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Treatment of long bones non-union: Factors associated with clinical outcome

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ABSTRACT

Objectives: Non-union is a common complication of long bone fracture with an approximate incidence of 2–30%. Several factors have been implicated in developing non-union, including patient and surgeon-related factors. The treatment approach depends on whether the non-union is hypertrophic or atrophic. Recently, there has been interest in identifying factors that may be associated with clinical outcomes following surgically treated non-union and the study aimed to study these factors.

Methods: This is a retrospective study spanning 5 years during which all information necessary for the study and data analysis were retrieved. The outcome was the healing of the surgically treated non-union, while other variables were considered as covariates. Initial bivariate logistic regression was done and only variables with $P < 0.5$ were further considered in the multiple logistic regression analysis (MLRA) to identify factors that significantly predict the healing of surgically treated non-union.

Results: The results of the bivariate logistic regression showed that the use of bone graft, duration of non-union, initial care given, and implant used had a $P < 0.5$, and these were the variables included in the MLRA. The result of the MLRA showed that plate and screw implant is the only independent predictor of healing following surgical treatment of long bone non-union (odds ratio = 14.36, z = 2.34, confidence interval: 1.725–172.433, $P < 0.0194$).

Conclusion: Plate and screw fixation predicts healing of long bone non-union. Future prospective studies are needed to validate the findings of this present study.

Keywords: Fractures, Management, Non-union, Risk factors, Treatment outcome

INTRODUCTION

Non-union is a common complication of long bone fracture with an approximate incidence of 2–30%.[1] While the Federal Drug Administration in the United States considers non-union to have occurred if a long bone fracture has failed to show healing progress after 9 months, other authors have suggested that the period should be revised from 9 months to 6 months.[2] Several factors, which are mostly patient-related, have been implicated in non-union development. Examples of patient-related factors include male sex, older patients, smoking, abuse of steroids, and patients with co-morbidities, especially, diabetes.[1] Other examples are surgeon-related factors such as excessive periosteum stripping, unstable fixation, and infection.[3]

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Long-bone non-union (LBNU) is heterogeneous in nature and is classified as either hypertrophic or atrophic depending on whether the non-union is due to excessive motion at the fracture site or due to problems with biology.[4] The heterogeneous nature of these non-unions introduces complexity in their management. LBNU can also be classified as septic and aseptic non-union,[5] and these are considered variants of hypervascular and avascular non-union. The ultimate goal of treating any non-union is to achieve clinical and radiological union with good functional outcomes,[6,7] and this explains the variety of treatment modalities available for managing this complication of fracture. The first principle is skeletal stabilization and the options available are plate and screws, intramedullary nailing, exchange nailing, nail-augmentation plate construct, and external fixation.[8] Adjunct to this skeletal stabilization is the use of biological agents, especially in atrophic non-union. Examples of such biological agents that have been used with success are iliac crest autograft, allograft, xenograft, synthetic bone graft, platelet-rich plasma, mesenchymal stem cells, and bone morphogenic proteins.[9] The use of these different modalities has been summed up in the "Diamond concept."[10]

Recently, there have been concerns about surgically treated non-union and the factors that may be associated with satisfactory clinical outcomes. Kugelman *et al*. found that low education and low socio-economic status were associated with poor functional outcomes, among other factors.[11] Similarly, Egol *et al*. found regions of non-union and sex as independent predictors of better pain scores and functional outcomes, respectively.[12] Poutoglidou and Krkovic,[13] in discussing their Cambridge experience of treating lower limb LBNU, found the septic type of non-union to be an independent factor that prolongs healing time. However, other factors other authors have suggested may contribute to the healing of LBNU. In particular, intraoperative compression and the use of bone graft are factors that have been found to contribute to the healing of LBNU,[14] though recently there has been debate on whether autograft is necessary for treating non-union.[15] However, these observations are from studies where no association test was done. Hence, there is a need to consider these factors as predictors of healing following the treatment of LBNU. Specifically, we are interested in whether intraoperative compression, intraoperative use of bone graft, choice of implant for fixation, and non-union type predict healing in surgically treated LBNU. Hence, the purpose of this present study is to find if the above-mentioned factors and other factors identified in other studies are associated with healing following surgical treatment of LBNU.

MATERIALS AND METHODS

This is a retrospective study spanning 5 years from January 1, 2017, to December 31, 2022, where all records of LBNU that were treated surgically were retrieved, and all information necessary for the study and data analysis were retrieved and entered into an Excel spreadsheet. For this study, cases are treated as non-union if (1) a fracture had not received any surgical treatment and there is no evidence of bridging callus in at least three cortices in two orthogonal radiological views or (2) if a fracture has been initially treated surgically requires further surgical intervention to achieve healing after 6 months of initial surgical treatment. Union following surgically treated long bone non-union was confirmed through case notes documentation and also through radiological evidence (bridging callus in at least three cortices) when available. Inclusion criteria are (1) ages between 18 and 80 years, (2) non-union of all long bones, (3) non-union managed operatively using either internal or external fixations, and (4) all patients followed up to a year. Some records were found inappropriate for the study and were excluded from the study. These were (1) records treated as a case of non-union but which did not meet the definition of non-union, (2) patients who were managed as a case of non-union whose fracture had not united following 6 months of follow-up, (3) patients who had more than three missing data, (4) patient with inadequate follow-up, (5) non-union managed non-operatively, and (6) non-union managed with retention of primary implant.

Statistical methods

The data were clean, recorded, and prepared in a format suitable for cross-tabulation, bivariate logistic regression analysis (BLRA), and multiple logistic regression analysis (MLRA).

The dependent variable was the healing of non-union at the last follow-up, while the independent variables were the age of the patients, sex, diagnosis, initial care of the long bone fracture, intra-operative use of bone graft, intraoperative use of compression, duration of non-union, follow-up duration, region of the non-union, and the implant used for treatment. Analysis of the non-union type was approached in two ways in this study: First as two types (septic and aseptic) and later as four types, where the aseptic type was further broken down into hypertrophic, oligotrophic, and atrophic. Furthermore, initial care was recoded into two variables: orthodox and traditional bone setters, where external fixators, intramedullary nailing, and compression plates were all combined into the orthodox group.

Initial cross-tabulations were done between the dependent variable and each of the categorical independent variables, while a boxplot diagram was drawn between the dependent variable and each of the continuous independent variables. The cross-tabulations and boxplots were individually assessed and when a variable shows a pattern with the dependent variable, a BLRA is conducted on such variable. This is done to reduce the number of multiple tests.

The *P*-value of the BLRA was assessed. If the $P \leq 0.5$, the variables were included in the MLRA to identify covariates statistically associated with the healing of LBNU. An initial MLRA (model 1) in which each independent variable is assumed to be additive was first constructed and assessed, and all statistically significant variables were identified. A second model (model 2) that included the interaction effect of all the independent variables together with their main effects was also constructed and assessed. If any interaction effect is statistically significant, such interaction effect is identified and used to build a third model (model 3), which includes only the main effect of the variables and the significant interaction identified in model 2. The result of this model is retained as the final model. If no statistically significant interaction effect is identified in model 2, model 1 is retained as the final model. In a situation where interaction effect model is identified, a likelihood-ratio test is used to assess model 1 and model 3 to assess the better model between the two models. All data were analyzed using R Statistical Software (v4.2.2; R Core Team 2022), and the level of statistical significance was set at $P \leq 0.05$.

RESULTS

After excluding the cases that did not meet the criteria for the study, only 40 records were found suitable for analysis. Table 1 shows the characteristics of the patients included in the study. The result of the preliminary cross-tabulations and box plot revealed that intra-operative use of bone graft, intraoperative compression, implant used, duration of non-union, and initial care of the long bone fractures were more likely to affect healing. The age of the patient, sex, region of non-union, and duration of follow-up did not show any difference in pattern with respect to healing. Hence, BLRA was not conducted for these variables. Table 2 shows the unadjusted effects of the BLRA. The results showed that only intraoperative use of bone graft, duration of non-union, initial care given, and implant used had a $P \leq 0.5$. These were the variables included in the MLRA.

The result of the MLRA with only the main effect is presented in Table 3, and it showed that plate and screw implant is the only independent predictor of healing following surgical treatment of LBNU (odds ratio = 14.36, z = 2.34, confidence interval (CI): 1.725–172.433, $P = 0.0194$). This result should, however, be interpreted with caution because of the wide CI. The model with interaction effect did not show any statistical significance for interaction and hence was not considered further in the analysis.

Table 1: The demographic characteristics of the patients.

	Overall (*n*=40) (%)
Age	
Mean (SD)	46.7 (13.2)
Median [Min, Max]	47.0 [24.0, 71.0]
Sex	21 (52.5)
Female	
Male	19 (47.5)
Diagnosis	20 (50.0)
Atrophic	
Hypertrophic	10 (25.0)
Oligotrophic	4 (10.0)
Septic	6 (15.0)
Region	
Lower	30 (75.0)
Upper	10 (25.0)
Initial care	
Linear ex-fix	1 (2.5)
Nail	2 (5.0)
ORIF	5 (12.5)
TBS	32 (80.0)
Implant used	
Circular ex-fix	10 (25.0)
Linear ex-fix	8 (20.0)
Nail	6 (15.0)
Plate and screws	16 (40.0)
Follow-up	
Mean (SD)	16.6 (14.6)
Median [Min, Max]	12.0 [6.00, 84.0]

TBS: Traditional bone setters, ORIF: Open reduction and internal fixation, SD: Standard deviation, ex-fix: External fixator.

DISCUSSION

The management of LBNU is evolving with propositions of different concepts and theories.[1,16] Little has been done to identify the factors contributing to its healing after surgical treatment. Poutoglidou and Krkovic[13] found septic non-union to be an independent factor that prolongs the healing of surgically treated LBNU, but this is at variance with the present study's findings. This present study did not find an association between non-union types and healing, and even though the reason for this is not immediately apparent, some differences between the two studies are worthy of note. Unlike the study of Poutoglidou and Krkovic, where the outcome was time to union, the outcome assessed in this present study was the presence or absence of healing following 6 months of follow-up. The 6-months limit was chosen because fracture types are expected to have healed by this period.[17] From our experience, accurately determining when union occurs during follow-up may be a challenge and hence, using time to union may introduce much bias, but using the presence

Table 2: The unadjusted effect predictor variables on healing of long bone non-union obtained from logistic regression.

Predictors (variable name)	LR test	OR for healing	95% CI for OR
Bone graft	χ^2 (1)=0.89, *P*=0.35		
Yes vs. No		1.89	0.501–7.288
Intraoperative compression	χ^2 (1)=0.29, *P*=0.59		
Yes vs. No		1.61	0.264–9.920
Initial care (care given)	χ^2 (1)=0.41, *P*=0.52		
Orthodox vs. TBS		1.67	0.338–8.296
Non-union duration	χ^2 (1)=4.03, *P*=0.06*		
		0.96	0.919–0.999
Implant used	χ^2 (3)=7.8 *P*=0.051		
Circular ex-fix vs. Linear ex-fix		2.33	0.342–18.000
Circular ex-fix vs. Nail		2.33	0.285–21.096
Circular ex-fix vs. Plate and screws		16.33	2.570–159.073

*Statistically significant, ex-fix: External fixator, TBS: Traditional bone setters, OR: Odds ratio, CI: Confidence interval, LR test: Log-likelihood ratio test, Orthodox – represents Nail, Linear ex-fix, and ORIF, ORIF: Open reduction and internal fixation.

Table 3: The adjusted effects of predictor variables on healing of long bone non-union obtained from logistic regression.

Predictor	OR	95% CI	*P*-value
Constant	0.67	0.052–7.162	0.74
Care given			
Orthodox vs. TBS	1.90	0.264–14.555	0.52
Implant used			
Circular ex-fix vs. Linear ex-fix	2.52	0.349–21.000	0.37
Implant used			
Circular ex-fix vs. Nail	2.04	0.218–21.000	0.53
Implant used			
Circular ex-fix vs. Plates and screw	14.20	1.725–172.433	0.02*
Use of bone graft			
No vs. Yes	0.69	0.311–3.638	0.67
Non-union duration	0.98	0.928–1.022	0.32

*Statistically significant. OR: Odds ratio, CI: Confidence interval, TBS: Traditional bone setters, ex-fix: External fixators, Orthodox – represents Nail, Linear ex-fix, and ORIF, ORIF: Open reduction and internal fixation

or absence of healing after 6 months of follow-up helps to correctly classify the clinical outcome of healing irrespective of which limb of the body is affected whether upper or lower limbs. Furthermore, their study used a larger sample size than the present study. Finally, unlike ours, their study was restricted to just the lower limbs, which included cases with both upper and lower limbs.

According to Egol *et al.*, region of non-union and gender are significantly associated with satisfactory clinical outcomes following surgical treatment of non-union,[12] but none of these factors were found to be significantly associated with union in our study. In their study, the clinical outcomes assessed were functional outcomes, and healing of the non-union was included as a covariate, unlike in our study, where healing of the non-union was the primary outcome. Combining the results of Egol *et al.*[12] and this present study, one may intuitively extrapolate that since clinical healing predicts functional outcomes, then factors that affect clinical healing should equally affect functional outcomes. However, the results of these two studies have not proven this. Could different factors affect the different outcomes, or are these findings just due to methodological differences? These questions can direct future research.

There are two other important findings from this present study: (1) among the possible implant of choice for the treatment of LBNU, compression plates and screws are the only implant that predicts healing (2) the use of autogenous bone graft does not predict healing. These two findings are further discussed.

Several authors have reported good to excellent results following the use of compression plates and screws for the treatment of LBNU.[14,18-20] Rosen was one of the earliest authors to report the excellent results obtained after using compression plates for treating non-union.[21] He achieved a 92.6% success rate even in cases where the non-union site was not excised or resected and, therefore, recommended compression plating for the treatment of LBNU. There are, however, reports of good to excellent results using other modalities, especially exchange nailing and circular external fixators for treating LBNU.[22] The success rate reported using exchange nailing for treating LBNU ranges between 72% and 100%,[23] while that of circular external fixators ranges between 87.5% and 100%.[24] To the best of our knowledge,

however, these other treatment modalities have not been previously considered as a factor that predicts the healing of surgically treated LBNU, hence, the result reported could have been due to chance. As important as the finding that only plate and screws predicted healing among other modalities of treatment in this present study, we advise caution in the interpretation of this finding for the following reasons: (1) Majority of the cases in this series were treated with plate and screws which may reflect surgeon preference and hence possible selection bias and (2) the wide confidence interval suggests an imprecise result that needs to be interpreted with caution.

Because of the traditional understanding that the avascular type of non-union is due to a problem with the biology of healing, the usual recommendation in treating such non-union is to use biological agents to facilitate healing.[6,25] Some orthopedic surgeons actually use such agents to treat all types of non-union.[9] The "diamond concept" of treating non-union patients supports this practice, and the successes achieved in treating avascular types of non-union patients have been attributed to this practice.[26] However, a critical literature review suggests that the atrophic non-union may not totally be avascular. Howard Rosen demonstrated in his study that atrophic non-union treated without bone graft healed primarily even in shorter periods. He suggested that atrophic non-union does not necessarily need bone grafts.[18] Reed *et al*., using histological studies to quantify the amount of blood vessels in hypertrophic, oligotrophic, and atrophic types of non-union, found no difference in the number of blood vessels seen in each type and therefore disproved the hypothesis that atrophic non-union are less vascular compared to hypertrophic non-union.[27] This present study found that using bone graft as an adjunct to non-union treatment does not predict the healing of LBNU and hence supports other authors who have questioned the indiscriminate use of bone graft to treat non-unions.[28]

This present study is not without limitations. First, there were some risk factors such as smoking, co-morbidities such as diabetes and hypertension, and type of fracture, whether open or closed, that were not assessed in this study due to the missingness of such data, and it is possible that the result could have been different if these factors were included in the analysis. Second, due to small sample size, the study may not have been adequately powered. Finally, selection bias may be inevitable due to the study's retrospective nature.

CONCLUSION

Identifying factors that enhance healing in the management of LBNU is very important to the orthopedic surgeons, considering how challenging their management can be. This study shows that compression plating, compared to other fixation methods and other factors, is the only factor that successfully predicts a good outcome in the management of LBNU.

Recommendation: In view of the small sample size of this present study, the authors recommend a larger cohort study, especially in low-resource settings where plates and screws are much more readily available to corroborate the findings of this study.

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Ethical approval: The research/study was approved by the Institutional Review Board at UI/UCH ETHICAL COMMITTEE, number UI/EC/24/0699, dated December 12, 2024.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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