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FACTORS ASSOCIATED WITH HUMERAL SHAFT NONUNION

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ABSTRACT

Background: The primary aim was to identify patient and injury factors independently associated with humeral diaphyseal fracture nonunion after non-operative management. The secondary aim was to determine the effect of management (operative/non-operative) on nonunion.

Methods: From 2008-2017, 734 humeral shaft fractures (732 consecutive skeletally-mature patients) were retrospectively identified from a trauma database. Follow-up was available for 663 fractures (662 patients, 90%) that formed the study cohort. Patient and injury characteristics were recorded. There were 523 patients (79%) managed non-operatively and 139 (21%) managed operatively. Outcome (union/nonunion) was determined from medical records and radiographs.

Results: The median age at injury was 57 (range 16-96) years and 54% (n=359/662) were female. Median follow-up was five (1.2-74) months. Nonunion occurred in 22.7% (n=119/524) of non-operatively managed injuries. Multivariate analysis demonstrated pre-injury NSAIDs (non-steroidal anti-inflammatory drugs; OR 20.58, 95% CI 2.12-199.48; p=0.009) and glenohumeral arthritis (OR 2.44, 95% CI 1.03-5.77; p=0.043) were independently associated with an increased risk of nonunion. Operative fixation was independently associated with a lower risk of nonunion (2.9%, n=4/139) compared with non-operative management (OR for non-operative/operative management 9.91, 95% CI 3.25-30.23; p<0.001). Based upon these findings, five patients would need to undergo primary operative fixation in order to avoid one nonunion.

Conclusions: Pre-injury NSAIDs and glenohumeral arthritis were independently associated with nonunion following non-operative management of a humeral diaphyseal fracture. Operative fixation was the independent factor most strongly associated with a lower risk of nonunion. Targeting early operative fixation to at-risk patients may reduce the rate of nonunion and the morbidity associated with delayed definitive management.

Level of Evidence: Level III (prognostic retrospective cohort study)

INTRODUCTION

The epidemiology of humeral diaphyseal fractures is well-established^{6,14,24,37,49,69,70}, but the effect of patient and injury characteristics upon fracture union is less clear. Some authors have reported an association between advancing age and nonunion following a humeral shaft fracture^{16,30}, whereas others have failed to identify such a relationship^{10,51}. Similarly, while smoking has been found to impair humeral diaphyseal fracture healing after both primary injury^{19,30,34,65} and nonunion treatment^{41,63,77}, conflicting evidence exists regarding its importance²³. There is also a lack of clarity about other suspected risk factors for nonunion including alcohol excess^{27,33,51,67} and obesity^{19,23,27,30}. There is a paucity of large studies analysing multiple factors to determine the strongest predictors of humeral shaft nonunion⁷⁸.

Humeral diaphyseal fractures can be managed non-operatively or operatively. Traditionally, non-operative management using a functional humeral brace has been preferred, with reported nonunion rates between 2% and 13%^{5,39,48,61,62,76}. However, recent studies have suggested this approach should be called into question^{4,25,59,60,67,68}, with nonunion occurring in up to 33% of patients³². This has led some to investigate and advocate for the increased use of early operative fixation in order to mitigate this complication^{20,25,43,54,73}.

The primary aim of this study was to identify patient and injury factors independently associated with humeral diaphyseal fracture nonunion after non-operative management. The secondary aim was to determine the effect of management (operative fixation/non-operative) on nonunion.

MATERIALS AND METHODS

Study cohort

In this retrospective cohort study, patients were identified from an established trauma database held at the study centre⁴⁹. All skeletally-mature patients (aged ≥ 16 years) sustaining a fracture of the humeral diaphysis – as defined by the *Arbeitsgemeinschaft für Osteosynthesefragen*-Orthopaedic Trauma Association (AO-OTA)⁴⁴ – between January 2008 and December 2017 were included. Other fracture patterns, re-fractures, pathological or periprosthetic fractures, non-residents and patients undergoing ‘delayed’ operative fixation (between six and 12 weeks post-injury) were excluded. Delayed procedures were rare (n=17) and not consistent with either primary operative fixation⁴ or failed non-operative management. Over the study period, 734 consecutive fractures were identified in 732 patients. Adequate follow-up was available for 663 fractures (662 patients), which formed the study cohort (**Figure 1**). Compared to the study cohort, patients lost to follow-up had a lower body mass index (median BMI 23.5kg/m² versus 26.9kg/m², p=0.003) and a higher incidence of open fractures (7.0%, n=5/71 versus 2.0%, n=13/663, p=0.009). There were no other differences between the study cohort and those lost to follow-up in terms of baseline patient or injury characteristics. The study centre is the only trauma unit serving a defined catchment population of approximately 710,000. The study was reviewed by the local NHS Research Ethics Service (NR/161AB6) and registered with the local musculoskeletal quality improvement group.

Patient background

The median age at injury was 57 years (range 16 to 96) and 54.2% (n=359/662) were female. Electronic patient records were reviewed. One or more medical comorbidities were documented in 70.1% of patients (n=464/662). Liver disease (2.0%, n=13/662) included viral hepatitis, alcoholic liver disease and non-alcoholic fatty liver disease. Inflammatory bowel

disease (1.2%, n=8/662) included Crohn's disease and ulcerative colitis. Cerebrovascular disease (5.1%, n=34/662) included transient ischaemic attack and stroke. Inflammatory arthritis (2.4%, n=16/662) included rheumatoid arthritis and psoriasis-related arthritis (mutilans). Skin conditions (1.7%, n=11/662) included eczema, psoriasis, cutaneous lupus and chronic idiopathic urticaria. Neuropsychiatric disorders (16.5%, n=109/662) included dementia, Parkinson's disease, schizophrenia, depression and anxiety. Ipsilateral glenohumeral arthritis was present in 6.2% of shoulders (n=41/663) and was diagnosed from medical records and/or radiographs taken at the time of injury. Regular use of non-steroidal anti-inflammatory drugs (NSAIDs) at the time of injury (2.1%, n=14/662) was documented. NSAIDs included ibuprofen, naproxen, diclofenac, COX-2 selective medications and high-dose aspirin; low-dose aspirin (75mg) was not considered an NSAID⁴⁷.

Smoking history and alcohol intake at the time of injury were recorded where this data was available from the medical record. Over one quarter (27.8%, n=167/601) were current cigarette smokers, 62.9% (n=344/547) consumed alcohol within recommended limits and 13.5% (n=74/547) consumed excess alcohol⁴⁶. Height and weight were used to calculate BMI, which was categorised according to WHO guidelines⁷⁵. Median BMI was 26.9kg/m² (15.0 to 59.7) and 30.7% (n=142/463) were classified as obese. Social deprivation was assessed using the Scottish Index of Multiple Deprivation (SIMD) 2016⁶⁶. Patients were assigned a deprivation score according to their postcode at the time of injury, with scores divided into five quintiles (one = most deprived, five = least deprived).

Injury characteristics

A fall from height was defined as any height greater than six feet¹⁵. The most common mechanism of injury was a fall from standing height (72.8%, n=477/655). The majority were left-sided injuries (52.0%, n=344/662) and only one was bilateral. Radiographs were reviewed

by a single author using a Picture Archiving and Communication System (PACS). Fractures were classified by location within the diaphysis (proximal, middle or distal) and according to the AO-OTA classification⁴⁴. Fractures most commonly occurred in the middle-third of the diaphysis (50.4%, n=334/663), followed by the proximal (28.1%, n=186/663) and distal thirds (21.6%, n=143/663). Open injuries (2.0%, n=13/663) were classified using the Gustilo and Anderson classification³¹. Concomitant radial nerve palsy (6.9%, n=46/663) and associated injuries (23.9%, n=158/661) were also documented. Associated minor injuries included uncomplicated head injuries, simple soft tissue injuries (contusions, lacerations, abrasions, incised wounds with no underlying structural injury) and ligament sprains; associated major injuries included other skeletal fractures or dislocations, soft tissue injuries with underlying neurovascular or tendon damage, or any solid organ injury.

Management

Management for all patients was determined by experienced consultant orthopaedic trauma surgeons. Of the study cohort, 21.0% of injuries (n=139/663) were managed operatively and 79.0% (n=524/663) were managed non-operatively.

Indications for fixation were determined from case notes and included patient preference (61.9%, n=86/139), polytrauma (10.8%, n=15/139), inadequate closed reduction (9.4%, n=13/139), open fracture (8.6%, n=12/139), progressive radial nerve deficit (5.8%, n=8/139), and involvement in a research investigation of an intramedullary (IM) implant (3.6%, n=5/139). The fixation technique was at the discretion of the treating surgeon and involved either open reduction and internal fixation (ORIF; 87.8%, n=122/139), IM nailing (9.4%, n=13/139) or other device (2.9%, n=4/139; flexible nails n=2/147, Rush Pin n=1/147, cerclage cables n=1/147). One patient with an open fracture underwent surgical intervention

consisting of debridement without fixation but was thereafter treated in a humeral brace and was included in the non-operative group. The patient went on to achieve union.

Standard non-operative management involved placement into a plaster of Paris ‘U-slab’ or above-elbow backslab in the Emergency Department, which was replaced by a functional brace following outpatient review. The type of plaster applied and timing of conversion to a brace was at the discretion of the treating surgeon, but study centre protocol is that this normally occurs within two weeks of injury.

Follow-up

Follow-up was undertaken using outpatient medical records and radiographs. Union was considered to have occurred if patients had reduced or absent pain at the fracture site and bridging callus across all fracture cortices or obliteration of all cortical fracture lines on plain radiographs prior to discharge from clinic, and no further surgical interventions were required^{45,74}. Nonunion was defined as a failure of the fracture to unite within six months of non-operative treatment^{35,40,43}, or where the treating surgeon considered that nonunion surgery was required beyond 12 weeks post-injury^{4,54}. The median follow-up for the study cohort was five months (range 1.2 to 74).

Statistical methods

Odds ratios (ORs) were calculated for contingency tables; the Haldane-Anscombe correction was used where a denominator was zero. The relationship between categorical variables was assessed using a chi-squared test or two-sided Fisher’s exact test (where the value of any cell was <5). The relationship between two groups of continuous non-parametric data was assessed using the Mann-Whitney U test (MWU). Significance was set at $p < 0.05$, 95% confidence intervals (CIs) and two-tailed p-values were reported.

Risk factors for nonunion identified as trending towards significance on univariate analysis ($p < 0.1$) were entered into a binary logistic regression model, to identify factors independently associated with nonunion adjusting for confounding variables. Additional forward and backward conditional modelling were used to verify the stability of the model. The linearity of continuous variables was determined using the Box-Tidwell transformation⁹; age at injury ($p = 0.415$) was linearly related to the log odds of nonunion.

RESULTS

Factors associated with nonunion after non-operative management

Nonunion occurred in 22.7% (n=119/524) of non-operatively managed injuries. Univariate analysis demonstrated that female gender (p=0.003), increasing age (p=0.003) and the presence of at least one medical comorbidity (p=0.014) were associated with nonunion. Comorbidities associated with nonunion were hypertension (p=0.017), chronic kidney disease (p=0.042), inflammatory arthritis (p=0.007) and glenohumeral arthritis (p=0.001). Pre-injury NSAIDs (p<0.001), being underweight (BMI<18.5kg/m², p=0.032) and class II obesity (BMI 35.0 to 39.9kg/m², p=0.011) were also associated with nonunion (**Tables I and II**). Injury characteristics, including injury energy (low/high; p=0.506), side of injury (dominant/non-dominant; p=0.852), fracture location (proximal/middle/distal; p=0.409), AO-OTA classification (p=0.636), the presence of an open fracture (p=1), associated radial nerve palsy (p=0.664) or concomitant injuries (p=0.305), were not associated with nonunion.

Multivariate analysis determined that pre-injury NSAIDs (adjusted OR 20.58, 95% CI 2.12 to 199.48; p=0.009) and glenohumeral arthritis (adjusted OR 2.44, 95% CI 1.03 to 5.77; p=0.043) were independently associated with nonunion following a non-operatively managed humeral shaft fracture (**Table III**).

Effect of management on nonunion rate

Operative fixation was associated with a significantly lower risk of nonunion (2.9%, n=4/139) compared with non-operative management (OR for nonunion following non-operative/operative management = 9.92, 95% CI 3.59 to 27.37; p<0.001; **Figure 2**), although there were significant baseline differences between the groups (**Table IV**). Based upon these results, five patients would need to undergo operative fixation (instead of non-operative

management) for one patient to avoid nonunion (absolute risk reduction = 0.198; number needed to treat [NNT] = 5.05).

With management (operative/non-operative) included in the model, non-operative management was the most influential predictor of nonunion (adjusted OR 9.91, 95% CI 3.25 to 30.23; $p < 0.001$). Pre-injury NSAID use (adjusted OR 6.78, 95% CI 1.50 to 30.61; $p = 0.013$) was also independently associated with nonunion (**Table V**).

DISCUSSION

This study has demonstrated that pre-injury NSAID use and glenohumeral arthritis were independently associated with nonunion following a non-operatively managed humeral diaphyseal fracture. No other patient or injury factors were independently associated with nonunion. Non-operative management itself was the independent factor most strongly associated with humeral shaft nonunion, when accounting for other confounding variables. Operative fixation was associated with a significantly lower risk of humeral diaphyseal nonunion, and this data challenges the traditional primacy of non-operative management of patients with these injuries. Further studies directly comparing the two treatment strategies are needed.

There are relatively few studies assessing the association between NSAIDs and fracture union⁷⁸, and there is considerable variation in study design and reported effects among those that do²¹. Post-injury NSAIDs have been found to have no effect on distal radius fracture healing^{3,18}. Conversely, postoperative NSAIDs have been observed to prolong healing time¹¹ and increase the risk of nonunion^{7,29} following IM nailing of acute tibial diaphyseal fractures. Bhattacharyya *et al.* reported that NSAID use from 61 to 90 days following a humeral diaphyseal fracture was associated with an increased risk of nonunion, although acknowledged this likely reflected persistent pain rather than NSAID-related suppression of fracture healing⁸. In contrast, our study specifically assessed pre-injury NSAIDs and demonstrated these to be the strongest independent risk factor for nonunion in non-operatively managed humeral diaphyseal fractures. Other longitudinal, population-based studies in the UK³³ and US²⁸ have identified that NSAID use prior to fracture increased the risk of nonunion. One possible explanation is that pre-injury NSAIDs have a more pronounced effect on cyclooxygenase (COX-2) inhibition at the time of fracture – with resultant suppression of the prostaglandin-mediated inflammatory phase of secondary bone healing – than NSAID use which only begins

after the injury²⁸. Our results are in-keeping with this emerging body of evidence that is a potential avenue for future research.

Arthritis of the shoulder and elbow have been implicated in the development of nonunion following fractures of the proximal^{38,58} and distal humerus^{2,55}, respectively. It is hypothesised that stiffness in a joint adjacent to a fracture leads to higher mechanical strain across the fracture³⁸, thereby preventing endochondral ossification and calcification of soft callus^{15,52}. To our knowledge, this is the first study to identify glenohumeral arthritis as a risk factor associated with humeral diaphyseal nonunion, and our findings suggest that primary operative fixation may have a role in reducing the nonunion rate among patients with shoulder arthritis and an ipsilateral humeral shaft fracture.

Existing small comparative studies of non-operative and operative management are contradictory in terms of union outcome following a humeral shaft fracture. While some have found equivalent rates of nonunion between non-operative and operative management^{35,42}, others have reported a difference in favour of patients managed surgically^{20,32,36,43,51,54,72,73}. A recent systematic review of retrospective studies suggested that operative fixation conferred a lower risk of nonunion without a significant increase in the rate of complications¹². A subsequent meta-analysis, including prospective randomised trial data⁴³, calculated that non-operative treatment was associated with a threefold increase in the odds of developing nonunion compared with operative management⁷¹. Existing studies are heterogenous in terms of design, patient background and operative interventions utilised. Our study confirmed operative fixation was associated with a lower risk of nonunion and identified it as the most influential factor in avoiding this morbid complication.

It is uncertain whether the apparent advantage in reducing the risk of nonunion justifies a more widespread recourse to primary operative intervention. Patients undergoing nonunion surgery following failed non-operative management are considered to be at greater risk of

postoperative complications^{1,17} and secondary nonunion^{17,32,57}. Even if union is achieved following nonunion surgery, patients are reported to have poorer functional outcomes than those undergoing primary fixation²⁵. These considerations seem to further support a management strategy that reduces the nonunion rate. Moreover, several comparative studies have shown acute surgical fixation to reduce the rate of malunion compared with functional bracing^{20,26,35,43,72}, with patient-reported outcomes that are equivalent²⁶ or slightly superior^{36,43,54}. The risk of iatrogenic radial nerve palsy and postoperative infection^{35,42,72,73}, as well as the potential increased costs associated with operative treatment, must be taken into consideration in future prospective comparative studies.

In light of this uncertainty, a pragmatic approach targeting patients most at risk of nonunion with early operative intervention may be most appropriate. However, factors previously reported to predict humeral diaphyseal nonunion – patient age^{16,30}, smoking^{19,30,34,65}, alcohol excess^{27,51,67} and proximal fracture location^{10,53,56,60,67,68} – were not found to be independently associated with nonunion in our study. We acknowledge our analysis may have been limited by missing data (8.4% for smoking, n=44/523; 16.6% for alcohol intake, n=87/523) in some instances. Nevertheless, predicting individuals most likely to develop humeral diaphyseal nonunion based on patient and injury factors alone appears to be challenging. A relatively small number of patients actually had the nonunion risk factors identified in our study, and for the majority of patients the most influential factor in developing a nonunion was the fact they had been managed non-operatively. Clinical signs²² and radiographic scores⁵⁰ have been shown to enhance identification of patients at risk of nonunion at an early stage in their non-operative management. When combined with patient-related risk factors it may be possible to achieve greater prognostic certainty and reduce the NNT with early surgical intervention.

The principal limitations of this study are the retrospective design and risk of selection bias. Management was at the discretion of the treating surgeon and patients managed operatively were significantly more likely to be younger, male, non-smokers, and to have no medical comorbidities, a high-energy or sport-related injury, a distal-third diaphyseal fracture, an open injury, an associated radial nerve palsy and a major injury associated with their humeral fracture. A range of indications and methods of operative fixation were used over the study period, but we suggest this variation is consistent with the current literature and clinical practice. Although selection bias is almost inevitable in these circumstances, this reflects the pragmatic nature of trauma care and should not limit the external validity of our findings^{13,64}. Most importantly, these potentially confounding factors were controlled-for in the regression analysis. Loss to follow-up was relatively low (9.7%), but it is difficult to assess the extent to which this may have had a bearing on the results of this study. Further work is needed to determine patient-reported outcomes following a humeral shaft fracture and the functional impact of nonunion.

CONCLUSIONS

Pre-injury NSAIDs and glenohumeral arthritis were independently associated with humeral diaphyseal nonunion following non-operative management. Operative fixation was the independent factor most strongly associated with a lower risk of nonunion. These findings may support increased use of primary operative fixation to reduce the rate of humeral diaphyseal nonunion, especially in patients at increased risk. Prospective randomised trials, including robust health economic analyses, are needed to adequately compare these two management strategies.

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TABLE LEGENDS**Table I:** Non-operative group – patient background and union outcome (n=523)

	Union (n=404)	Nonunion (n=119)	OR (95% CI)	p-value (test)
Gender (n, %)				
Male	187, 46.3%	37, 31.1%	1.91 (1.24-2.95)	.003* (CS)
Female	217, 53.7%	82, 68.9%		
Age at injury (years)				
Mean $\pm$ SD	57.1 $\pm$ 19.0	63.2 $\pm$ 18.1	-	.003* (MWU)
95% CI	55.2-59.0	59.9-66.5		
Median (range)	59.4 (16.7-95.1)	65.3 (17.6-96.5)		
Current smoker (n, %)				
No	252, 62.4%	84, 70.6%	0.90 (0.57-1.43)	.654 (CS)
Yes	110, 27.2%	33, 27.7%		
Unknown	42, 10.4%	2, 1.7%		
Current alcohol intake (n, %)				
Teetotal (reference)	77, 19.1%	28, 23.5%	-	.657
Normal	207, 51.2%	65, 54.6%	0.86 (0.52-1.45)	.576
Excess	47, 11.6%	12, 10.1%	0.70 (0.33-1.51)	.365 (all CS)
Unknown	73, 18.1%	14, 11.8%		
BMI (kg/m ²)				
Mean $\pm$ SD	27.7 $\pm$ 6.5	28.8 $\pm$ 7.3	-	.130 (MWU)
95% CI	26.9-28.5	27.4-30.3		
Median (range)	26.6 (15.0-54.0)	27.5 (15.8-59.7)		
BMI classification (n, %)				
Underweight	7, 1.7%	6, 5.0%	3.43 (1.06-11.14)	.032* .091
Normal (reference)	96, 23.8%	24, 20.2%	-	
Overweight	94, 23.3%	36, 30.3%	1.53 (0.85-2.76)	.155
Obesity class I	44, 10.9%	18, 15.1%	1.64 (0.81-3.32)	.170
Obesity class II	18, 4.5%	13, 10.9%	2.89 (1.25-6.71)	.011* .135
Obesity class III	13, 3.2%	7, 5.9%	2.15 (0.78-5.99)	
Unknown	132, 32.7%	15, 12.6%		(all CS)
SIMD quintile (n, %)				
1 (most deprived)	53, 13.1%	18, 15.1%	1.42 (0.72-2.81)	.309
2	92, 22.8%	35, 29.4%	1.59 (0.90-2.82)	.110
3	82, 20.3%	16, 13.4%	0.82 (0.41-1.61)	.559
4	64, 15.8%	23, 19.3%	1.50 (0.80-2.84)	.206
5 (least deprived) (reference)	113, 28.0%	27, 22.7%	-	.209 (all CS)

BMI, body mass index; CI, confidence interval; CS, chi-squared test; MWU, Mann-Whitney 'U' test; SD, standard deviation; SIMD, Scottish Index of Multiple Deprivation; ***significant at the p<0.05 level**

Table II: Non-operative group – medical background and union outcome (n=523)

		Union (n=404)	Nonunion (n=119)	OR (95% CI)	p-value (test)
Comorbidities (n, %)	None ≥1	109, 27.0% 295, 73.0%	19, 16.0% 100, 84.0%	1.95 (1.14- 3.33)	.014* (CS)
IHD (n, %)	No Yes	372, 92.1% 32, 7.9%	107, 89.9% 12, 10.1%	1.30 (0.65- 2.62)	.455 (CS)
Cardiac failure (n, %)	No Yes	398, 98.5% 6, 1.5%	118, 99.2% 1, 0.8%	0.56 (0.07- 4.72)	1 (FE)
Atrial fibrillation (n, %)	No Yes	392, 97.0% 12, 3.0%	113, 95.0% 6, 5.0%	1.74 (0.64- 4.73)	.276 (CS)
Hypertension (n, %)	No Yes	303, 75.0% 101, 25.0%	76, 63.9% 43, 36.1%	1.70 (1.10- 2.63)	.017* (CS)
PMR (n, %)	No Yes	400, 99.0% 4, 1.0%	116, 97.5% 3, 2.5%	2.59 (0.58- 11.72)	.197 (FE)
PVD (n, %)	No Yes	397, 98.3% 7, 1.7%	117, 98.3% 2, 1.7%	0.97 (0.20- 4.73)	1 (FE)
Asthma (n, %)	No Yes	373, 92.3% 31, 7.7%	109, 91.6% 10, 8.4%	1.10 (0.53- 2.32)	.795 (CS)
COPD (n, %)	No Yes	385, 95.3% 19, 4.7%	109, 91.6% 10, 8.4%	1.86 (0.84- 4.12)	.121 (CS)
Liver disease (n, %)	No Yes	395, 97.8% 9, 2.2%	116, 97.5% 3, 2.5%	1.14 (0.30- 4.26)	.740 (FE)
Diabetes mellitus (n, %)	No Yes	366, 90.6% 38, 9.4%	106, 89.1% 13, 10.9%	1.18 (0.61- 2.30)	.624 (CS)
IBD (n, %)	No Yes	399, 98.8% 5, 1.2%	116, 97.5% 3, 2.5%	2.06 (0.49- 8.77)	.390 (FE)
CKD (n, %)	No	395, 97.8%	112, 94.1%		.042* (CS)

Factors Associated with Humeral Shaft Nonunion

	Yes	9, 2.2%	7, 5.9%	2.74 (1.00-7.53)	
Epilepsy (n, %)	No	393, 97.3%	116, 97.5%	0.92 (0.25-3.37)	1 (FE)
	Yes	11, 2.7%	3, 2.5%		
CVD (n, %)	No	383, 94.8%	108, 90.8%	1.86 (0.87-3.97)	.106 (CS)
	Yes	21, 5.2%	11, 9.2%		
Multiple sclerosis (n, %)	No	398, 98.5%	117, 98.3%	1.13 (0.23-5.69)	1 (FE)
	Yes	6, 1.5%	2, 1.7%		
Hypothyroidism (n, %)	No	389, 96.3%	111, 93.3%	1.87 (0.77-4.52)	.159 (CS)
	Yes	15, 3.7%	8, 6.7%		
Osteoporosis (n, %)	No	374, 92.6%	104, 87.4%	1.80 (0.93-3.47)	.077 (CS)
	Yes	30, 7.4%	15, 12.6%		
Inflammatory arthritis (n, %)	No	398, 98.5%	112, 94.1%	4.15 (1.37-12.59)	.007* (CS)
	Yes	6, 1.5%	7, 5.9%		
Glenohumeral arthritis (n, %)	No	387, 95.6%	104, 87.4%	3.10 (1.51-6.36)	.001* (CS)
	Yes	18, 4.4%	15, 12.6%		
Skin disease (n, %)	No	395, 97.8%	119, 100.0%	0.17 (0.01-3.01) [‡]	.220 (FE)
	Yes	9, 2.2%	0		
Neuropsychiatric disease (n, %)	No	334, 82.7%	94, 79.0%	1.27 (0.76-2.12)	.360 (CS)
	Yes	70, 17.3%	25, 21.0%		
Illicit drug use (n, %)	No	395, 97.8%	115, 96.6%	1.53 (0.46-5.05)	.505 (FE)
	Yes	9, 2.2%	4, 3.4%		
Pre-injury NSAIDs (n, %)	No	403, 99.8%	109, 91.6%	33.28 (4.17-265.50)	<.001* (FE)
	Yes	1, 0.2%	9, 7.6%		
	Unknown	0	1, 0.8%		

CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CS, chi-squared test; CVD, cerebrovascular disease; FE, Fisher's exact test; IBD, inflammatory bowel disease; IHD, ischaemic heart disease; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; OR, odds ratio; PMR, polymyalgia rheumatica; PVD, peripheral vascular disease;

[‡]Haldane-Anscombe correction; *significant at the p<0.05 level

Table III: Independent predictors of nonunion ($p < 0.05$) following a non-operatively managed humeral diaphyseal fracture (Nagelkerke $R^2 = 0.127$)

Predictors in the model		OR	95% CI		p-value
			Lower	Upper	
Pre-injury NSAIDs	No				
	Yes	20.584	2.124	199.476	.009*
Glenohumeral arthritis	No				
	Yes	2.436	1.028	5.774	.043*

B, regression coefficient; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; ***significant at the $p < 0.05$ level**

NB. The following variables were entered into this model: Gender; age at injury; comorbidities; hypertension; chronic kidney disease; osteoporosis; inflammatory arthritis; glenohumeral arthritis; pre-injury NSAIDs; BMI classification

Table IV: Baseline patient (n=662) and injury (n=663) characteristics for operative *versus* non-operative management

	Operative	Non-operative	p-value (test)
Gender (n, %)			
Male	79, 56.8%	224, 42.8%	.003* (CS)
Female	60, 43.2%	299, 57.2%	
Age at injury (years)			
Mean $\pm$ SD	44.7 $\pm$ 19.0	58.5 $\pm$ 19.0	<.001* (MWU)
95% CI	41.5-47.8	56.9-60.1	
Median (range)	41.0 (16.4-92.4)	61.3 (16.7-96.5)	
Comorbidities (n, %)			
None	70, 50.4%	128, 24.5%	<.001* (CS)
≥ 1	69, 49.6%	395, 75.5%	
Pre-injury NSAIDs (n, %)			
No	135, 97.1%	512, 97.9%	.507 (FE)
Yes	4, 2.9%	10, 1.9%	
Unknown	0	1, 0.2%	
Current smoker (n, %)			
No	98, 70.5%	336, 64.2%	.025* (CS)
Yes	24, 17.3%	143, 27.3%	
Unknown	17, 12.2%	44, 8.4%	
Current alcohol intake (n, %)			
Teetotal	24, 17.3%	105, 20.1%	.855 (CS)
Normal	72, 51.8%	272, 52.0%	
Excess	15, 10.8%	59, 11.3%	
Unknown	28, 20.1%	87, 16.6%	
BMI (kg/m ²)			
Mean $\pm$ SD	28.2 $\pm$ 6.7	28.0 $\pm$ 6.7	.772 (MWU)
95% CI	26.7-29.7	27.3-28.7	
Median (range)	27.2 (17.9-52.2)	26.8 (15.0-59.7)	
BMI classification (n, %)			
Underweight	2, 1.4%	13, 2.5%	.914 (CS)
Normal	23, 16.5%	120, 22.9%	
Overweight	33, 23.7%	130, 24.8%	
Obesity class I	12, 8.6%	62, 11.8%	
Obesity class II	8, 5.8%	31, 5.9%	
Obesity class III	4, 2.9%	20, 3.8%	
Unknown	57, 41.0%	148, 28.2%	
SIMD quintile (n, %)			
1 (most deprived)	20, 14.4%	71, 13.6%	.905 (CS)
2	30, 21.6%	127, 24.3%	
3	24, 17.3%	98, 18.7%	
4	27, 19.4%	87, 16.6%	
5 (least deprived)	38, 27.3%	140, 26.8%	

Factors Associated with Humeral Shaft Nonunion

Injury mechanism (n, %)				
Fall from standing	64, 46.0%	413, 78.8%	<.001* (CS)	
Fall from height	10, 7.2%	15, 2.9%		
Sport	26, 18.7%	36, 6.9%		
Road traffic accident	18, 12.9%	18, 3.4%		
Other	20, 14.4%	36, 6.9%		
Unknown	1, 0.7%	6, 1.1%		
Injury energy (n, %)				
Low	104, 74.8%	480, 91.6%	<.001* (CS)	
High	34, 24.5%	38, 7.3%		
Unknown	1, 0.7%	6, 1.1%		
Side of injury (n, %)				
Right	73, 52.5%	244, 46.7%	.420 (CS)	
Left	66, 47.5%	278, 53.2%		
Bilateral	0	1, 0.2%		
Side of injury (n, %)				
Dominant	64, 46.0%	196, 37.5%	.134 (CS)	
Non-dominant	53, 38.1%	243, 46.5%		
Bilateral	0	1, 0.2%		
Unknown	22, 15.8%	83, 15.9%		
Fracture location (n, %)				
Proximal	17, 12.2%	169, 32.3%	<.001* (CS)	
Middle	51, 36.7%	283, 54.0%		
Distal	71, 51.1%	72, 13.7%		
AO-OTA type (n, %)				
A	82, 59.0%	347, 66.2%	.055 (CS)	
B	53, 38.1%	173, 33.0%		
C	4, 2.9%	4, 0.8%		
AO-OTA group (n, %)				
A1	50, 36.0%	220, 42.0%	.035* (CS)	
A2	7, 5.0%	37, 7.1%		
A3	25, 18.0%	89, 17.0%		
B2	50, 36.0%	140, 26.7%		
B3	3, 2.2%	34, 6.5%		
C2	3, 2.2%	2, 0.4%		
C3	1, 0.7%	2, 0.4%		
Open fracture (n, %)				
No	128, 92.1%	522, 99.6%	<.001* (FE)	
Yes	11, 7.9%	2, 0.4%		
Radial nerve palsy (n, %)				
No	119, 85.6%	498, 95.0%	<.001* (CS)	
Yes	20, 14.4%	26, 5.0%		
Associated injury (n, %)				
No	101, 72.7%	402, 76.7%	.285 (CS)	

Factors Associated with Humeral Shaft Nonunion

	Yes	38, 27.3%	120, 22.9%	
	Unknown	0	2, 0.4%	
Associated injury, minor (n, %)				
	No	12, 31.6%	27, 22.5%	.258 (CS)
	Yes	26, 68.4%	93, 77.5%	
Associated injury, major (n, %)				
	No	17, 44.7%	79, 65.8%	.020* (CS)
	Yes	21, 55.3%	41, 34.2%	

AO-OTA, *Arbeitsgemeinschaft für Osteosynthesefragen*-Orthopaedic Trauma Association; BMI, body mass index; CI, confidence interval; CS, chi-squared test; FE, Fisher's exact test; MWU, Mann-Whitney 'U' test; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; SIMD, Scottish Index of Multiple Deprivation; ***significant at the p<0.05 level**

Table V: Independent predictors of nonunion ($p < 0.05$) following a humeral diaphyseal fracture (Nagelkerke $R^2 = 0.175$)

Predictors in the model		OR	95% CI		p-value
			Lower	Upper	
Pre-injury NSAIDs	No				
	Yes	6.784	1.503	30.609	.013*
Primary management					
Operative fixation					
Non-operative		9.909	3.248	30.234	<.001*

B, regression coefficient; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; ***significant at the $p < 0.05$ level**

NB. The following variables were entered into this model: Gender; age at injury; comorbidities; hypertension; chronic kidney disease; osteoporosis; inflammatory arthritis; glenohumeral arthritis; pre-injury NSAIDs; BMI classification; primary management

FIGURE LEGENDS

Figure 1: Identification of study cohort (n, number of fractures)

Figure 2: Primary management and union outcome for study cohort (n, number of fractures)