November 8, 2021

Quantum Leaps in Statistical Analyses of Measuring the Impact of time to Surgery

Clary J. Foote, MD, MSc

McMaster University, Hamilton, Canada

Other Contributors:

Chad P. Coles, MD

Division of Orthopaedics, Dalhousie University, Halifax, Canada

Aleksi Reito, MD, PhD

Tampere University Hospital (TAUH), Tampere, Finland

Khalid Al-Hourani, MD

Department of Orthopaedics, The Royal Infirmary of Edinburgh, Edinburgh, United Kingdom

Michael Bosse, MD

ATRIUM Musculoskeletal Institute, Carolinas Medical Center, Charlotte, USA

Anthony Bozzo, MD, MSc

McMaster University, Hamilton, Canada

Jowan Penn-Barwell MD, PhD

Academic Department of Military Surgery and Trauma, Royal Centre for Defence Medicine (RCDM), Birmingham, UK

Ross Leighton, MD

Division of Orthopaedics, Dalhousie University, Halifax, Canada

Harmeeth Uppal MD

Orthopaedic Trauma and Fracture Specialists, OTFS, San Deigo, USA

Jeffrey M. Smith, MD

Orthopaedic Trauma and Fracture Specialists, OTFS, San Deigo, USA

Geoffrey Mareck, MD

University of Southern California, Los Angles, USA

Xavier Griffin, MD, Ph.D

Division of Trauma & Orthopaedic Surgery, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK

Paul Tornetta III, MD

Department of Orthopedics, Boston University Medical Center, Boston, USA

GOLIATH Investigators Investigators

Invited Commentary on Delay in Initial Debridement for Open Tibial Fractures and Its Possible Impact on Patient Outcomes: A Single-Center Prospective Cohort Study

The investigators had two purposes for their prospective observational study of 1896 open tibial fractures. First, they sought to identify if there was an association between time to debridement and adverse events such as deep infection, amputation, nonunion, and mortality. They excluded patients that were debrided within 24 hours from injury, using a >24-48 hour group as the reference category and comparing outcome rates to those that were debrided >48-72 and >72-96 hours after injury. Second, they also investigated the association between time from injury to antibiotic prophylaxis using a dichotomous 12-hour cutoff from injury.

Methodologically, they analyzed the delay to debridement groups using a standard chi-squared and presumably a univariate logistic regression, stratifying for Gustilo type (grouped into Gustilo type I, II, and III without substratification among Gustilo type IIIs). They did not identify an association between Gustilo type III fractures and very late debridement although was “a 3%” (Odds ratio 1.03) increase in the deep infection rate between the >24-48 hour and the >48-72 hour cohorts (p=0.48). There were also trends

for increased odds for delay for Gustilo type I fractures.

We performed an independent analysis across Gustilo types and there was a clear increase in the odds of infection associated with surgery >48 hours (OR 1.44, 95% CI 1.11 to 1.86, p=0.006). However, when we used aggregated their estimates across the Gustilo subgroups, it resulted in a much smaller estimate from the data they provided across the Gustilo types estimates which resulted in a much smaller estimate (OR 1.10, 95% CI 0.78 to 1.55, p=0.57). We require data from the original authors to investigate this discrepancy.

For those that were debrided >48 hours after injury, compared to >24-48 hours, the odds of amputation increased 3-fold (OR 3.15, 95% CI 1.69 to 5.89, p<0.001). It is unclear from the paper when the amputations took place. Because there is a greater amputation rate in the delayed debridement groups, it is unclear if this impacted the infection rates. Specifically, if having more delayed amputations in the >48 hours debridement groups resulted in a reduced number of at risk of infection and therefore artificially reduced the deep infection rates in these cohorts.

We performed three analyses based on assumptions that, 1) amputations occurred early (prior to any risk of infection), 2) amputations were incurred as a result of deep infection and were not accounted for in the analyses, and 3) amputations occurred secondarily due to the occurrence of infection and were accounted for in the analyses.

One, we removed the amputations from the total count of patients in each time window (and also those that died) as they may have incurred the amputation “early” (assumption one=competing risk). When this was conducted, it raised the odds of infection for Gustilo type III fractures that were delayed >48 hours from injury (OR 1.51, 95% CI 1.03 to 2.23, p=0.04; ~8.7% increase in the deep infection rate). In scenario two, the amputation cases may not have been accounted for as infections. If we assume the amputations were all due to deep infection (a strong assumption), it raises the estimate to OR=2.19 (95% CI 1.55 to 3.09, p<0.001; ~16.7% increase in the deep infection rate) for >24-48 versus >48 hours. The last possible scenario is that those that incurred infection and were amputated were accounted for in both outcomes. The problem with this scenario is it would suggest that the deep infections associated with greater delays to initial debridement may be more aggressive (i.e. superinfections), leading to a 3-fold odds increase in the amputation rate with debridement >48 hours. Therefore, reporting that there is not an increase in an “infection problem” with delayed debridement would be neglecting this very crucial fact. Specifically, even though the infection rate may have remained stable over time the severity of the infections (and their consequences) increased progressively.

To give some quantification around the potential disparity in the severity of the infection outcome, one could consider the amputation rate among the total infections for those debrided >24-48 versus >48 hours. Compared with the >24-48 group, the odds of amputation among the deep infected is 2.7-fold higher for those debrided >48 hours (95% CI 1.38 to 5.29, p=0.004). So this metric would suggest the infections incurred after very late debridement may be 3-times more aggressive. Among those infected that were debrided >24-48 hours, only 12.1% got an amputation in contrast to 27.2% for those infected debrided >48 hours (ARI 15.1%, 95% CI 6.4 to 23.7%, p=0.006). Therefore, all of the sensitivity analyses suggest inferior outcomes with delay to debridement >48 hours from injury compared to >24-48 hours from injury, mediated through either a higher deep infection rate and/or more severe infections leading to a substantial increase in the odds of amputation. The authors made note of the increased risk of amputation qualitatively in the results.

From the TIIME Study Registry Gustilo type III open fractures, we conducted analyses looking at the impact of time to debridement on the amputation rate. The was higher early likely related to injury severity and decreased for the first nine-hour (OR 0.76, 95% CI 0.58 to 1.00, p=0.049, Figure 1). In the stratified spline model, the amputation rate stayed slow and stable from nine to 12 hours, increasing thereafter. When comparing amputation rates around 10 hours to those at 24 hours from injury to debridement the amputation rate increased by 2.05-fold (95% CI 1.00 to 4.21, p=0.05, Figure 1).

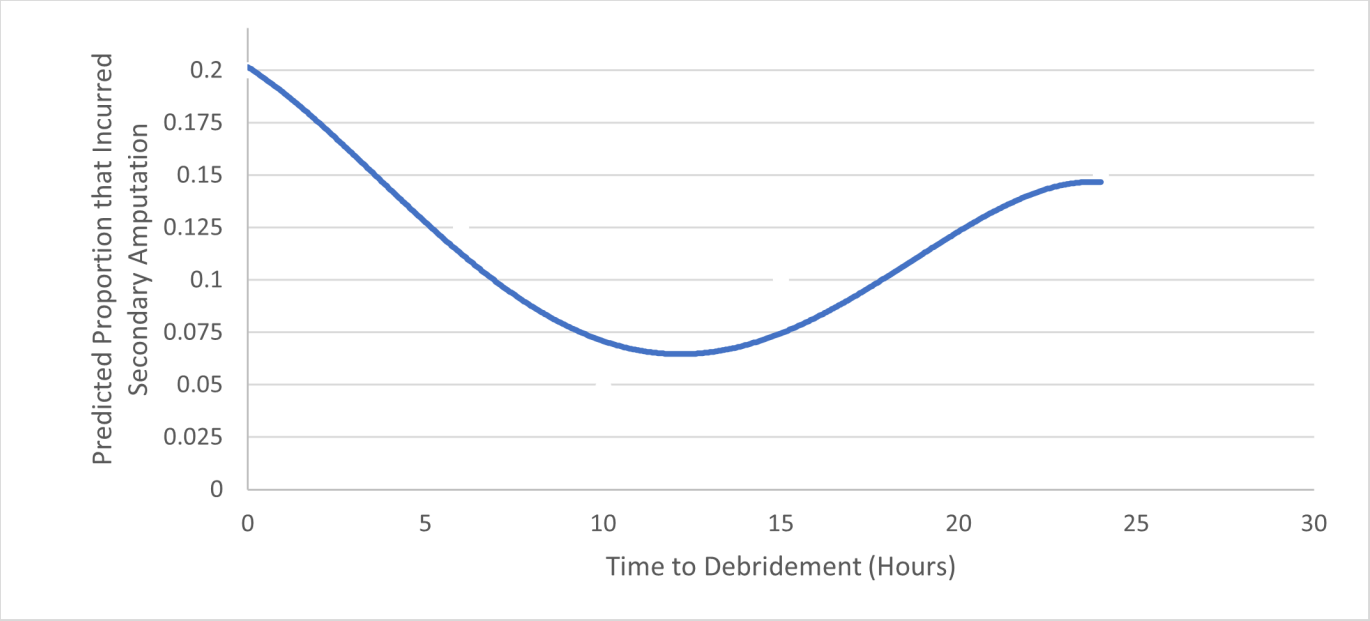

Figure 1: Stratified spline model of the amputation rates across times from injury to debridement.

Figure 2 shows data from the TIIME Registry that shows the impact of further delays to flap coverage

from the timing of nailing in Gustilo type III fractures requiring flap coverage. It leads to an increased amputation rate. Compared with nailed and flapped early, coverage at 6 days had a 1.72-fold higher amputation rate (95% CI 0.86 to 3.43, p=0.13). Compared with the total time to surgery of 10 hours, the total time to debridement and flap coverage >72 hours increased the amputation rate by 2.19-fold (95% CI 1.11 to 4.35, p=0.03). Those that become infected with definitive surgery late that get infected have a 2.17-fold higher amputation rate than those that received definitive surgery early and get infected (95% CI 0.44 to 10.7, p=0.34). From our work, this suggests that a rising infection rate is not the only concern with delayed surgery but also more impactful nosocomial infections that carry with it a greater likelihood of delayed amputation due to infection. This suggests that accounting for the amputation rate in analyses is critical for 1) adjusting the infection rates appropriately, 2) gauging the severity of infections.

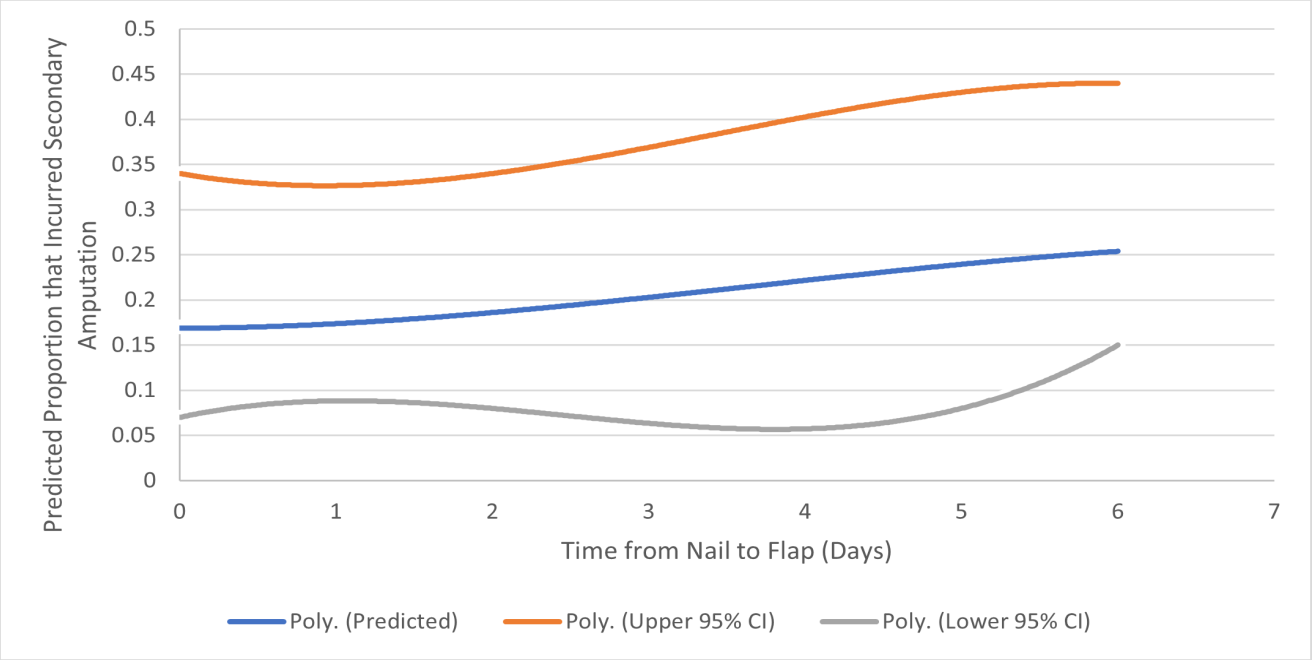

Figure 2: Spline analyses showing the association between time to flap coverage and the secondary amputation rate.

The GOLIATH Collaboration has limited access to some datasets involving patients with lengthy delays (1-4). When we aggregate this data across all Gustilo types, it suggests an increase in the infection rate of 1.37-fold with surgery >48 hours (95% CI 1.09 to 1.73, p=0.006, very low confidence) versus >24-48 hours. However, compared with surgery ?12 hours, delays >48 hours carry with it a 2.63-fold (95% CI 1.48 to 4.68, p=0.001, moderate confidence) higher risk of infection. In Gustilo type III fractures the 1.37 estimate increases to 1.55 (95% CI 1.06 to 2.26, p=0.02, low confidence) of >48 versus >24-48 hours. Compared to timing to surgery of ?12 hours, >48 hours carries with a 2.98-fold increase in the infection rate (95% CI 1.55 to 5.70, p=0.001). In the final analysis, the rates of infection seem to rise with further

delays, and the aforementioned reanalyses of the paper and our adjunct data from the TIIME Registry suggest a progressive rise in more virulent infections leading to an increased amputation rate.

In summary, time to debridement has been especially challenging to study. Historically analyses have been plagued with pitfalls such as arbitrary dichotomization of time, lack of adjustment for confounders, and failure to stratify analyses in the face of profound effect modification (i.e interaction) from Gustilo type as well as interactions between debridement and other treatments. In the context of substantial delays to antibiotics and surgery, valid analyses become even more challenging to minimize time measurement bias (e.g. more time spent in the antibiotics to surgery window), among other analytical problems. In addition, outcome adjudication can be especially challenging if the infections are of variable severity and may be competing with other outcomes such as amputation that may further bias the results. We encourage continued collaboration on the front of open fracture care to improve the breadth of available data (that can be collated where appropriate) with a central mission: To optimize reporting by utilizing data experts within musculoskeletal trauma research collaboratives to produce the most valid results. As the silent pandemic of open fractures roars on, that afflicts hundreds of thousands each year, we strive to get a more complete understanding of the natural history of these injuries to minimize adverse events and improve the probability of functional recovery. To achieve this, we need global cooperation within orthopaedic traumatological networks.

References

1. Al-Hourani K, Foote, CJ; Duckworth, A; White, T; Kelly, M; Tornetta P III. Re-evaluation of the Risk of Infection Based on Time from Definitive Fixation to Flap Coverage in Type IIIB Open Fractures: SPARTA (Supporting Plastics Orthopaedics Alliance Reducing Trauma Adverse Events). AAOS; San Deigo2021.
2. Duyos OA, Beaton-Comulada D, Davila-Parrilla A, Perez-Lopez JC, Ortiz K, Foy-Parrilla C, et al. Management of Open Tibial Shaft Fractures: Does the Timing of Surgery Affect Outcomes? J Am Acad Orthop Surg. 2017 Mar;25(3):230-8. Epub 2017/02/16.
3. Marecek GP, J.T.; Heckmann, N. Delayed Debridement of Open Tibia Fractures Beyond 24 and 48 Hours Does Not Appear to Increase Infection and Reoperation Risk. 2021.
4. Tahir MA, N; Shaikh, S.A.; Jamali, A.R.; Choudry, U.K.; Khan, S. . Delay in Initial Debridement for Open Tibial Fractures and Its Possible Impact on Patient Outcomes: A Single-Center Prospective Cohort Study. JBJS [Internet]. 2021. Available from: https://hub.jbjs.org/reader.php?id=207313&rsuite_id=2781299&native=1&source=JBJS_Open_Access/6/1/e20.00027/fulltext&topics=ta#to .

Conflict of Interest: None Declared