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Risk Factors for the Development of Heterotopic Ossification in Seriously Burned Adults: A NIDRR Burn Model System Database Analysis

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Abstract

Purpose—Heterotopic ossification (HO) is a debilitating complication of burn injury; however, incidence and risk factors are poorly understood. In this study we utilize a multicenter database of adults with burn injuries to identify and analyze clinical factors that predict HO formation.

Methods—Data from 6 high-volume burn centers, in the Burn Injury Model System Database, were analyzed. Univariate logistic regression models were used for model selection. Cluster-adjusted multivariate logistic regression was then used to evaluate the relationship between clinical and demographic data and the development of HO.

Results—Of 2,979 patients in the database with information on HO that addressed risk factors for development of HO, 98 (3.5%) developed HO. Of these 98 patients, 97 had arm burns, and 96

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had arm grafts. Controlling for age and sex in a multivariate model, patients with >30% total body surface area (TBSA) burn had 11.5x higher odds of developing HO (p<0.001), and those with arm burns that required skin grafting had 96.4x higher odds of developing HO (p=0.04). For each additional time a patient went to the operating room, odds of HO increased 30% (OR 1.32, p<0.001), and each additional ventilator day increase odds 3.5% (OR 1.035, p<0.001). Joint contracture, inhalation injury, and bone exposure did not significantly increase odds of HO.

Conclusion—Risk factors for HO development include >30% TBSA burn, arm burns, arm grafts, ventilator days, and number of trips to the operating room. Future studies can use these results to identify highest-risk patients to guide deployment of prophylactic and experimental treatments.

Keywords

Extremity trauma; burn injury; heterotopic ossification

Introduction

Heterotopic ossification (HO), the ectopic formation of lamellar bone, is a complication of numerous types of trauma, including hip arthroplasty, electrical injury, neurological injuries and thermal injury.[1, 2] Historically, initial accounts of heterotopic ossification originated during World War I, a time during which medical care had improved enough to allow soldiers to survive the initial trauma and for physicians to examine post-injury complications.[3] The discovery of conditions such as fibrodysplasia ossificans progressiva, a congenital form of HO, also provided an initial understanding of the abnormal presence and growth of bone as it relates to the pathophysiology behind heterotopic ossification.

Today, we see heterotopic ossification most commonly as a direct consequence of extremity trauma and wartime trauma due to injuries sustained in Afghanistan and Iraq, and also after hip replacement surgery.[4–6] Risk factors in these etiologies include concomitant polytrauma, infection, and blast injuries. Additionally, close to 20% of patients with spinal cord injuries and traumatic brain injuries develop HO.[7] Neurogenic HO (NHO) always occurs below the level of the spinal cord injury, with the most common area located around the hip. It has long been noted that, among spinal cord injury (SCI) patients, NHO forms less frequently in patients with lumbosacral or cono-caudal lesions that are able to regain ambulation (21). Complete, transverse SCI is also associated with a greater risk of HO formation than incomplete SCI (19). Furthermore, in SCI patients the presence of spasticity is a significant risk factor for the formation of HO, which is rare in limbs not affected by spasticity (22).

It is important to also consider burn injury as a specific cause of HO that must also be studied, given the different pathophysiology of burn injuries.[8, 9] Whereas traumatic hip arthroplasties develop HO at the surgical site, burn induced HO patients have a cutaneous injury and do not have direct trauma to the site of HO. Interestingly, though less common, the HO can develop in areas where the patient did not even have cutaneous injuries. The incidence of heterotopic ossification after burn injury is quoted between 0.2 and 4%, with the elbow, shoulder, and hip being the most commonly affected joints. [9–15] However,

these low incidences have been reported in single center retrospective studies that look at a heterogeneous population of burn patients where the majority of the patients have small burn injuries (<10% TBSA). Furthermore, these studies have been underpowered in their ability to detect and assess risk factors.

Large databases such as the Uniform Data System for Medical Rehabilitation (UDSMR®) facilitate more in depth analysis of outcomes, allowing for improved treatment strategies; however, they have not included data on heterotopic ossification.[9, 16, 17] The Burn Injury Model Systems (BMS) program, funded by the National Institute on Disability and Rehabilitation Research (NIDRR), is a Model Systems program established to research the delivery, demonstration, and evaluation of medical, rehabilitation, and other services designed to meet the needs of individuals with severe burn injuries. Established by the National Institute on Disability and Rehabilitation Research (NIDRR) in 1993, the Burn Injury Model System (BMS) seeks to improve the lives of individuals with disabilities following burn injury. This study analyzes the burn model system database to evaluate the incidence and risk factors related to heterotopic ossification with the belief that this will allow for better prediction of patients at high risk. Identification of high-risk patients is especially important in a condition like HO where treatments are limited and are fraught with significant side effects. Identification of risk factors in a large multicenter population will provide insight into the etiology of HO.

Methods

Data Collection

Data was collected from six burn centers (Baltimore, MD; Galveston, TX; Dallas, TX; Denver, CO; Boston, MA; Seattle, WA) as part of the Burn Injury Model System Database as previously described.[18] Since 1994, the BMS has maintained a longitudinal database of demographic, injury, and outcome information. The BMS database enrollment criteria for adult patients include:

- 18 – 64 years of age with a burn injury ≥20 % total body surface area
- ≥ 65 years of age with a burn injury ≥10 % total body surface area
- ≥ 18 years of age with a burn injury to their face/neck, hands or feet
- ≥ 18 years of age with a high voltage electrical burn injury

Study data are collected and electronically entered into the centralized BMS database. After providing informed consent, subjects were enrolled and their initial data collected at the time of discharge from their acute hospitalization as previously described.[19] Data that was sought from the dataset included demographic data (age, sex, ethnicity, date and type of burn, presence of preexisting medical problems, hospital site), the percentage total body surface area burned (TBSA), the presence of inhalation injury, number of ventilator days, body site burned, number of trips to the operating room, body sites grafted, the presence of joint contractures, the number of days from the injury to discharge from the acute burn hospitalization, the presence of exposed bone in wounds, and the presence or absence of heterotopic ossification. In this study we included patients entered into the dataset from

10/5/1993-6/30/2013. From 10/5/1993-6/30/2013, 5,176 people were eligible for enrollment. Of these 1,039 were under 18 years old. 371 people were deceased at time of discharge, 202 people were eligible but refused, and 63 people were eligible but missed/not approached by the BMS for enrollment (Figure 1). Heterotopic ossification was listed as a unique variable in the dataset, however, the site of HO was not reported. BMS captures patients that are representative of those in the NBR – with an emphasis on those with more severe burns since NBR has a lot of minor burns.[9] Previously, studies have demonstrated that this database is comparable to the National Burn Repository Additionally, these studies proved, "terms of demographic composition of subjects/generalizability to the whole population."

Data Analysis

Demographic and clinical parameters were evaluated with frequencies and percentages. For continuous variables, mean ± standard deviations as well as median and interquartile range were calculated, and sample distribution was analyzed with unpaired t-test. Kolmogorov-Smirnov test was utilized to assess distribution of categorical variables.

Examination of patient demographics combined with major events in the acute hospitalization was sought to allow a better understanding of the possible contributors to development of this condition. Identification of factors predictive of developing HO was done with univariate logistic regression models for each data element. This helped identify variables that potentially contributed to the development of HO. Although looking at these variables in isolation from the rest of the clinical picture is inadequate to understand each ones relationship to developing HO, using univariate analysis for model selection guided our multivariate modeling.

On initial analysis, all enrolled patients in the database were included (Figure 1). We then dropped those with missing data on HO (total 704) and did not see substantial change in univariate results. In more closely analyzing patients with missing data on heterotopic ossification, we found that 219 of these patients died before 90 days post-injury, well before the 6-month evaluation (first set data collection point for patients discharged after burn care). Of the remaining 485 with missing HO data, we used chi-square and t-test to confirm that age, gender, ICU days, ventilator days, TBSA burn over 30%, arm burns, and arm grafts all did not differ significantly from the group of patients with data on HO (all $p>0.1$). This supported our assumption that missing data was missing at random, and not due to anything inherent about the patients in this database. Considering that the group with missing data did not significantly differ from our analysis cohort, and wanting to avoid over-inflating our results with an imputations approach, we used listwise deletion and accepted the loss of power by simply eliminating patients with incomplete HO data from this initial database analysis. Additionally, we controlled for hospital-level variation in data collection by adjusting for clustering in our model (see below), another way of offsetting potential data collection shortcomings that may have been institution-based.

After isolating our final analysis cohort, the variables found to have significant predictive relationship to HO in univariate analysis were used in multivariate logistic regression models to identify those that remained predictive when controlling for potential confounders, providing more clinically useful and applicable analysis of this data. These

models allowed us to reduce confounding effects of different variables on each other, and on our results. Additionally, multivariate models provide composite odds of HO development considering multiple risk factors together, rather than in isolation from each other. All models used cluster adjustment methods to control for the multi-institutional nature of this database. Knowing that some of these variables may strongly predict HO development, if we had concern about separation or quasi-separation we would then proceed to verify our regression results with Firth methodology. The downside of Firth methodology in our model is that it limits our ability to cluster-adjust; however, if odds ratios remained relatively consistent between the two models, this would verify that our logistic model did not violate key assumptions or present inappropriate results.

With this multi-step model development approach, we reached the highest-yield multivariate model and limited the addition of non-significant predictor variables that would only serve to further confound results and reduce overall model power. Odds ratios are reported for predictive explanatory variables. Model performance was evaluated by area under the receiver operating curve (AUROC) as well as Hosmer-Lemeshow goodness-of-fit testing.

Results

Demographics

The Burn Model System database had a total of 4,137 adult burn patients eligible for enrollment during the period examined. Of them, 3,501 were enrolled at hospital discharge but only 2,797 patients had complete information related to the presence or absence of HO. This group became our analysis cohort. This includes 2,120 (75.8%) males and 677 (24.2%) females. This split is similar to the overall split in sex in the BMS database. Mean age was 42.4 years old, with mean age of males 41.6 years and females 44.8 years. Burn injuries ranged from TBSA of less than 1 to 99 %. Mean TBSA burn was 18.8 %. Of the patients in this database with complete information, 98 were known to develop HO (3.5%; See Table 1 for burn etiology and Table 2 for more complete demographic data by HO status). Every year included in the study had patients with HO, and HO incidence was relatively consistent year to year, ranging from 1.5% to 8% of all burns reported each year.

Univariate analysis of predictors of heterotopic ossification – model selection

Results from this analysis were not conclusive of any relationship between predictors and HO; rather, these results helped guide our multivariate model design (below). Overall, demographic data elements did not predict the occurrence of HO. Age, sex, ethnicity, and number of medical comorbidities were all non-significant when analyzing their effect on HO formation. Hospital providing care was not a significant predictor of HO development. When looking at details of the burn injury, however, several variables increased odds of HO formation. When analyzed as a continuous variable, each increase of 1% TBSA burn was associated with increased odds of HO formation (OR 1.07, $p<0.001$). Any days on a ventilator increased odds of HO formation (OR 5.35, $p<0.001$), and each additional day on a ventilator beyond the first brought increased odds of HO formation as well (OR 1.06, $p<0.001$).

When evaluating TBSA burn as a categorical variable, those patients with >30% burn (OR 21.3, p<0.001) had significantly higher odds of developing HO. In addition to the size of the burned area, 97 of the 98 patients that developed HO hand an arm burn (OR 48.3, p<0.001), and 96 of 98 had an arm graft (OR 54.9, p<0.001). Those patients with joint contractures also had increased odds of developing HO (OR 41.2, p<0.001), though we were unable to determine if the HO caused the contracture. Additionally, inhalation injury (OR 4.6, p<0.001) and exposed bone (OR 5.5, p<0.001) were associated with higher odds of HO formation. Finally, days to discharge was associated with HO (OR 1.03, p<0.001). Burns to other regions of the body (including leg, trunk, perineum, head and neck, hand) were significant in univariate analysis; however, when added to multivariate models, none of these other regions reached significance (data not shown, see below).

Multivariate Analysis

Considering the univariate results, we then evaluated these variables using multivariate models. Arm burn and arm graft were nearly collinear, and also were almost directly predictive of HO. As a result, we combined these factors in to one variable “arm burns requiring skin grafts” for analysis.

Although not significant in univariate analysis, age and sex were put in the multivariate model to control for these commonly referenced demographic elements in evaluating other clinical risk factors. As mentioned above, burns in any body region other than arm did not remain significant in multivariate analysis, and were therefore dropped during multivariate model selection.

When controlling for age, sex, and the cluster effect of different hospitals, arm burns requiring skin grafts (OR 96.4, p=0.04), TBSA burn >30% (OR 11.5, p<0.001), and number of trips to OR (OR 1.32, p<0.001) remained significant, while contracture, inhalational injury, and bone exposure did not (Table 3). Days on the ventilator also remained significant (OR 1.035, p<0.001), with each additional day increasing odds of HO by 3.5%, even though inhalational injury was not a significant predictor. Every OR trip increased odds of HO by about 30%, and having TBSA burn over 30% increased odds of HO by over 11x.

As evidenced in our results, arm burn requiring skin graft correlated so strongly with HO that we were concerned that separation had occurred. Re-running the model with Firth methodology (but no cluster adjustment) found that all of our results remained relatively unchanged – minimal differences in ORs and all significant variables remained significant – allowing us to use our logistic model. Additionally, goodness-of-fit testing confirmed good model fit (p=1.00), and AUROC was 0.973.

Discussion

The majority of publications on burn related HO formation have focused on single center outcomes making results difficult to interpret. With the Burn Injury Model System National Database, we are better able to assess a large number of patients across multiple institutions. This is the first multicenter study of burn patients to assess the predictors of heterotopic ossification. We found that predictors include large burn injuries (>30% TBSA), arm burns

requiring skin grafts, number of trips to the operating room, and number of ventilator days. The high prevalence in arm burns is interesting from an anatomical standpoint. Further studies are needed to evaluate if certain aspects of the elbow such as the superficial location of the ulnar nerve increase its risk of HO development.[20] Though not all of these are modifiable, we do think we can improve delirium, early mobility and early extubation, which would decrease days on the ventilator and ventilator associated pneumonia. Several of these findings were consistent with smaller, single institution reports such as increased TBSA.[21] Current gaps in burn induced HO understanding include identifying risk factors, isolating the progenitor cells, early diagnosis and prevention. By analyzing large clinical groups such as the BMS database, we believe we are better able to understand those clinical factors associated with burn induced HO. Such understanding of the nature of this process also allows clinicians to compare this process in a cutaneous injury to those who develop HO from other types of trauma such as crush or amputation.

In addition to modifying known risk factors, knowing which burn patients are at highest risk and would benefit from such a prophylactic strategy could improve future outcomes. Additionally, physical therapy is a modifiable risk factor known to play a role in HO formation. Though active range of motion is thought to mitigate burn contractures, the role of passive range of motion on burn contractures as well as its effect on joint trauma and heterotopic ossification is unknown.

Development of heterotopic ossification has been shown to require an inflammatory insult, which requires a more substantial thermal injury burden than are described in previous studies.[22–27] Thus, we believe a worthwhile analysis would include a population with a larger number of patients with large (>20% TBSA) burn injuries with more substantial global inflammation. Although the exact cause of HO in burn patients remains unknown, studies report central factors leading to the development of HO as duration of immobilization, percentage of total body surface area burned, and therapy performed during the recovery process.[11] Heterotopic ossification is known to require three main components, including an inflammatory insult, osteopotent cells and an osteogenic environment. Burn injury is unique because of the large inflammatory response. We have previously shown that burn injury causes an upregulation of osteogenic gene signaling.[8] Furthermore, others have shown that number of days on the ventilator and trips to the operating room increases the inflammatory response to a burn injury.[28–32] The mechanism driving HO formation in nerve injury and immobilization has thus been a topic of much study. HO has also been found in association with peripheral nerves in SCI patients (19). Current evidence is that trauma leads to neurogenic inflammation, which is mediated by substance P and CGRP release from peripheral sensory nerves, which initiates the formation of HO (4,20).

The laboratory work-up of a patient with suspected heterotopic ossification is somewhat limited and mainly based on the clinical history. Given that the pathophysiology of HO is linked to an imbalance of factors leading to abnormal calcium phosphate deposition in tissues, some have tried to isolate whether serum calcium, phosphorous, and alkaline phosphatase levels can be used to reliably diagnose HO. These values are oftentimes normal in this patient population or abnormal due to other factors (i.e. sepsis or metabolic causes of

electrolyte imbalance). Thus, no current confirmatory laboratory test exists. Presence of HO requires invasive surgical resection which has significant risk and leaves over 75% of patients with functional deficits.[1, 11, 33, 34] Thus, patients would greatly benefit if physicians were better able to predict which patients are at high risk and then deploy highly sensitive imaging techniques at an early timepoint.

The most common early treatment approaches include bisphosphonates, anti-inflammatories, and single dose radiation therapy, which despite some success, have significant side effects and thus are not viable treatments for all patients at risk for HO.[35–41] Indomethacin has also been used, but is not an adequately effective prophylaxis for HO.[42, 43] Other treatments such as radiation also cause potentially detrimental effects to surrounding tissues and make subsequent operations more challenging. Identification of which patients are prone to HO progression will limit therapy to those with greatest need, and thus may reduce complications by preventing unnecessary prophylactic treatments in patients not prone to HO formation and progression.

Future studies will use this database to identify risk factors for HO formation and perhaps focus prophylactic treatments in those patients with risk factors. If employing a new prophylactic strategy such as a bone morphogenetic inhibitor or an anti-inflammatory, clinicians would first want to enroll patients with these risk factors.[26, 38, 44–47] Thus, we believe that our results identify new predictors of HO risk including burns that involve the upper extremity, greater surface area burns, increased number of trips to the operating room and increased ventilator days. This will allow communication between the surgeon and occupational therapist to identify those at high risk for HO. Furthermore, once prophylactic strategies are developed, these at risk patients should be targeted first.

This study and database does have several notable limitations. First of all, we only have 98 patients who developed HO. This may be an accurate representation of HO rate in the burn population, or could be the result of under diagnosis and/or missing data. We assumed that missing data in our analysis was missing at random, which we believe is accurate although cannot confirm. Additionally, patients were required to provide consent and those patients who did not consent were not included. Though this was a low percentage, we do not know if those patients were different from those patients who did provide consent as we are unable to collect their information. Either way, this consent and low number limits the strength of our analysis and results. Age, for example, demonstrated a trend and may have been significant if there was a greater n. Nonetheless, this is the largest burn cohort of its kind with data on heterotopic ossification and thus represents a relevant preliminary step to more in depth studies. By using univariate analysis to filter through some of the potential predictors we attempted to minimize this limitation, but for the variables that did not reach significance we cannot rule out limitations due to sample size. Regardless, this is the largest civilian database to date and is a starting point for future studies.

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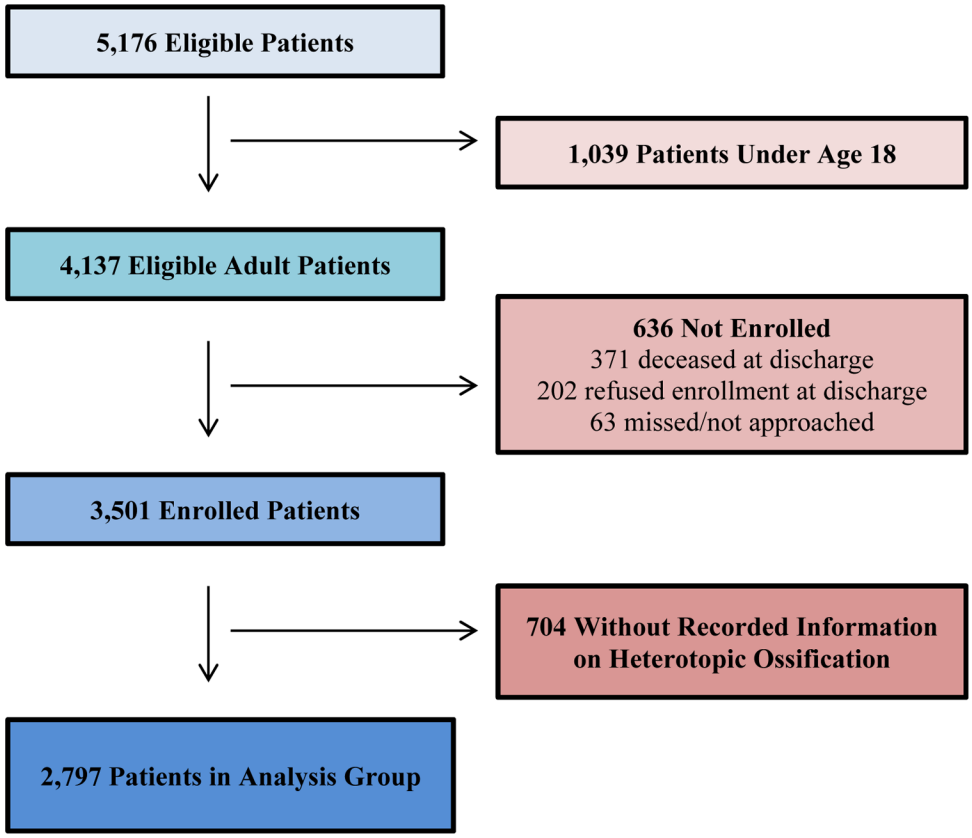

Figure 1.
Flow chart of patient enrollment and analysis group development

Table 1

Burn Etiology

Etiology of Burn Injury	All Patients (% of total)	Without HO (% without HO)	With HO (% with HO)
Fire/Flame	1706 (61%)	1621 (60%)	85 (87%)
Scald	240 (8.6%)	238 (8.8%)	2 (2%)
Contact with hot object	130 (4.7%)	129 (4.8%)	1 (1%)
Grease	245 (8.8%)	244 (9%)	1 (1%)
Tar	45 (1.6%)	45 (1.7%)	0
Chemical	57 (2%)	54 (2%)	3 (3.1%)
Electricity	181 (6.5%)	178 (6.6%)	3 (3.1%)
UV Light	4 (0.1%)	4 (0.15%)	0
Other Burn	11 (0.4%)	11 (0.4%)	0
Frostbite/Cold	5 (0.2%)	5 (0.2%)	0
Flash	123 (4.4%)	120 (4.5%)	3 (3.1%)
Other Skin Diseases	2 (0.1%)	2 (0.1%)	0
Unknown/Not Reported	21 (0.8%)	21 (0.8%	0

Table 2

Demographic information

Characteristics	With HO	Without HO	p-value*
Age (years)			p = 0.441
Mean ± SD	42.4 ± 13.3	41.5 ± 15.8	
Median (IQR)	41.25 (19.8)	40.4 (21.8)	
Range	18–77	18–94	
Hospital Days>			p < 0.001
Median (IQR)	74 (48)	20 (21)	
Range	21–451	0–716	
Gender			p = 0.682
Men [n, %]	81 (83%)	2039 (76%)	
Women [n, %]	17 (17%)	660 (24%)	
TBSA& **Burn**>			p < 0.001
Median (IQR)	47 (28)	14 (19)	
Range	15–89	0.1–99	
Ethnicity			p = 0.867
White	72 (73.5%)	1874 (70%)	
Black, non-Hispanic	7 (7.1%)	349 (13%)	
Hispanic	11 (11.2%)	312 (11.6%)	
Pacific Islander	0	12 (0.5%)	
Asian	3 (3.1%)	59 (2.2%)	
Native American	4 (4.1%)	55 (2.2%)	
Multiracial	0	12 (0.5%)	
Other	1 (1%)	13 (0.5%)	
Unknown	0	7 (0.3%)	
Concomitant Medical Problems			p = 0.785
Yes	30 (31%)	919 (34%)	
No	64 (65%)	1691 (63%)	

*Group distribution comparisons using unpaired t-test (age, TBSA burn) or Kolmogorov-Smirnov test (gender, ethnicity, medical problems)

>Significant difference between groups

&TBSA = total body surface area

Table 3

Multivariate Logistic regression model results of variables related to development of HO

Clinical Factor	Effect on Development of HO		
	Odds Ratio	95% confidence interval	p-value
Arm Burns Requiring Skin Grafts	96.4*	1.19, 7806	0.04
TBSA burn > 30%	11.5*	6.0, 21.9	<0.001
Number of Trips to Operating Room (each trip)	1.32*	1.18, 1.40	<0.001
Number of Days on Ventilator (each day)	1.034*	1.03, 1.04	<0.001
Contracture	6.26	0.79, 49.5	0.082
Inhalation Injury	1.40	0.57, 3.43	0.466
Bone Exposure	1.52	0.36, 6.44	0.569
Age	1.01	0.99, 1.02	0.07
Gender (Female)	0.64	0.38, 1.12	0.11

* significant, with $p<0.05$