes

Of the 495 patients recruited, 438 (88%) were followed-up at 6 months and 430 (87%) were followed up until 12 months. Of those reviewed at 12 months, 197 (82%) were open fractures and 233 (91%) were closed.

Infection

The SSI and DSI rate in the overall cohort of study participants was 2% (11/510) and 6% (30/494) (Table 5). None of the patients who developed a SSI, went on to have a DSI. There was a statistically higher rate of SSI and DSI in the open fractures compared to closed (Table 6). However, the was no statistically significant difference in late infection rates between the two groups (open 7/217 (7%) vs 4/254 (4%), p= 0.227). When the gunshot wound fractures were removed from the analysis, open fractures had a statistically increased risk of late infection when compared to the closed injuries (open 5/104 (5%) vs 3/234 (1%), p = 0.49)

Fracture healing

There was an overall delayed union rate of 18% (85/479 fractures) and of the 85 fractures that developed delayed union, 67% (57 fractures) healed between 6 – 9 months. Therefore, there was a non-union rate of 5.8% (28/479 fractures) within the whole study cohort. Open fractures had a statistically higher rate of delayed and non-union when compared to closed injuries (Tables 6 & 7).

Quality of life

At the 6-month follow-up, the mean EQ-5D-3L index score for patients with open fractures (n=240 fractures) was 0.828 (SD 0.074), while the mean score for patients with closed fractures (n=255 fractures) was 0.835 (SD 0.071). There was comparable health-related quality of life outcomes for patients with open and closed fractures (p=0.295).

Overall outcomes

The odds of a patient developing delayed union and non-union were higher in patients with open fractures compared to closed fractures (2.52, 95%CI: 1.55 – 4.10 and 3.11, 95%CI: 1.34 – 7.21 respectively). Patients with open fractures also had higher odds of developing early infection compared to patients with closed fractures (3.09, 95%CI: 1.51 – 6.32). These increased odds remain after accounting for potential confounders (Table 8). However, there is no evidence to suggest that the association between open and closed fractures differs in relation to the odds of developing late infections. The EQ-5D-3L index scores showed no significant association with either open or closed fractures, both in crude analysis and after adjusting for potential confounders, indicating that fracture type does not impact health-related quality of life in this study population.

Discussion

This is one of the first and largest studies to compare the clinical and health quality of life outcomes of patients with closed and open fractures that have undergone internal fixation in a LMIC.

Most of our patients were young adult males of working age. Patients with closed fractures were more likely to be HIV positive, with a higher BMI when compared to those who suffered an open injury. Both groups of patient's excellent pre-injury quality of life (EQ5D-L).

Closed fractures were more commonly associated with injuries from high-energy mechanisms, for example motor vehicle accidents. Whereas more than half of all open fractures were as the result of a gunshot injury. When gunshot wound fractures were excluded, very similar proportions of open and closed fractures were caused by high-energy mechanisms.

The overall delayed union rate in the overall study population was 18%. There is little evidence currently available that accurately reports the risk of delayed union of tibia and femur fractures following internal fixation. This is likely due to the varying definitions of delayed union available in the literature and commonly researchers report delayed union rates that would be classified as non-unions by definitions used in this study. Furthermore, the majority of research to date has focused on fracture non-union, rather than delayed union of fractures (33). However, an accepted figure of 15% has been used in the past and confirmed from previous research, the majority of which was from research in a high-income setting (34-37). Therefore, the overall delayed union rate in our study mirrors that reported in the literature, despite inaccuracies in a definitive definition.

The overall non-union rate reported in our study was 5.8% across the study population. Matching published data available in the literature which has reports non-union rates from 1.1-12.5% for femur and tibia fractures, for both open and closed injuries (37, 38).

The rate of deep surgical site infection (DSI) and superficial site infection (SSI) in the study population was 6% and 2% respectively. Recent literature indicates that the rate of post-operative SSIs in tibia and femur fractures, following fracture fixation, ranges from 3.4–4.2% and DSI rate of between 4.1- 6.4% (39). However, huge variations have been reported in the literature, from 2% to 88% depending on the area of the bone fractured and the fixation method used (40-43). Again, the rate of DSIs and SSIs in our study mirrors that published in the literature in cohorts undergoing similar procedures.

There was a statistically higher rate of SSI and DSI in the open fractures compared to closed but not late infection (Table 6). Gunshot wound fractures have been reported to have a lower rate of infection compared to open fractures through blunt mechanisms.(44) Therefore, as expected, when the gunshot wound fractures were removed from the analysis, open fractures had a statistically increased risk of late infection when compared to the closed injuries. Additionally, open fractures had a statistically higher rate of delayed and non-union when compared to closed injuries (Tables 6 & 7). These overall differences between outcomes in open compared to closed injuries in our study population are very similar to the published literature, the majority of which were undertaken in a high-income countries.(37), (38), (45), (46), (40), (47), (41), (43)

Strengths of the study include a large sample size of 495 patients, and a comprehensive capture of detailed demographic and clinical information. One of the main criticisms is that it was undertaken in a middle-income country and how translatable the evidence is too other LMIC. We acknowledge this as a limitation but South Africa has the highest income inequality in the world, with a Gini coefficient of around 0.67.(48) The Gini coefficient is a widely used statistical measure of how income is distributed in the population of a country. Therefore, although the country is classified as a middle-income country, the World Bank (2023) estimates that 18.2 million people (30% of the population) in South Africa live in extreme poverty. Conversely in Malawi, a low-income country with a population of just over 20 million people, only 14 million people (70% of population) live in extreme poverty.(49) Furthermore, 75% of the global population live in middle income countries, compared to 12% in low and 16% in high income countries.(50) Therefore, although our study was undertaken in a relatively well resource healthcare setting, significant economic inequalities mean that evidence from this study could have value and be translatable to other LMIC and a significant proportion of the global population. Our findings can also set a benchmark for other LMICs to use when comparing their own surgical outcomes from varying healthcare and resource settings.

Other limitations include missing data, and the studies focus on two tertiary centers, potentially limiting generalisability to other populations and healthcare systems across SSA. Additionally, the primary study sample size calculations were undertaken study as part of the HIV in Orthopaedic Skeletal Trauma (HOST) Study (16), a multicentre prospective case-cohort study focused on HIV and fracture healing.

Conclusion

Our study demonstrates comparable outcomes of infection and fracture healing rates in patients who undergo internal fixation for lower limb fractures in a resource-limited setting, when compared to study populations in high-income countries. This is the first study to report medium-term outcomes of a large cohort of patients who have undergone fracture surgery in a LMIC and sets a benchmark for future research into the clinical effectiveness of potential interventions to improve patient outcomes in this setting.

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Table 1: Demographic information per patient (n=495)

		Open fractures (n=240 patients)		Closed fractures (n= 255 patients)		p-value
Category		n	%	n	%	
Sex	male	204	85%	188	74%	
	female	36	15%	67	26%	**0.002**
Transferred from a district hospital	Yes	70	29%	61	24%	
	No	170	71%	194	76%	0.177
Age	18 - 30	104	45%	107	42%	
	31 - 40	78	33%	75	29%	
	41 - 50	39	17%	49	19%	
	51 - 60	9	4%	17	7%	
	60+	3	1%	7	3%	0.365
Drinks any alcohol	Yes	113	47%	109	43%	
	No	127	53%	146	57%	0.332
Current steroid use	Yes	0	0%	0	0%	
	No	240	100%	255	100%	0.999
Smoking status	Smoker	134	56%	136	53%	
	Non-smoker	106	44%	119	47%	0.577
HIV status	Negative	211	88%	198	78%	
	Positive	29	12%	56	22%	**0.003**
BMI, kg/m2	<18.5 (underweight)	17	8%	28	13%	
	18.5 - 24.9 (normal)	126	60%	109	48%	
	25 - 29.9 (overweight)	40	19%	57	25%	
	30+ (obese)	27	13%	31	14%	**0.042**
	Not recorded	30	-	30	-	
Crowding index, number of people per room	2 or less	185	78%	203	82%	
	3	34	14%	31	12%	
	4	11	5%	9	4%	
	5	2	1%	3	1%	
	6 or more	4	2%	2	1%	0.783
	Not recorded	4	-	7	-	
Disability Rating Index score pre-op	<50% (no disability)	239	100%	251	100%	0.999
	>=50% (disability)	0	0%	0	0%	
	Not recorded	6	-	4	-	
EQ-5D-3L index score	Mean (SD) pre- injury	0.898 (0.010)		0.898 (0.011)		0.982

Table 2: Injury characteristics per patient (n=495)

		Open fractures (n=240) patients		Closed fractures (n=255 patients)		
Category		n	%	n	%	p-value
Mechanism of injury	Low energy fall (e.g. fall from standing)	3	1%	24	10%	
	High energy fall (e.g fall from height)	8	3%	16	6%	
	Motor vehicle accident -driver / passenger	34	14%	80	31%	
	Motor vehicle accident - pedestrian	57	24%	117	46%	
	Assault - gunshot wound	124	52%	0	0%	
	Assault - sharp (knife/machete)	0	0%	2	1%	
	Assault - blunt	11	5%	13	5%	
	Crush injury	3	1%	3	1%	**0.0001**
Two or more fractures to tibia/femur	Yes	18	8%	29	11%	
	No	221	92%	226	89%	0.142
Other injuries	Yes	83	65%	85	67%	
	No	157	35%	170	33%	0.769
Pre operatic prophylactic antibiotics	Yes	238	99%	253	99%	
	No	2	1%	2	1%	0.951
No. IM nailings performed per participant	1	224	93%	229	89%	
	2	14	6%	24	9%	
	3	2	1%	1	1%	
	4	0	0%	1	1%	0.239

Table 3: Site and severity of fracture (n=542)

		Open fractures (n=260 fractures)		Closed fractures (n= 282 fractures)		
Category		n	%	n	%	p-value
Fracture site	Tibia	148	57%	139	49%	
	Femur	112	43%	143	51%	0.075
Injury severity score >16	Yes	43	17%	70	25%	
	No	216	83%	212	75%	**0.019**

Table 4. Open fracture characteristics and management

		n = 260 (%)
Open fracture initial management	IM nailing	220 (85)
	Washout and plaster only	26 (10)
	Washout and external fixator	14 (5)
Gustilo Anderson Classification	I	136 (52)
	II	31 (12)
	IIIA	74 (29)
	IIIB	16 (6)
	IIIC	3 (1)

Table 5: Infection outcomes per fracture (n=542)

		Open fractures (n=260)		Closed fractures (n= 282)		Univariate analysis
Category		n	%	n	%	p-value
Superficial surgical site infection	Yes	10	4%	1	1%	**0.04**
	No	233	96%	266	99%	
	Missing data	17	-	15	-	
Deep surgical site infection	Yes	20	8%	10	4%	**0.036**
	No	232	92%	262	96%	
	Missing data	8	-	10	-	
Early infection (either superficial or deep)	Yes	30	12%	11	4%	**0.001**
	No	223	88%	261	96%	
Late infection	Yes	7	3%	4	2%	0.227
	No	210	97%	254	98%	
	Missing date	43	-	24	-	

Table 6. Union status per fracture at 6 months

		Open fractures (n=221) 3 hardware failures and 36 lost to follow up		Closed fractures (n= 258) 24 lost to follow up		
Category		n	%	n	%	p-value
Union status 6 months	Union	166	75%	228	88	<0.0001
	Delayed union	55	25%	30	12	

Table 7. Union status per fracture at 12 months

		Open fractures (n=221) 3 hardware failures and 36 lost to follow up.		Closed fractures (n= 258) 24 lost to follow up		
Category		n	%	n	%	p-value
Union status 12 months	Union	201	91%	250	97%	0.006
	Non union	20	9%	8	3%	

Table 8: Association between open and closed fracture and outcomes

Outcomes	Crude odds, OR (95%CI)	p-value	Adjusted odds* aOR (95%CI)	p-value
Delayed union	**2.52 (1.55 – 4.10)**	**<0.001**	**2.22 (1.29 – 3.82)**	**0.04**
Non union	**3.11 (1.34 – 7.21)**	**0.008**	**2.79 (1.12 – 6.94)**	**0.003**
Early infection	**3.09 (1.51 – 6.32)**	**0.002**	**3.46 (1.39 – 8.62)**	**0.008**
Late infection	2.12 (0.61 – 7.34)	0.237	3.61 (0.93 – 14.09)	0.064
EQ-5D-3L index	Crude coefficient: 0.99 (0.98 – 1.01)	0.337	Adjusted coefficient: 0.99 (0.98 – 1.01)	0.357

* Data presented as the adjusted Odds ratio (aOR) and its 95% confidence interval (CI) from weighted logistic regression, which took variable in column as outcome, fracture status (open/closed) as the key predictor, controlling for age, sex, HIV status, BMI status.