Early Identification of Loss to Follow-Up in Orthopaedic Trauma Patients: Development of a Multivariable Risk Prediction Model

Aidan P. Sweeney (apsween@emory.edu)
Emory University School of Medicine

Michael McDonald
Henry Ford Hospital, Michigan

Victoria Kravets
Emory University School of Medicine

Kay E. Bush
Emory University School of Medicine

Michael A. Maceroli
Emory University School of Medicine

Marcos Coutinho Schechter
Emory University School of Medicine

Mara L. Schenker
Emory University School of Medicine

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Abstract

**Background:** Loss to clinic follow-up is common among orthopaedic trauma survivors. The purpose of this study was to develop a prediction tool to identify patients at risk for orthopaedic trauma clinic follow-up non-adherence.

**Methods:** Comprehensive social determinants of health (SDOH) assessment surveys were administered to adult patients (age ≥18) who were hospitalized with orthopaedic trauma injuries at an urban Level 1 trauma center. Clinic follow-up adherence within the 90-day post-operative period was examined using adherence fractions ([number of attended follow-up visits]/[number of attended follow-up visits + number of missed visits]). Adherence fractions ≥0.75 were considered to be “High” and £0.75 considered to be “Low”. Demographic and SDOH factors, including the Distressed Communities Index (DCI), were analyzed for their association with clinic follow-up adherence. A risk prediction tool for follow up non-adherence was developed using a multivariable logistic regression model.

**Results:** 294 patients were included for final analysis. Higher community distress, more severe injury, lack of private insurance, lower education levels, no primary care physician, financial and relationship instability, and lack of transportation were significantly associated with low clinic follow up adherence (p<0.05, Table 2 and 3). Low clinic adherence (£0.75) was also significantly associated with presentation to the emergency department within the 90-day post-operative period (p<0.01). The final risk prediction model included 5 covariates: “Distressed” or “At Risk” DCI levels, lack of private insurance, high school or lower education, no primary care physician, and male gender (n=210, AUROC=0.65, 95% CI = 0.57-0.72). The maximum possible risk score was 8. The mean score for patients with low clinic adherence was 4.0±1.6 and 3.1±1.75 for those with high adherence (p<0.01).

**Discussion:** Coordinated care of patients in the aftermath of trauma is imperative to improve healthcare quality and patient outcomes. This study suggests that post-trauma clinic adherence may be predicted at the time of hospital discharge based on a combination of five demographic and SDOH risk factors. We offer a predictive tool for such behavior, which we visualize as a valuable component in a social work discharge plan. Future studies should assess interventions for patients at high risk for follow up non-adherence.

**Background:**
Loss to follow-up is a common problem in the orthopaedic trauma patient population. Nonadherence creates challenges for the orthopaedic trauma surgeon, for the healthcare system, and for the clinical researcher. From a clinical perspective, follow-up visits are pivotal for monitoring postoperative recovery and adjusting treatment protocol. Patients who miss their appointments are at higher risk for poor outcomes and more likely to present to the emergency department for postoperative complications (1, 2). In addition to the harm this causes the patient, these behaviors also place financial stress on the healthcare system by unnecessarily increasing resource utilization and cost of care leading to limited
quality of healthcare delivery(3, 4). Furthermore, follow-up nonadherence also restricts the validity and effectiveness of orthopaedic trauma outcomes research by biasing study results, which in turn, slows the clinical advancement of the field(5, 6). It is abundantly clear that increasing clinic follow-up in this patient population serves to benefit both the patient and the healthcare system as a whole.

Early anticipation and identification of trauma patients at risk for low clinic adherence is one approach by which health care teams can address this issue before it materializes. Doing so would allow healthcare providers to coordinate post-discharge trauma care and facilitate clinic follow up for at-risk patients(7). Though limited, some studies have investigated risk factors for nonadherence in orthopaedic trauma patients and have demonstrated that a wide array of sociodemographic and clinical factors, including insurance status, drug use, distance to clinic, and fracture type, place these patients at significant risk(8–12). To our knowledge, no prior work has used this information to create an actionable model that can identify patients at risk for clinic nonadherence prior to hospital discharge. The purpose of this study was to build upon the existing literature surrounding risk factors for nonadherence as well as develop a prediction tool that would help identify patients at risk for loss to follow-up based on a comprehensive social determinants of health assessment at the time of trauma hospital discharge.

**Methods:**

**Patient Population**

Institutional review board approval was obtained for this study. Informed consent was obtained via an electronic consent form. There was no form of compensation for participation. Study participants were recruited during initial inpatient admission from the emergency department of a high-volume, urban Level 1 trauma center from May 2018 – August 2019. Inclusion criteria were patient age over 18 years and at least one orthopaedic injury requiring orthopaedic traumatologist consultation. Exclusion criteria included patients who were unable to consent to study participation for any legal or medical reasons.

**Study Design**

This was a prospective study with data collected from a comprehensive social determinants of health survey administered by study personnel and completed by patients during their initial hospital stay. Additional data collection included evaluation of the Electronic Medical Record (EMR) for follow-up adherence as well as 1-year follow up phone screenings. Follow up adherence data was collected retrospectively. Surveys were comprised of over 150 social determinant of health factors, which were adapted from standardized questionnaires developed by the Centers for Disease Control (CDC)(13, 14), National Institute of Health (NIH)(15), and World Health Organization (WHO)(16). Surveys included but were not limited to the following variables: socioeconomic status, race/ethnicity/cultural context, gender/sexual identity, social relationships, environment, psychiatric illness, and substance use. Patient health questionnaire-2 (PHQ-2), primary care - post-traumatic stress disorder (PC-PTSD), and the modified Frailty Index (mFI) were used to screen for depression, post-traumatic stress disorder, and additional...
medical co-morbidities(17–19). Injury Severity Score (ISS) and Distressed Community Index scores were also collected(20, 21).

**Outcome Measurements**

The primary outcome of interest was follow-up adherence within the 90-day post-operative period. Adherence was evaluated using adherence fractions, defined as: \( \frac{\text{[number of attended follow-up visits]}}{\text{[number of attended follow-up visits + number of missed follow-up visits]}} \). Adherence fractions \( \geq 0.75 \) were considered to be “High” and \(< 0.75 \) considered to be “Low”, as done previously(22). Cancelled appointments were not used in the calculation of the compliance fraction. SDOH variables drawn from the aforementioned surveys were then used to evaluate variables associated with “High” versus “Low” adherence. Participants could skip any survey question and missing data was not imputed. Thus, the denominator for each question is based on the number of respondents to that question and not the entire cohort.

**Statistical Analysis**

RStudio Version 1.2.5402 was used for all statistical analyses(23). Within-group means and standard deviation were calculated for all demographic data. Univariate analysis was used to examine the associations between demographic parameters, injury factors, SDOH factors, and follow up adherence. Student t-tests were used for continuous variables and chi-square tests were used for categorical variables with an alpha level of 0.05. Multivariable logistic regression models were conducted using both forward and backward selection approaches. The best fit multivariable logistic regression model was selected by comparing the Area Under the Receiver Operating Characteristics (AUROC) and Akaike information criterion (AIC) of each model. Patients with missing information were excluded from the model. The selected model was then used to develop a novel risk prediction tool based on weights assigned similar to the Charlson co-morbidity methods(24). Covariates were chosen based upon their statistical significance and clinical accessibility, that is: variables easily accessible either via (1) chart review or (2) a standard patient history.

**Results:**

329 patients were initially enrolled from May 2018 – August 2019, 35 were excluded due to lack of available follow-up information. Of the remaining 294 patients, 100 patients demonstrated low \(< 0.75 \) follow-up adherence (34%) and 194 patients demonstrated high \( \geq 0.75 \) follow-up adherence (66%) (Table 1). For the low follow-up adherence cohort, the average age was 42.3 years ± 17.5 with 31 (32%) female patients, 66 (68%) male patients, and 3 patients with missing gender data (Table 1). The mean DCI score was 61.6 ± 24.4 (Table 1). For the high follow-up adherence cohort, the average age was 45.4 years ± 17.6 with 82 (43%) female patients, 107 (57%) male patients, and 5 patients with missing gender data (Table 1). The mean DCI score was 53.4 ± 27. There was a significant difference between mean DCI scores in low versus high adherence groups, indicating lower follow-up in patients from more economically distressed zip codes \((p = 0.01, \text{Table 1})\).
Table 1
Demographic Data

|                      | Low Compliance | High Compliance | p - value |
|----------------------|----------------|-----------------|-----------|
| Patients             | 100 (34%)      | 194 (66%)       |           |
| Age                  |                |                 | 0.16      |
| Mean (SD)            | 42.3 (17.5)    | 45.4 (17.6)     |           |
| Median (min, max)    | 41 (18, 94)    | 44 (18, 96)     |           |
| Gender               |                |                 | 0.08      |
| Female               | 31 (32%)       | 82 (43%)        |           |
| Male                 | 66 (68%)       | 107 (57%)       |           |
| Race                 |                |                 | 0.78      |
| Black or African American | 69 (71%)    | 130 (69%)       |           |
| Other                | 28 (29%)       | 59 (31%)        |           |
| DCI Score            |                |                 | 0.01*     |
| Mean (SD)            | 61.6 (24)      | 53.4 (27)       |           |
| Median (min, max)    | 64.2 (8.2, 98.2)| 49.5 (2.2, 98.2)|           |
| DCI Tier             |                |                 | 0.13      |
| Distressed           | 24 (27%)       | 45 (24%)        |           |
| At Risk              | 29 (32%)       | 38 (20%)        |           |
| Mid-Tier             | 16 (18%)       | 38 (20%)        |           |
| Comfortable          | 16 (18%)       | 43 (23%)        |           |
| Prosperous           | 5 (6%)         | 22 (12%)        |           |

*Statistically significant (p < 0.05). Values are n (%) unless otherwise denoted.

On univariate analysis, the following variables demonstrated a significant difference when comparing low versus high adherence cohorts: ISS (p = 0.02), insurance (p = 0.04), education level (p = 0.02), primary care provider (PCP) status (p = 0.01), transportation status (p < 0.01), difficulty paying for basics (p = 0.02), difficulty paying for prescriptions (p = 0.02), relationship change (p = 0.03), and ED visit in the 90-day postoperative period (p < 0.01) (Table 2 and Table 3). The remaining variables that were not found to be statistically significant included: frailty score (p = 0.89), PHQ-2 score (p = 0.11), discharge disposition (p = 1.00), homelessness (p = 0.30), bus stop presence (p = 0.19), cell phone status (p = 1.00), cell number change (p = 0.06), all tested mental health comorbidities (see Table 3), all tested substance use (see Table 4), living change (p = 0.19) and crime conviction (p = 1.00).
| Table 2 | Social Variables |
|---------|------------------|
|         | Low Compliance   | High Compliance | p-value |
| ISS     | 0.02*            |                 |
| Mean (SD) | 14.3 (10.8)   | 11.5 (9.6)      |         |
| Median (min, max) | 10 (1, 45)   | 9 (4, 50)       |         |
| Frailty (mFI-5) | 0.89           |                 |
| Mean (SD) | 0.5 (0.9)    | 0.5 (0.8)       |         |
| Median (min, max) | 0 (0, 3)    | 0 (0, 4)        |         |
| PHQ-2 Total Score | 0.11          |                 |
| Mean (SD) | 1.2 (1.7)    | 1 (1.7)         |         |
| Median (min, max) | 0 (0, 6)    | 0 (0, 6)        |         |
| Insurance | 0.04*           |                 |
| Private | 23 (28%)       | 68 (45%)        |         |
| Government | 23 (28%)    | 33 (22%)        |         |
| Uninsured | 36 (44%)    | 50 (33%)        |         |
| Education level | 0.02*         |                 |
| Greater than high school | 21 (22%) | 67 (36%) |         |
| High school or lower | 75 (78%) | 119 (64%) |         |
| Discharge Disposition | 1.00         |                 |
| Home | 79 (83%)       | 157 (84%)       |         |
| Not Home | 16 (17%)    | 31 (16%)        |         |
| Homeless | 0.30           |                 |
| No | 11 (61%)       | 32 (78%)        |         |
| Yes | 7 (39%)        | 9 (22%)         |         |
| Primary Care Provider | 0.01*        |                 |
| No | 60 (60%)       | 85 (44%)        |         |
| Yes | 40 (40%)       | 108 (56%)       |         |
| Lack of transportation made getting prescriptions difficult | 0.00* |         |
| Low Compliance | High Compliance | p-value |
|---------------|----------------|---------|
| No            | 10 (56%)       | 37 (90%)|
| Yes           | 8 (44%)        | 4 (10%) |

Lack of transportation made getting to work difficult

| Low Compliance | High Compliance | p-value |
|---------------|----------------|---------|
| No            | 12 (67%)       | 35 (90%)|
| Yes           | 6 (33%)        | 4 (10%) |

*Statistically significant (p < 0.05). Values are n (%) unless otherwise denoted.

| Table 3. Social Variables cont. |
|--------------------------------|
| | Low Compliance | High Compliance | p - value |
|-----------------|----------------|---------------|
| Autism          |                |               | 0.45       |
| No              | 96 (96%)       | 190 (98%)     |            |
| Yes             | 4 (4%)         | 4 (2%)        |            |
| Schizophrenia   |                |               | 0.52       |
| No              | 94 (94%)       | 187 (96%)     |            |
| Yes             | 6 (6%)         | 7 (4%)        |            |
| Bipolar         |                |               | 0.26       |
| No              | 92 (92%)       | 186 (96%)     |            |
| Yes             | 8 (8%)         | 8 (4%)        |            |
| Anxiety         |                |               | 0.32       |
| No              | 85 (85%)       | 174 (90%)     |            |
| Yes             | 15 (15%)       | 20 (10%)      |            |
| PTSD            |                |               | 0.43       |
| No              | 95 (95%)       | 178 (92%)     |            |
| Yes             | 5 (5%)         | 16 (8%)       |            |
| Eating Disorder |                |               | 0.34       |
| No              | 99 (99%)       | 194 (100%)    |            |
| Yes             | 1 (1%)         | 0 (0%)        |            |
|                                      | Low Compliance | High Compliance | p-value |
|--------------------------------------|----------------|----------------|---------|
| Depression                           |                |                | 0.38    |
| No                                   | 82 (82%)       | 168 (87%)      |         |
| Yes                                  | 18 (18%)       | 26 (13%)       |         |
| Difficulty paying for basics         |                |                | 0.02*   |
| Not hard at all                      | 3 (17%)        | 28 (44%)       |         |
| Somewhat hard                        | 5 (28%)        | 21 (33%)       |         |
| Very hard                            | 10 (56%)       | 14 (22%)       |         |
| Difficulty paying for prescriptions  |                |                | 0.02*   |
| No                                   | 7 (39%)        | 45 (71%)       |         |
| Yes                                  | 11 (61%)       | 18 (29%)       |         |
| Relationship change                  |                |                | 0.03*   |
| No                                   | 12 (67%)       | 56 (89%)       |         |
| Yes                                  | 6 (33%)        | 7 (11%)        |         |
| ED Visit in 90 day Post-Op           |                |                | 0.00*   |
| No                                   | 55 (55%)       | 158 (81%)      |         |
| Yes                                  | 45 (45%)       | 36 (19%)       |         |

*Statistically significant (p < 0.05). Values are n (%) unless otherwise denoted.
|                                    | Low Compliance | High Compliance | p - value |
|------------------------------------|----------------|-----------------|-----------|
| Cigarette use                      |                |                 | 0.07      |
| No                                 | 43 (52%)       | 100 (65%)       |           |
| Yes                                | 39 (48%)       | 53 (35%)        |           |
| Tobacco use                        |                |                 | 0.50      |
| No                                 | 74 (90%)       | 132 (86%)       |           |
| Yes                                | 8 (10%)        | 21 (14%)        |           |
| Marijuana use                      |                |                 | 0.13      |
| No                                 | 52 (63%)       | 113 (74%)       |           |
| Yes                                | 30 (37%)       | 40 (26%)        |           |
| Cocaine use                        |                |                 | 0.67      |
| No                                 | 94 (94%)       | 186 (96%)       |           |
| Yes                                | 6 (6%)         | 8 (4%)          |           |
| Crime conviction                   |                |                 | 1.00      |
| No                                 | 13 (72%)       | 47 (76%)        |           |
| Yes                                | 5 (28%)        | 15 (24%)        |           |
| Living change                      |                |                 | 0.19      |
| No                                 | 12 (67%)       | 52 (83%)        |           |
| Yes                                | 6 (33%)        | 11 (17%)        |           |
| Bus Stop                           |                |                 | 0.19      |
| No                                 | 22 (28%)       | 56 (37%)        |           |
| Yes                                | 58 (72%)       | 95 (63%)        |           |
| No phone                           |                |                 | 1.00      |
| No                                 | 17 (94%)       | 38 (93%)        |           |
| Yes                                | 1 (6%)         | 3 (7%)          |           |
| Cell Number Change                 |                |                 | 0.06      |
| No                                 | 13 (76%)       | 38 (95%)        |           |
A best fit logistic regression model was created with variables chosen based on the univariate analyses and clinical accessibility. Parameters included in the model were DCI ("Distressed" or "At Risk"), lack of private insurance, high school or lower education level, lack of PCP, and male gender (n = 210, AUROC = 0.65, CI = 0.57–0.72). There was a total of 84 non-respondents to at least one of the questions included in the model. Lack of private insurance was found to be a statistically significant predictor for follow up nonadherence, imparting an odds ratio of 2.0 (CI = 1.05–3.99) for follow up nonadherence compared to patients with private insurance coverage (p = 0.04, Table 5). “Distressed” or “At Risk” DCI status and male gender also increased the odds of follow up nonadherence by a factor of 1.8 (CI = 0.93–3.23) and 1.9 (CI = 1.00-3.82) respectively, however these findings were not significant (p = 0.07 and 0.05 respectively, Table 5). High school or lower education level (OR = 1.2, CI = 0.59–2.40, p = 0.64) and lack of a PCP (OR = 1.3, CI = 0.70–2.52, p = 0.38) did not largely impact follow up nonadherence and were not statistically significant predictors (Table 5). Table 5 presents the point scores for all the parameters used in the logistic regression model. The maximum possible risk score was 8. There was a statistically significant difference between the mean score for patients with low adherence (4.0 ± 1.6) versus those with high clinic adherence (3.1 ± 1.75, p < 0.01).

**Table 5**

Logistic Regression Analysis for Follow-up Nonadherence with Associated Risk Scores

| Parameter                      | Risk Score | Odds Ratio (95% CI)        | p - value |
|-------------------------------|------------|---------------------------|-----------|
| DCI (Distressed or At Risk)   | 2          | 1.8 (0.96–3.23)           | 0.07      |
| No Private Insurance          | 2          | 2.0 (1.05–3.99)           | 0.04*     |
| High School or Lower          | 1          | 1.2 (0.59–2.40)           | 0.64      |
| No PCP                        | 1          | 1.3 (0.70–2.52)           | 0.38      |
| Male Gender                   | 2          | 1.9 (1.00–3.82)           | 0.05      |

*Statistically significant (p < 0.05).

**Discussion:**

Follow-up nonadherence is common in the orthopaedic trauma clinic and creates challenges for multiple players in the healthcare field. Orthopaedic trauma surgeons are unable to make adjustments to postoperative treatment plans, trauma outcomes research is subject to bias, and patients are at higher risk for poor outcomes and more likely to present to the emergency department for treatment of postoperative complications. These behaviors also increase resource utilization and cost of care, and
subsequently, limit the quality of future healthcare delivery. Early anticipation and identification of trauma patients at risk for low clinic adherence is one method by which healthcare providers can address this issue before it materializes. The purpose of this study was to identify risk factors for follow-up nonadherence in orthopaedic trauma patients, and then to use these risk factors to build a predictive model that will assist healthcare providers in identifying at-risk patients prior to hospital discharge.

The results of our study demonstrate that there is an array of sociodemographic and clinical factors associated with follow-up nonadherence (Table 2, 3, and 4). We found that higher DCI scores, more severe injury, lack of insurance, government insurance, lower education levels, financial and relationship instability, lack of transportation and lack of PCP were significantly associated with lower clinic follow-up adherence (Tables 1, 2 and 3). There was also a significant association between low clinic adherence and ED visits within the 90-day post-operative period, indicating that this could be an area for quality improvement (p < 0.01, Table 3). Additionally, our multivariate logistic regression model using clinically applicable parameters including “Distressed” or “At Risk” DCI levels, insurance status, education level, gender, and PCP availability demonstrated that lack of private insurance status significantly increased the odds of patient follow-up nonadherence by 2-fold (OR = 2.0, CI = 1.05–3.99, p = 0.04, Table 5). “Distressed or “At Risk” DCI scores and high school or lower education levels also demonstrated similar predictive trends, though were not statistically significant (Table 5). Moreover, the prediction model yielded a maximum possible risk score of 8 (Table 5). Patients with low clinic adherence (< 0.75) had a mean score of 4.0 ± 1.6, while patients with high clinic adherence (≥ 0.75) had a mean score of 3.1 ± 1.75. The difference was statistically significant (p < 0.01), suggesting that this could be a viable predictive tool of patients at-risk for follow-up nonadherence, and thus, valuable in coordinating post-discharge care efforts.

Though the literature on risk factors for follow-up nonadherence in orthopaedic trauma is limited, some studies have reported similar results as those shown here. In 2014, Whiting et al. reported insurance status and injury complex severity as significant risk factors for nonadherence in the orthopaedic trauma clinic with the first follow-up appointment(9). Studies by Zelle et al. and ten Berg and Ring also found male gender, uninsured or governmentally insured patients, and single patients to be significantly at-risk for follow-up nonadherence at 1- and 6-month follow-up visits after injury(10, 12). Contrary to what we were able to show here, Whiting et al. and Zelle et al. both reported smoking status as a statistically significant risk factor for loss to follow-up. Specifically, Zelle et al. noted that illicit drug abuse significantly increased risk for follow-up nonadherence at any time point, not only at 6 months(9, 10). Notably, tobacco and illicit drug use have previously been correlated with lower socioeconomic status and lower levels of education – which were two factors we found significantly associated with loss to follow-up in this investigation(25, 26). In any case, all of these studies agree that risk factors for follow-up nonadherence are invaluable data points and can allow for healthcare teams to identify patients at high risk for follow-up nonadherence. Our prediction tool can help automate this identification process, and subsequently, allow for healthcare providers to design and implement strategies to improve follow-up in these populations.
Our risk prediction model scores patient’s risk for lack of follow-up on a scale from 0 to 8 based upon a set of risk factors (24). On average, scores greater than or equal to 4.0 were shown to be associated with a lower clinic adherence fraction, and thus, identify patients who would benefit from a more targeted treatment approach prior to and following hospital discharge. These approaches could include extended care efforts such as virtual visits, mobile emergency medical services, and mobile x-ray services, which already exist at our institution. Though our risk prediction model requires validation in future studies, we envision this tool as a valuable component of a social work discharge plan. The impact this simple intervention could have extends far beyond the principal benefit of improved follow-up. Patients will have better outcomes as presentation to clinic will allow the orthopaedic surgeon to appropriately adjust postoperative treatment plans and recognize and treat complications early. Additionally, orthopaedic researchers will be able to conduct clinical trials with less bias, and therefore, be able to identify avenues for continued innovation in the field. Lastly, the healthcare system will be subject to far less financial stress as increased clinic adherence will decrease emergency department utilization, decrease subsequent hospital readmissions, and decrease overall patient cost of care. We believe this will lead to improved quality of healthcare delivery and a better patient experience.

This study has several limitations. First, given our sample size, it is possible that our study may have been underpowered to detect clinically meaningful differences in some variables, such as tobacco and illicit drug use, which have been shown in other studies to correlate significantly with poor follow up (9, 10). Further, this was a single-center study and may not be generalizable to other urban or rural trauma centers. Larger, multicentered studies are necessary to validate and improve our model. Lastly, we are not able to ascertain why patients missed clinic visits, such as scheduling errors, follow-up at another institution, and even death. This subjects our study to potential information bias and could mean that our true adherence rate was higher than what is presented here.

Conclusions:

This study demonstrates that post-trauma clinic adherence may be anticipated at the time of hospital discharge based upon several sociodemographic and clinical risk factors. We offer a predictive model of such behavior based on these parameters, which we visualize as a valuable component in a social work discharge plan in the near future. Such a prediction tool will allow for coordinated care of at-risk trauma patients following hospital discharge through extended care options such as virtual visits, mobile emergency medical services, and mobile x-ray services. Coordinated care services such as these will allow for improved patient outcomes, efficient hospital resource utilization, improved quality of care, and an overall better patient experience.

Abbreviations

- SDOH: Social determinants of health
- DCI: Distressed Communities Index
Declarations

- **Ethics approval and consent to participate**: Emory institutional review board approval was obtained for this study; IRB ID: MODCR001-IRB00096056. Informed consent was obtained from patients via an electronic consent form. All methods were carried out in accordance with relevant guidelines and regulations.

- **Consent for publication**: Not applicable.

- **Availability of data and materials**: The datasets and/or analyzed during the current study are available from the corresponding author on reasonable request.

- **Competing interests**: The authors declare that they have no competing interests.

- **Funding**: Emory Department of Orthopaedics.

- **Authors contributions**: MM was a major contributor to data interpretation and manuscript write up. VK and KB were responsible for data acquisition and analysis. MAM and MCS were major contributors to manuscript revision. MLS was responsible for idea conception, study design and was also a major contributor to manuscript revision. AS prepared all tables and led data interpretation and manuscript write up. All authors have read and approved the submitted version of this manuscript.

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