Revisiting Union: A New Perspective on an Old Outcome

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**Abstract**

**Background:** To present the inherent and unique challenges associated with utilizing fracture healing as an outcome measure in foot and ankle orthopedics, specifically the statistical methods used in assessing time to union.

**Methods:** In a previously published manuscript assessing the effect of delayed weightbearing on time to union following intramedullary (IM) screw fixation of Jones (Zone 2 fifth metatarsal base) fractures, patients were divided into early weightbearing (EWB, \(n=20\)) and delayed weightbearing (DWB, \(n=21\)) cohorts (within or beyond 2 weeks, respectively). Time to union was determined and compared between the 2 cohorts using cumulative link model analysis, with delayed union (12.5 weeks) defined from established literature.

**Results:** Cumulative link model analysis demonstrated no significant differences in time to union (EWB: 25% by 6th week, 55% by 12th week; DWB: 33% by 6th week, 43% by 12th week; \(P = .819\)) or delayed unions (EWB, 20% vs DWB, 24%; \(P > .999\)).

**Conclusion:** Our analysis using cumulative link models, or ordinal regression, in the statistical analysis of time to union, determined that early weightbearing following IM screw fixation in Jones fractures appeared to be safe without delaying fracture healing. This statistical approach can be considered when describing a continuous outcome captured by infrequent observations.

**Keywords:** fracture healing, fracture union, Jones fracture, statistical methods, cumulative link model

Fracture healing occurs continuously through osseous bridging across the fracture site, with an endpoint of radiographic union defined as the disappearance of the fracture site on multiple radiographic views. It is widely used throughout the orthopedic literature as a primary outcome measure, but the methods used to monitor, report, and compare this effect often involve obtaining observations both selectively and at relatively dispersed intervals (eg, 2, 6, and 12 weeks postoperatively). As such, the choice of statistical models to best present fracture healing data is challenging, and conventional reporting of measures of central tendency (ie, mean, median, SD) and comparisons (ie, Student \(t\) test, Mann-Whitney \(U\) test) may not be appropriate.

Here we discuss the current limitations in the modeling of continuous variables with a focus on fracture healing following the operative treatment of Jones fractures, though the concepts we present can be applied more broadly in determining time to union following orthopedic procedures of the foot and ankle. Specifically, we propose a novel use of cumulative link models in the ordinal analysis of fracture healing.

**An Elusive Endpoint**

As we discussed in a recent retrospective cohort study comparing early and delayed weightbearing protocols after intramedullary fixation of Jones fractures,\(^1\) the difficulties associated with using fracture union as an outcome measure are often overlooked. The preferred approach has generally been to report measures of central tendency (ie, means, medians) and to compare differences with Student \(t\) tests, Mann-Whitney \(U\) tests, etc (Table 1).\(^1\) In some cases, authors have employed such continuous statistics without addressing the nature of the follow-up protocol,\(^2\) whereas others have reported follow-up at 2, 6, and 12 weeks.
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Table 1. Statistical Methods Commonly Used in the Clinical Literature to Evaluate Fracture Healing.

| Test/statistic                  | Recommended usage                                                                 | Common errors/pitfalls                                                                 |
|--------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Central tendency               | Characterize the “average”/50th percentile of continuous data                     | Mean best suited to normal distribution. Usage assumes sampling that reasonably approximates the underlying distribution. Leads to inaccurate conclusions when used to describe data obtained with discontinuous/irregular observations—increasingly problematic with increasing irregularity. |
| Student t test                 | Comparison of means of 2 samples of continuous, normally distributed data          | Sparse/discontinuous observations and/or irregular sampling not compatible with assumption of continuity. Normality assumptions often not checked (eg, Shapiro-Wilk test), and difficult to justify when sampling is irregular. |
| Analysis of variance (ANOVA)   | Comparison of means of 3 or more samples of continuous, normally distributed data | Same as Student t test.                                                                 |
| Mann-Whitney U test            | Assessment for stochastic dominance with 2 samples of interval/continuous data; preferred over Student t test when samples are not normally distributed | Sparse/discontinuous observations and/or irregular sampling not compatible with assumption of continuity. |
| Kruskal-Wallis test            | Assessment for stochastic dominance with 3 or more samples of interval/continuous data; preferred over ANOVA when samples are not normally distributed | Same as Mann-Whitney U test.                                                                 |
| Chi-square test                | Evaluate distributional/frequency differences in categorical variables            | Generally more appropriate than any method intended for continuous data when observations are sparse/irregular/discontinuous; however, unable to evaluate ordinal differences. |
| Fisher exact test              | Evaluate distributional/frequency differences in 2×2 categorical data, especially with smaller samples | Same as chi-square test.                                                                 |

postoperatively but reported a mean ± SD union time of 10.8 ± 3.7 weeks.1

In our study, we also targeted follow-up at 2, 6, and 12 weeks postoperatively, and in an earlier version of the manuscript had reported median union times, comparing cohorts with the Mann-Whitney U test. After initial submission, a reviewer pointed out the practical implausibility of reporting union times that did not correspond with the time points at which observations were obtained, as this implied either a weighted average across follow-up visits or deviation from the stated protocol. Though we had eschewed the use of means, SDs, and t tests—all of which are best-suited to normally distributed continuous data—we had to agree this was not the best approach, and undertook substantial revisions before arriving at the analysis in its published form.

**Fundamental Flaws**

Over the course of revisions, we came to appreciate 4 main barriers to using fracture union as an outcome measure. First, fracture healing does not occur discreetly as a singular event but reported a mean ± SD union time of 10.8 ± 3.7 weeks.1

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**Fundamental Flaws**

Over the course of revisions, we came to appreciate 4 main barriers to using fracture union as an outcome measure. First, fracture healing does not occur discreetly as a singular event is to obtain increasingly frequent observations at regular intervals. This would mean performing at minimum daily examinations and radiographs, which is clearly not feasible in real-world practice.

Second, overreliance on radiographs to determine fracture union can be problematic when anatomically reduced fractures are rigidly fixed. In such situations, the strain environment favors primary bone healing without the formation of bridging callus. Instead, radiographs demonstrate progressive disappearance and consolidation of the fracture lines. This is the case for most Jones fractures treated with intramedullary screw fixation.

Third, follow-up times in clinical practice are inconsistent. Some patients may schedule their “6-week visit” for the fifth or seventh week after surgery. This results in observations obtained in batched follow-up, which is difficult to represent with the conventional statistical methods.

Fourth, there is a certain unavoidable degree of subjectivity involved in determining adequate healing and union, both clinically and radiographically.3,10 Furthermore, assessments of fracture union are marred by poor reproducibility.5 Given the little variation between surgical techniques, the surprising variability of union times reported in the literature (5.7 weeks10 to 10.8 weeks1) perhaps illustrates the inconsistency with which union is determined. We propose a statistical model that may be more forgiving and therefore help alleviate current limitations in determining time to union in fracture healing.

**Breaking Barriers: Statistical Solutions**

Categorical data can be nominal or ordinal in nature. These are distinguished by whether or not the categories have an inherent order structure. Examples of nominal data include sex and occupation; examples of ordinal data include Likert-type scales and comparisons in batched times.
(eg, early, routine, delayed). Approaches suited for analysis of differences between nominal data (chi square, Fisher exact) would not account for the ordered nature of measured responses if they were used to compare treatment groups for outcomes observed in batched follow-up—the only difference between “early” and “delayed” levels would be that they are separate “bins.”

Analyses that are specifically adapted to this phenomenon are not commonly encountered in the orthopedic literature, though examples of other possible methods are seen in other fields.\textsuperscript{6,7} One approach is to use methods developed for analyzing interval censored data. For each patient, we may have a time point at which they are known not to be united and a later time point in which they are known to be united. Thus, the time of interest lies in that interval.

Alternatively, cumulative link models, or ordinal regression, can be considered as they are equipped for the analysis of ordered categorical variables.\textsuperscript{5,9} Though an in-depth discussion is beyond the scope of this review, cumulative link models are also called proportional odds models because of the requirement for data to satisfy the assumption that relationships between each pair of ordered outcomes is the same. Commonly used statistics software offer procedures to check the proportional odds assumption, and when using this approach it is critical that the ordinal outcome does not violate the fundamental proportional odds assumption.\textsuperscript{2}

Ultimately, in our analysis, we adopted a cumulative link model. This model allowed for an ordinal approach that is ideal for analyzing fracture union by determining the likelihood that fractures would be healed by certain time points (eg, “healed by 6 weeks” < “healed by 12 weeks” < “healed after 12 weeks”) with an accurate and robust comparison between treatment groups. Furthermore, it does not require any assumptions about the overall distribution of the effect.

Though we are unaware of other examples in the orthopedic literature that employ such an ordinal approach, we recommend it in situations when the desired effect is continuous yet observations are irregular and/or infrequent. Although this model is an effective way to minimize bias and present fracture healing data for clinical decision making and research, the current lack of consensus in the clinical and radiographic determination of fracture healing remains an inherent challenge.

In summary, fracture healing and time to union are challenging to determine. Methods most commonly employed in the analysis of this continuous phenomenon are often not justified by the manner in which observations were obtained. When evaluating fracture healing as an outcome measure, clinicians should recognize the assumptions underpinning various continuous statistical methods. They should attempt to appraise the limitations created by the manner in which observations were obtained, and consider the constraints these place on statistical models. We suggest considering an ordinal analysis when the outcome of interest is temporally continuous and observations are obtained infrequently and/or at irregular intervals.

### Ethics Approval

Ethical approval was not sought for the present study because it is a review article.

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