A novel analytical tool to assess spine injury risk in impact biomechanics

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ABSTRACT

Impact biomechanics experiments often result in multiple types, severities, or classifications of injury due to external mechanical loading, inertial or contact induced. It is important to examine the effect of biological variability on these types of injuries to determine human tolerance and develop injury criteria for improving safety. The goal of this work is to present the Competing Risks Analysis (CRA) process using the Fine and Gray Proportional Subdistribution Hazard model that is commonly used in the medical literature. CRA allows measuring the effect of biological variability on each injury type separately by the subdistribution hazard ratio (SHR), where an SHR > 1 indicates in increase in rate of a type of injury. CRA is demonstrated in this investigation by examining the effect of spinal curvature on bone only, ligament only, and bone and ligament combined injuries in a contact-induced loading head-neck experimental model conducted by the authors and other published data from literature studies. The CRA shows that the rate of bone only injuries without lordosis is roughly 3 times as with lordosis and the rate of bone and ligament combined injuries are roughly 3 times that for lordosis compared to no lordosis. The CRA can be used in other experimental with multiple outcomes from experiments using post mortem human surrogates (PMHS) and or computational modeling studies.

INTRODUCTION

Impact biomechanics experiments using post mortem human surrogates (PMHS) are conducted to determine human tolerances and develop injury criteria for military, automotive, and other applications. Biological variability is inherent in this type of experimental model. Multiple outcomes are common in PMHS experiments. For example, external loading to the spine can produce pure bony injuries, ligament injuries with no bone fractures, or a combination of bone fractures and ligament disruptions, or the spine may remain intact after the test, i.e., no injuries. Biological features of the tested specimen also influence outcomes, giving researchers the ability to generalize them to different populations. For example, from a series of 42 PMHS sled tests, to obtain injury tolerance data, 45 years of age was selected in the automotive environment for side impact crashworthiness, while vertical impact loading studies have used a lower age to protect soldiers in the military [Kuppa *et al.* 2003, NATO 2007, Yoganandan *et al.* 1996]. The bone mineral density of the spine/hip, determined by x-ray absorptiometry or quantitated computed tomography, is used as a parameter to develop gender- and age-specific tolerance [Hansson *et al.* 1980]. The total body mass (subject weight) is used in crashworthiness for different size occupants. Methods such as equal stress equal velocity (EQEV) normalization or impulse momentrelated normalization techniques are used for this purpose [Yoganandan *et al.* 2014]. While common demographic factors such as those cited above are included in the analysis (statistical or other models, EQEV) to describe human response to injury, other biological variables can affect outcomes, i.e., injuries, injury mechanisms, and injury tolerances. The geometry of the tested PMHS specimen is a potential variable, and this may include overall or local changes, e.g., the severity of degeneration of the disc or curvature in spine studies. The objective of this study is to present an analytical tool, termed Competing risks analysis (CRA), to statistically quantify these types of variables on the outcomes of an experiment. The feasibility of the CRA tool is demonstrated using spinal curvature-based parameter in the production of head-neck trauma according to different types of injuries (bone, ligament and combination) in this study.

General competing risks type analyses are common in the medical literature. The analysis methods allow for accurate adjustment for multiple end-points in survival, or censored, data. The need for this in analyzing certain biological variations in impact biomechanics studies is straight forward. PMHS specimens can not only receive injury, but, as described earlier, they can be of multiple different types of injuries. In the modern survival analysis methods used in the literature for impact biomechanics studies, adding the type of injury as a covariate is not fully appropriate. The CRA presented here accurately takes this into account, along with the censoring aspect of the data, to evaluate the effect of spinal curvature, lordosis, on an example dataset that produced multiple injury types.

METHODS

Statistical Background

Analysis of impact biomechanics experiments were originally often performed using simple binary regression models, such as logistic regression [Pintar *et al.* 1997, Viano *et al.* 1989]. The binary variable, with 1 indicating an injury, is used as the outcome, and the measured metric (such as maximal force) is used as a covariate. If other factors are warranted for analysis (sex, age, lordosis, etc), they are also included as covariates. The typical logistic regression takes the following form

$$\log \frac{p}{1-p} = \beta_0 + m\beta_1 + x\beta_2$$

where p is the probability of injury, m is the metric value, x are the other factors, and the β terms are the unknown parameters to be estimated. There are a few issues with using a model such as this in impact biomechanics. The first is that it is possible that there could be positive predicted probability of injury at a zero value of the metric. The second, and most relevant for this work, is that it ignores the censoring aspect of the data.

Data from impact biomechanics is censored because if an injury did not occur at a particular metric value there is more information than just “no injury”. It is known that the true metric value that would cause injury is larger than that particular metric value. These are right-censored datapoints. For injury datapoints, there are two possibilities. Either the measured metric value was exactly where the injury was caused, an exact or uncensored datapoint, or that the true metric value causing injury was smaller than the measured value, a left censored datapoint. There also exists possibilities in repeated testing scenarios where multiple metric values are measured and the true value causing injury is known to be between two points, an interval censored datapoint. The logistic regression model does not take this extra information into account.

This led to the use of survival analysis of impact biomechanics experiments because they accurately take these censoring issues into account, [Petitjean *et al.* 2015, Petitjean *et al.* 2009] . Parametric survival models are usually fit where a parametric distribution is chosen, and its shape and scale parameters are estimated from the data. Typical distributions are shown below, as characterized by their cumulative density function.

$$Weibull: 1 - \exp\left(-\left(\frac{m}{\lambda}\right)^{\gamma}\right)$$

$$\text{Loglogistic: } \frac{1}{1 + \left(\frac{m}{\lambda}\right)^{-\gamma}}$$

$$\text{Lognormal: } \Phi(\gamma \log \lambda m)$$

where m is again the metric value, $\Phi(x)$ is the cumulative distribution function for a standard normal random variable, and λ and γ are typically referred to as shape and scale parameters. The effect of covariates is typically modeled through the λ term through an exponential link function. While the parametric survival models ensure that a zero value of the metric results in a zero estimated injury probability and takes the censoring aspect of the data into account, it cannot easily take multiple types of injury into account. This led to the need of competing risks analysis, the principal objective of this study.

Competing Risks Analysis

In much the same way that logistic regression lost information by not considering the censoring aspect of the data, usual parametric survival analysis can lose information when multiple types of injuries are present. Consider the case where a specimen could get one of three different types of injury, for example a bone only injury, a ligament only injury, or a bone and ligament combination injury. For a given specimen, receiving one type of injury precludes the observance of at what metric value the other type of injuries would have occurred, as the experiments are typically not repeated after an injury is observed.

Competing risks data is commonly observed in the medical literature [Eguchi *et al.* 2017, Lloyd-Jones *et al.* 1999, Pencina *et al.* 2009]The gold-standard regression model for such data is the Fine and Gray proportional subdistribution hazards model [Fine and Gray 1999]. Instead of modeling the probability of specific type of injury at a metric value directly, it instead models the instantaneously probability of receiving that type of injury, given that no injury due to that specific injury type up until the metric value has occurred. This is termed the subdistribution hazard, $\lambda_k(f)$. It has the following mathematical form.

$$\lambda_k(m) = \lim_{\Delta m \to 0} \frac{\text{Prob}\{m \leq M < m + \Delta \text{m}, I = k \mid M \geq m \text{ or } (M < m \text{ and } I \neq k)\}}{\Delta m}$$

where m is the metric value, M is the true metric value at which injury would occur, I is an indicator of the different types of injury, and k is which type of injury is to be modeled or is of interest. In order to measure the effects of other covariates, the Fine and Gray proportional subdistribution hazards model is constructed as

$$\lambda_k(m \mid x) = \lambda_{k0}(m) \exp(x\beta)$$

where x are the other covariates and $\lambda_{k0}(m)$ is a flexible non-parametric baseline subdistribution hazard function. The reason the subdistribution hazard is modeled is because it allows a one-to-one correspondence of the covariate effect to the cumulative incidence function (CIF) for an injury cause k. The CIF is given as the probability of an injury of a specific type occurring sometime before the metric value m,

$$C_k(m \mid x) = \text{Prob}\{M < m,\ I = k \mid x\} = 1 - \exp\{-\int_0^m \lambda_k(u \mid x)du\}.$$

Thus, the interpretation of β is clear. It is however more common to interpret $\exp(\beta)$, the subdistribution hazard ratio (SHR), as the relative change in rate of the injury type. For example, if $\beta = \log 2$ then SHR$=$ 2. A value of SHR greater than 1 implies an increase in the covariate leads to an *increase* in the rate of that type of injury. Thus, in the example, an increase in the covariate doubles the rate at which that type of injury occurs.

Data Analysis

The CRA method was demonstrated using a real-world dataset measuring the effect of spine curvature, lordosis, on three types of injury; bone only, ligament only, or bone and ligament combined.

Data description. Impact loading to the head from human cadaver head-neck complex experiments reported in literatures was used in the study. In the first subgroup of experiments, specimens free of pre-existing spinal abnormalities and trauma were obtained by screening medical records and obtaining pretest x-ray and CT scans [Pintar *et al.* 1998, Yoganandan *et al.* 1991, Yoganandan *et al.* 1990]. Head-neck complexes isolated from the cadavers were rigidly fixed at the T2-T3 level, and a load cell was attached inferior to the fixation. The preparations were placed on a testing device and the natural cervical spine lordosis was removed by preflexing the specimen. Impact loading to the vertex of the head was applied with the piston of the testing apparatus. The specimens underwent posttest x-rays, CT, and cryomircotomy to document injuries to bones, ligaments, and joints. The maximum axial forces measured at the inferior end of the specimen along with injuries were obtained.

In the second subgroup of experiments, a similar protocol was followed [Nightingale *et al.* 1997, Nightingale *et al.* 1996, Nightingale *et al.* 1996]. The human cadaver specimens were screened, and head-T1 specimens were fixed at the T2-T3 level. The natural lordosis of the specimen was preserved by orienting the cervicothoracic joint at a downward angle of 25 degrees with respect to the transverse plane. A torso mass of 16 kg, approximating the effective mass of the torso in dynamic events, was added to the specimen, placed on the testing device which was fixed to the inferior end of the load cell. The inverted head-spine specimens were dropped to deliver the impact to the head. A load cell was attached to the inferior end of the preparation to measure the axial loading on the cervical spine.

In the third subgroup of experiments, the protocol was similar to the second subgroup with the exception that the osteoligamentous column from the occiput to T2 was used [Saari *et al.* 2013]. The absence of the head in the cervical column was accounted for by attaching an artificial head to the superior end of the spine. The T1-T2 level was fixed, and the C4-C5 intervertebral disc was maintained in the horizontal alignment in the cervical lordosis posture. The head-spine specimens were prepared with and without the simulation of follower load mechanism [Patwardhan *et al.*

2000]. The specimens were attached to the drop test carriage and a simulated torso mass of 15 kg was used, similar to the second subgroup of experiments. A load cell attached to the distal end of the preparation measured the axial loading on the cervical spine. As before, the inverted specimens were dropped to accept impact to the head, and injuries for each specimen and maximum axial forces measured at the distal end of the preparation were obtained to meet the objectives of the study.

Analysis: The three subgroups are combined into one final dataset. The dataset consisted of a maximal force value, an injury indicator, what type of injury if one occurred (bone only, ligament only, bone and ligament combined), lordosis status, age, and gender. CRA was performed for each of the three injury types use the Fine and Gray proportional subdistribution hazard model. The effect of lordosis was measured by its SHR value. A hypothesis test of whether SHR is equal to 1 was performed, with type I error controlled at 0.05. A step-wise selection procedure was conducted to determine whether adjustment for age or gender was necessary when evaluating the effect of lordosis. R version 3.5.3 was used to conduct the analysis [Team 2014].

RESULTS

The total sample size was 51 with 31 specimens having lordosis. A breakdown of injury type by lordosis status is provided in Table 1. There was a total of 16 bone only injuries, 5 of which were with lordosis, 10 ligament only injuries, 6 of which were with lordosis, and 19 bone and ligament combined injuries, 14 of which were with lordosis. A summary of age and gender is provided in Table 2.

Injury type	**Overall (51)**	**Lordosis (31)**	**No Lordosis (20)**
None	6	6	0
Bone only	16	5 (20%)	11 (55%)
Ligament only	10	6 (24%)	4 (20%)
Bone and ligament	19	14 (56%)	5 (25%)
Any	45	25	20

Table 1: Counts of injury type by lordosis status. Numbers in column headers are sample size and numbers in parentheses in the table are the percent of lordosis status injuries (column sum adds to 100%).

Covariate	**Overall (51)**	**Lordosis (31)**	**No Lordosis (20)**
Age, mean (SD)	63.7 (14.0)	64.5 (13.3)	62.4 (15.3)
% Male	62.7%	67.7%	55.0%

Table 2: Covariate summary by lordosis status. Numbers in parentheses are sample size.

The median maximal force for bone only, ligament only, and bone and ligament injuries for specimens with lordosis were 1.8 kN, 2.2 kN, and 1.7 kN respectively. For specimens without lordosis, these were 3.7 kN, 2.8 kN, and 3.7 kN. These data are summarized in Figure 1.

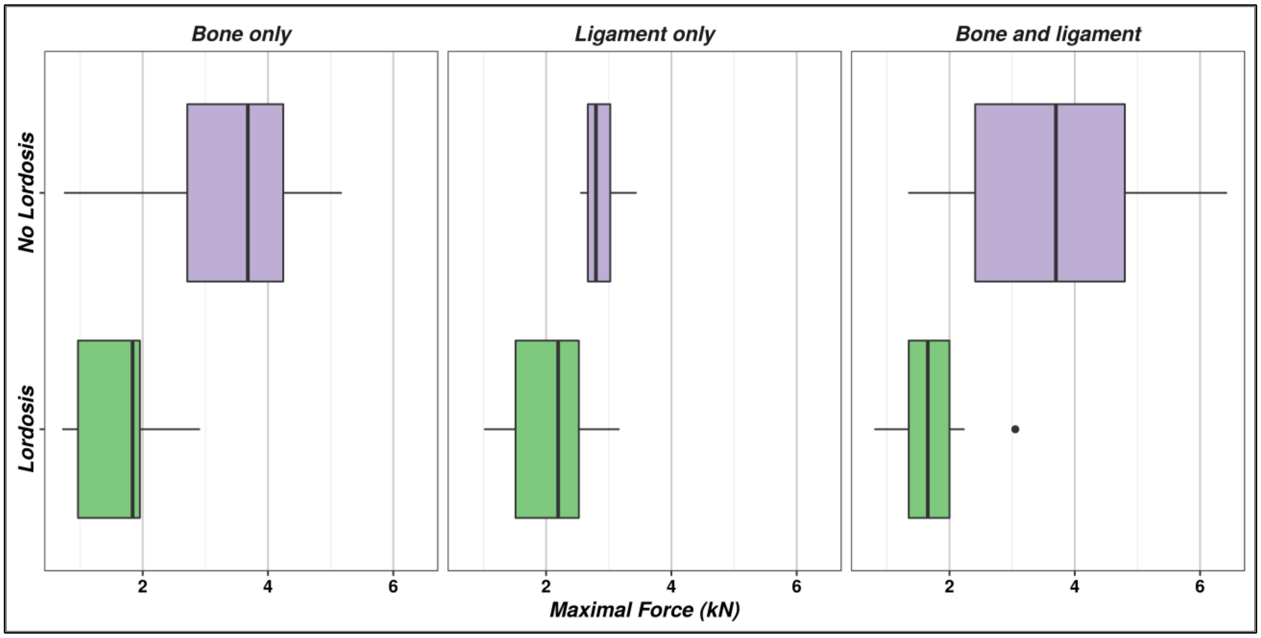

Figure 1: Boxplots of maximal forces by injury type and lordosis status.

For all three injury types, both age and gender were selected out of the model. The SHR for lordosis for bone only, ligament only, and bone and ligament injuries were 0.31 (p = 0.026), 1.1 (p = 0.83), and 2.7 (p = 0.038).

DISCUSSION

Specimens with lordosis had a greater proportion of bone and ligament combined injuries while specimens without lordosis had a larger amount of the bone only injuries. There also seemed to be no large difference between specimens with or without lordosis regarding the age or gender covariates. Both of these findings are corroborated by the results of the Fine and Gray proportional subdistribution hazards model. Both age and gender weren't chosen by the selection process meaning the estimate of the effect of lordosis does not differ based on these covariates. It should be noted that an earlier study that included gender and age include in the statistical model, did not incorporate the curvature in the analysis [Pintar, Yoganandan and Voo 1998]. The SHR for bone and ligament injuries was significant at 2.7, indicating that the rate of these injuries is nearly 3-fold more for specimens with lordosis compared to those without. The SHR for bone only injuries was significant at 0.31. This is equivalent to an SHR of $1/0.31 = 3.2$ for no lordosis compared to lordosis. That is, specimens that do not have lordosis have about 3 times the rate of bone only injuries compared to those with lordosis. The CRA analysis demonstrates a natural step for injury assessment in impact biomechanics by allowing analysis of multiple types of injury. The subdistribution hazards approach presented in this work examines the interdependency of injury types from one or more experimental datasets that have a common-type of insult (in the demonstration example, contact loading). This approach can be extended to other body regions in impact biomechanics experiments.

CONCLUSIONS

In summary, this study presented the CRA analytical tool to statistically account for and explain the differing outcomes from PMHS impact tests. Its feasibility was shown using published data from previously tested PMHS head-neck experiments. Specific to the experimental dataset analyzed in this work, the CRA showed the varying affect spinal curvature can have on different types of outcomes in impact biomechanical studies, wherein its presence either increased the rate of different outcomes. This statistics-based study is hoped to inform researchers to examine multiple injury outcomes using the novel methods presented in this work for a more inclusive treatment of data and outcomes.

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