Understanding the long-term impacts of burn injury on the circulatory system

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Background: While the most obvious impact of burn injury is on the skin, systemic responses also occur after burn injury that lead to wide-spread changes to the body, including the heart. The aim of this study was to assess if burn injury in mid-aged and older adults is associated with increased long-term admissions and death due to diseases of the circulatory system.

Methods: A population-based longitudinal study using linked hospital morbidity and death data from Western Australia was undertaken of adults aged at least 45 years when hospitalized for a first burn injury (n=6004) in 1980–2012 and a frequency matched non-injury comparison cohort, randomly selected from Western Australia’s electoral roll (n = 22,673). Crude admission rates and cumulative length of stay for circulatory diseases were calculated. Negative binomial and Cox proportional hazards regression modelling were used to generate incidence rate ratios (IRR) and hazard ratios (HR), respectively. HR was used as a measure of the mortality rate ratio (MRR).

Results: After adjustment for demographic factors and pre-existing health status, the burn injury cohort had 1.46 times (95% Confidence Interval (CI): 1.36-1.56) as many admissions and almost three times the number of days in hospital with a circulatory system diagnosis (IRR, 95%CI: 2.90, 2.60-3.25) than the uninjured cohort for circulatory diseases. The burn cohort had higher admission rates for ischaemic heart disease (IRR, 95%CI: 1.21, 1.07-1.36), heart failure (IRR, 95%CI: 2.29 1.85-2.82) and cerebrovascular disease (IRR, 95%CI: 1.57, 1.33-1.84). The burn injury cohort was found to have increased long-term mortality caused by circulatory system diseases (MRR, 95%CI: 1.11, 1.02-1.20).

Conclusions: Findings of increased hospital admission rates, prolonged length of hospital stay and increased long-term mortality related to circulatory system diseases in the burn injury
cohort provide evidence to support that burn injury has long-lasting systemic impacts on the heart and circulation.

Keywords: burns; long-term health; cardiac; adults; population-based cohort.
Understanding the long-term impacts of burn injury on the heart

1. Background

While the most obvious impact of burn injury is a visible scar that remains for life, there are hidden impacts of burn injury that may have long-lasting consequences. The main contributors to adverse outcomes in severely burned patients are the profound metabolic and inflammatory changes that occur in response to the initial injury, which have been shown to persist for at least three years post burn. [1] Increasingly basic scientific and clinical evidence of multiple profound systemic inflammatory responses after burn injury are being identified, with significant impacts being demonstrated after both minor and severe burns.[2-5]

Increased sympathetic activity is a critical part of the acute coordinated response to burns, modulating energy substrate mobilization, cardiovascular and hemodynamic compensation and contributing to the immune response and healing. Although the short-term activation of these stress response mechanisms is vital, the prolonged duration and increased magnitude of their activity leads to deleterious effects on metabolism, immune function and cardiovascular function. [6]

Cardiac stress, mediated by increased catecholamine, is a hallmark of severe burn injury. It is characterised by marked tachycardia, increased myocardial oxygen consumption, and increased cardiac output, and remains one of the main determinants of survival in large burns. [7] Cardiac stress has been shown to persist for at least two years post-burn; however, it is currently unknown how long these conditions persist beyond this phase. [1, 7] Myocardial depressant factors are known to be present in burn serum and contribute to burn-generated
cardiac contractile dysfunction. [8] However, much of the cellular and molecular mechanism for its role in the development of the cardiac deficiencies remains unknown.

With the advances in medical management of burns and the increasing number of people surviving major injury, studies of the health burden of burn injury need to include long-term morbidity indicators. Such burden of disease estimates need to be used to support health policy decisions relating to clinical, preventive and health service delivery. [9, 10] To date there have been limited studies to investigate long-term health impacts of burn and non-burn injuries. This is in part due to the cost and logistic difficulty in accessing data of large samples of people with follow up over extended periods.

Linked health administrative data provide the opportunity to explore long-term health impacts in terms of patient hospital care or service needs. [11-15] While limitations of the usefulness of linked administrative data exist, these data provide a cost-effective method to carry out long-term population level research which would otherwise not be possible. Hospitalisations and associated length of hospital stay (LOS) are considered valid measures of disease outcomes and burden.[16] Recent analysis of population-based health administrative data identified increased long-term mortality after both severe and minor burn injury. [17, 18] Given the potential for longer-term impacts of burns on the heart, the aim of this study was to use population-based linked health administrative data to assess if adults 45 years and older surviving a burn injury have increased longer-term hospital service use for circulatory diseases and mortality caused by circulatory diseases, controlling for demographic factors and pre-existing comorbidities.

2. Methods
This study forms part of the Western Australian Population-based Burn Injury Project - a population-based retrospective cohort study using linked health administrative data provided from the Western Australian Data Linkage System (WADLS). The WADLS is a validated record linkage system that routinely links administrative health data from core datasets (including the Hospital Morbidity Data System and the Western Australia Death Register) for the entire population of Western Australia. [13] Project protocol was approved by the Human Research Ethics Committees of the University of Western Australia and the Western Australian Department of Health.

A de-identified extraction of all linked hospital morbidity (Hospital Morbidity Data System (HMDS)) records for all persons aged 45 years and older admitted to hospital with a first (index) burn injury in Western Australia, for the period 1 January 1980 to 30 June 2012, was undertaken by WADLS staff. The index burn injury was defined as the first hospital admission in a patient record set with a burn injury as the principal and/or additional diagnosis using the International Classification of Diseases (ICD) codes Version 9 (ICD9-CM) 940-949 and Version 10 (ICD10-AM) T20-T31. A population-based comparison cohort was randomly selected from the Western Australian Electoral Roll; any person with an injury hospitalisation during the study period was excluded from this cohort by WADLS. The resultant uninjured comparison cohort was frequency-matched on birth year (4:1) and gender of the burn injury cases for each year from 1980-2012.

Hospital and death data were linked to each cohort (burn, non-injury) for the period 1980-2012. Hospital admissions data included principal and additional diagnoses, external cause of injury, age and gender, Aboriginal status, index admission and separation dates, mode of separation, burn injury characteristics (total burns surface area percent - TBSA%), burn depth)
and geographic location (census collectors district (~200 households), postcode). Indices of social disadvantage (Socio-economic Indices for Areas (SEIFA) [19]) and remoteness (Accessibility Remoteness Index of Australia (ARIA+)[20]) were supplied for the burn and uninjured cohorts. Mortality data included the date and cause of death, classified using ICD9-CM and ICD10-AM disease and external cause codes. Admissions for diseases of the circulatory system (combined and sub-groups) were identified using principal diagnosis data (refer to Table 1 for ICD codes).

Age was categorised into three groups (45-54, 55-64 and 65+ years) and Aboriginal status was classified by record of Aboriginal or Torres Strait Islander status on any admission record. TBSA% was classified by ICD supplementary codes (948 ICD9CM; T31 ICD10AM) and categorised into three groups: minor burns (TBSA<20%), severe burns (TBSA≥20%), and burns for which TBSA% was unspecified. Comorbidity was assessed using the Charlson Comorbidity Index (CCI) [21] using principal and additional diagnosis fields in the hospital morbidity data with a 5-year look back period. [22] The derived CCI score was then used to classify comorbidity at baseline (0 CCI=0; 1 CCI>0). Indices of social disadvantage were partitioned into quintiles from the most disadvantaged to the least disadvantaged. The geographic remoteness index ARIA+ was used to classify geographical disadvantage and access in terms of physical distance from services by five remoteness categories: major cities, inner regional, outer regional, remote and very remote.

The final discharge date for the index burn admission was used as the study start for follow-up for the burn cases and the respective frequency matched non-injury controls. The total number of years a person was at risk (person-years) was estimated from this final discharge date. Categorical and non-parametric continuous variables were compared using χ2 and
Kruskal–Wallis tests, respectively. A P-value of 0.05 or lower was considered indicative of statistical significance.

The total number of cardiovascular admissions after burn injury discharge and the cumulative length of stay for cardiovascular diagnoses were used as outcome measures. The hospitalisation of the index injury was not included in these outcomes. Analyses were undertaken on the total burns and uninjured cohorts (that is, included those with and without prior admission for disease of the circulatory system). Crude yearly admission rates were calculated for these variables. Adjusted rate ratios were calculated between our exposure variables (burn injury versus no injury) and our outcome measures using negative binomial regression. Demographic information (gender, Aboriginality, age group (45-54; 54-64; 65+), social disadvantage (SEIFA quintiles), remoteness of place of residence (ARIA+), year of admission) and information on health status (any comorbidity at baseline, previous history of cardiovascular disease) were included as covariates in the models.

Survival analyses of incident hospital use for the most common circulatory disease sub-groups (ischaemic heart disease, heart failure, cerebrovascular disease), were conducted using the Kaplan Meier method and Cox proportional hazards models. Analyses were conducted on data that excluded persons that had a prior hospitalisation for a disease of the circulatory system using a 5-year look back period, and also excluded members of the burn cohort if there was a record of a non-burn injury admission (prior or post index burn). Covariates included in the Cox models were gender, Aboriginality, age group (45-54; 54-64; 65+), social disadvantage (SEIFA quintiles), remoteness of place of residence (ARIA+), any comorbidity at baseline (5-year look back period) and year of admission (quintiles of admission year). The proportional hazard assumption for the burn injured versus non-injured was tested using scaled and
unscaled Schoenfeld residuals and by adding a group-by-time interaction term. Where preliminary analyses demonstrated nonproportionality, adjusted hazard ratios (HR) and 95% confidence intervals (CI) for first record of admission for the circulatory disease sub-group for burn vs. non-injury cohorts were modelled for time periods guided by Aalen's linear hazard models and plots. Cox proportional hazard regression was also used to estimate the impacts of burn injury on long-term mortality caused by diseases of the circulatory system, while adjusting for previously listed covariates. The hazard ratio was used as a measure of the mortality rate ratio (MRR).

Attributable risk percentages (AR%) were calculated as the adjusted rate ratio (IRR, HR) minus one, divided by the adjusted rate (IRR, HR) ratio, multiplied by 100. AR% was used to estimate the proportion of long-term hospital use, incident hospital use and long-term mortality associated with diseases of the circulatory system, where burn injury was a component cause. Statistical analyses were performed using Stata version 12 (StataCorp. LP, College Station, United States of America).

3. Results

3.1 Cohort characteristics

During the period January 1980 to June 2012, there were 6,006 persons aged 45 years and older hospitalised for a first burn injury; 4% had severe burns of 20% TBSA or greater, 54% had burns of less than 20% TBSA and for 42%, the TBSA was unspecified. Nineteen percent of the burn cohort had experienced full thickness burns, 37% partial thickness, 18% erythema and 29% had experienced burns for which the burn depth was unspecified; an individual may have multiple burns sites and depths recorded. Among the burn cohort, 31% had a record of a non-burn injury admission (before or after index burn). Of those that were hospitalised for
a first burn injury, 83% were discharged to home, 12% were transferred to acute care hospitals, 2% to aged care facilities, and 3% died in hospital.

Refer to Table 2 for baseline socio-demographic and comorbidity variables for the burn and non-injury cohorts. A total of 22,633 persons randomly selected and frequency matched on age and gender to index burn cases were included in the comparison non-injury cohort. The burn injury cohort comprised significantly higher proportions of Aboriginal people, and people who were socially disadvantaged and living in regions outside of major cities when compared with the non-injured comparison cohort. Persons in the burn injury cohort were more likely to have pre-existing comorbidity and a prior admission for a circulatory disease, than the non-injured cohort.

3.2 Admissions for diseases of circulatory system – rates and cumulative length of stay

There were 5,015 hospital admissions with a primary diagnosis of a circulatory system disease after burn injury discharge (total burn cohort) for a total of 54,279 days in hospital. Ischaemic heart disease and heart failure were the most common cardiovascular disease sub-categories, accounting for over 50% of all circulatory readmissions (see Table 3), for a total of 9,675 and 10,641 days in hospital, respectively.

Unadjusted incidence rates for circulatory system admissions and length of stay using the total burn and uninjured cohorts are shown in Figure 1. These graphs shown an increase in the number of admissions and time spent in hospital for burn patients during the first 10-15 years after the incident burn. After 15 years, there appears little difference between these groups. There was only a small percentage of cases for which there was more than 25 years follow up.
After adjustment for demographic factors and pre-existing health status, the burn cohort had 1.46 times (95%CI: 1.36-1.56) as many circulatory system admissions to hospital, and almost three times the number of days in hospital with circulatory system diagnosis (IRR, 95%CI: 2.90, 2.60-3.25) over the 33 year period, than the comparison cohort. These findings in turn suggest that the burn cohort experienced an excess of 32% (AR%) of admissions and an excess of 65% (AR%) of all days spent in hospital for diseases of the circulatory system, after their burn discharge, when compared with the uninjured cohort.

Unadjusted admission rates for the most common circulatory system sub-conditions are shown in Figure 2. After controlling for demographic factors and previous health status, the burns cohort had a high rate of admissions for ischaemic heart disease (IRR, 95%CI: 1.21, 1.07-1.36), heart failure (IRR, 95%CI: 2.29 1.85-2.82) and cerebrovascular disease admissions (IRR,95%CI: 1.57, 1.33-1.84). The burns cohort also spent longer in hospital for ischaemic heart disease admissions (IRR 95%CI: 1.84, 1.33-2.56), heart failure admissions (IRR, 95%CI: 5.79, 3.17-10.56) and cerebrovascular admissions (IRR, 95%CI: 3.20, 1.82-5.65), after controlling for previous health status and demographic factors, when compared with the non-injured cohort.

3.3 Incident admissions

Survival analyses were performed on 2,951 adults with burn injury (no prior circulatory disease admission and no record of other principal diagnosis injury admission) and 20,559 uninjured adults (no prior circulatory disease admission) to examine incident or first time admissions for ischaemic heart disease, cerebrovascular disease and heart failure; all models were adjusted for confounders.
There were 264 and 2097 incident ischaemic heart disease admissions in the burn and uninjured cohorts, respectively. Evidence of nonproportionality was found with respect to the effect of burns on incident ischaemic heart disease admissions. Aalen plots suggested an effect of burn injury within the first 5 years. After adjusting for confounders, analysis revealed an increased rate of first admissions in the first 5 years post-burn discharge (HR, 95%CI: 1.41, 1.15-1.72). This increase incidence equated to 29% (AR%) of incident ischaemic heart disease admissions in the first five years being attributed to the burn injury. No difference was found for severe burns (HR, 95%CI: 0.40, 0.10-1.62), or minor burns (HR, 95%CI: 1.21, 0.91-1.59); however adults with burns of unspecified TBSA had elevated admission rates (HR, 95%CI: 1.56, 1.19-2.05). Significant differences were found for both males (HR, 95%CI: 1.29, 1.03-1.63) and females (HR, 95%CI: 1.82, 1.23-2.72) with burns, when compared with respective genders of the uninjured cohort.

There were 124 incident admissions for cerebrovascular diseases in the burn cohort and 1031 in the uninjured cohort. Evidence of nonproportionality was found with modelling of incident admission rates for cerebrovascular diseases. Aalen plots suggest an effect of burn injury within the first 8 years. After adjusting for confounders, there was an increased rate of first admissions in the first 8 years after burn injury discharge (HR, 95%CI: 1.50, 1.16-1.92), suggesting 33% (AR%) of incident admissions were attributable to burn injury. An increased rate was found for both males (HR, 95%CI: 1.45, 1.06-1.99) and females (HR, 95%CI: 1.56, 1.02-2.37), when compared with the respective genders of the uninjured cohort. Those with minor burns (HR, 95%CI: 1.61, 1.12-2.32) had elevated admission rates over the study period. Severe burns (HR, 95%CI: 1.04, 0.33-3.25) and burns of unspecified TBSA (HR, 95%CI: 1.28, 0.91-1.80) were not associated with a significant increase in incident admissions.
There were 122 and 795 incident admissions for heart failure in the burn and uninjured cohorts, respectively. Evidence of nonproportionality was found in the modelling of incident heart failure admissions. Aalen plots suggested an effect of burn injury in the first five years after burn discharge on first time admissions for heart failure, with a much larger effect occurring in the first three months. After adjusting for health status and demographics, there was an increased rate in first admissions for heart failure within the first three months after hospital discharge for burn injury (HR, 95%CI: 9.68, 4.35-21.52), suggesting 90% (AR%) of incident admissions for heart failure within the first three months after burn were attributable to burn injury. In addition, for the period from three months to five years after burn injury, after adjusting for confounders there was an increased rate in first admissions for heart failure (HR, 95%CI: 1.53, 1.05-2.22). This suggests an additional 35% of incident admissions for heart failure between 3 months and five years after burn discharge were attributable to burn injury. Those with minor burns had greater rates of incident admissions for heart failure both during the first three months (HR, 95%CI: 14.68, 5.70-37.79) and from three months to five years (HR, 95%CI: 1.72, 1.04-2.84), as compared with uninjured controls. Those with burns of unspecified TBSA had greater incident admissions only during the first three months (HR, 95%CI: 4.49, 1.31-15.39). There were no severe burn incident admissions for heart failure within the first five years after burn. Gender-specific analysis found significant increase in admission rates during the first three months post burn discharge for both males (HR, 95%CI: 9.79, 3.76-25.53) and females (HR, 95%CI: 9.98, 2.39-41.68), as compared to the uninjured cohort. However, males continued to have greater incident admissions from three months to five years after burn injury (HR, 95%CI: 1.89, 1.19-3.01).
3.4 Long-term mortality

There were 897 and 2,813 deaths caused by circulatory system diseases in the burn and uninjured cohorts, respectively. Cox regression modelling found no evidence of nonproportionality. After adjustment for confounders, compared with the uninjured cohort, adults with burns were found to have significantly increased long-term mortality caused by circulatory system diseases (MRR, 95%CI: 1.11, 1.02-1.20), equating to approximately 10% (AR%) or 90 of these deaths attributable to burn injury.

4. Discussion

This population-based study quantifies long-term hospital use and mortality for diseases of the circulatory system by burn injury patients in Western Australia from 1980 to 2012, after controlling for socio-demographic factors and pre-existing comorbidities. Overall, the burn injured cohort had approximately 50% greater rate of hospitalisations and three times the length of stay in hospital in the 33 year study period after the burn injury, than the uninjured comparison cohort. The data showed elevated numbers of admissions and time spent in hospital for burn patients during the first 10-15 years after the incident burn, after which time there was little difference between the burn and uninjured cohorts.

The burn cohort experienced an excess of 32% post-burn admissions and 65% of all days spent in hospital for diseases of the circulatory system over the study period, when compared with the uninjured cohort. The burn cohort (total) was found to have higher rates of admissions for ischaemic heart disease, heart failure and cerebrovascular disease admissions, when compared with the uninjured cohort. For the burn cohort, long-term mortality caused by circulatory system diseases was 1.12 times that for the uninjured cohort, with 10% of these deaths attributable to burn injury. These findings support that while burn injury primarily
affects the skin, it is a chronic disease with longer-term impacts on the circulatory system after burn injury discharge.

To focus assessment on the specific impact of burn injury, analyses were undertaken on individuals with no principal diagnosis non-burn injury admissions (in the burn cohort) and no prior admission for circulatory system disease (in the burn and uninjured cohorts). Results identified significantly higher rates after burn injury discharge for first time admissions for ischaemic heart disease in the first five years, cerebrovascular diseases for the 8-year post-burn discharge period, after adjustment for confounders, equating to 29% and 33% of respective first time admissions, being attributable to burn injury. The incidence of heart failure admissions was significantly elevated for burn survivors for five years post-burn discharge. Burn injury accounted for 90% of incident heart failure admissions in the first three months after burn discharge, with an additional 35% of incident admissions for heart failure between 3 months and five years attributable to the burn.

Examination of burn severity and first time hospital service use for diseases of the circulatory disease found minor burns to be associated with higher rates of first time admissions over the study period for both cerebrovascular disease and ischaemic heart disease. Higher rates of first time admissions for heart failure were associated with all burn severity classification for the first three months after burns, with minor minor burns having a significant impact on elevated admission rates till five years after burn discharge. However, severe burns were only associated significantly with increased incident admissions for heart failure three-months post-burn discharge. This finding may reflect the small numbers of severe burn survivors and incident admissions and / or perhaps a “healthy survivor” effect whereby survivors of severe
burns represented a more robust patient group. Our previous work identified increased long-term all-cause mortality for adults 45 years and older for all sub-groups of burn severity. [17]

Gender specific analyses found both males and females with burns, compared respectively with uninjured males and females, to have significantly higher rates of first time admissions for ischaemic heart disease for the first 5 years and for cerebrovascular disease over the study period, after hospital discharge for burn injury. Both males and females with burns had significantly higher incident heart failure admissions in the 3-months post-burn discharge period, with the impact of burn injury in males extending to five years post-burn discharge, when compared with respective uninjured gender-specific subgroups.

The impact of burn injury on sympathetic activity has long been recognised and it is clear that in the acute phase after burn injury, sympathetic changes are critical to survival. However, it is the long-term sustained activation that has the potential to negatively affect outcomes. This long-term activation has been previously demonstrated to persist for up to 3 years in pediatric patients with a severe burn. [1]. However, one of the key questions arising from these studies was whether the observed changes had the potential to progress to pathological changes affecting morbidity or mortality. The data presented here suggest that this is the case, with an elevated risk of a range of diseases of the circulatory system sustained for up to 15 years post-burn in adults at least 45 years old when hospitalised for their burn.

There is increasing evidence that the use of non-selective beta-blockers is beneficial in burn patients, when used both in the acute phase and for longer durations (up to 1 year). [26-28] Propranolol administration for two weeks post burn to decrease admission heart rate by 15%, also augments net protein balance in muscle, decreases loss of lean mass and lowers resting energy expenditure. [29] Cardiac function is improved by propranolol administration because
of reductions in cardiac work load. [30] However, the use of beta-blockers has been investigated in patients with severe burns and whilst markers of cardiac physiology can be used to suggest benefits of use, it will be important to investigate in the future the long-term morbidity and mortality in treated patients. The evidence presented here suggests that therapeutic intervention may reduce long-term cardiac morbidity. The data also supports expanding trials of therapeutic interventions to include non-severe injuries. Non-severe burns are by far the most common burn injury presentations to hospitals in the developed world and their potential long-term systemic impacts have largely been ignored.

Increasingly, evidence is suggesting that patients with non-severe injuries have health impacts that persist long after they are discharged from hospital. Whilst it is clear that not all patients are affected, there is a need to investigate whether those patients that would benefit from therapeutic intervention can be identified, to reduce this increase in morbidity and mortality associated with non-severe injury.

**Study limitations and strengths**

To our knowledge the Western Australian Population-based Burn Injury Project is the first population-based study of burn injury admissions with a non-injured comparison group, and with an extended follow-up period to examine long term risk of diseases among older adults with burn injury. Data of single centre studies of paediatric severe burns (no control)[31] and 3-year follow-up of pathophysiology (with control)[1] have been reported, with a study of older burn patients using state-wide health data with a 2-year follow-up.[32] While longer term impacts on health service use of injury (all-types) in adults using population-based linked data has been reported, the representation of burn patients was small.[33] A non-injured control cohort was used to enable examination of the potential systemic health impacts of
trauma caused specifically by burn injury and providing a measure of the background risk. [25] The study assumption was that after adjusting for baseline confounders, any excess in hospital use for diseases of the circulatory system and mortality was predominantly associated with the burn injury. Future research will examine potential differences between burn and non-burn injury and long-term health impacts.

This study included and adjusted for measures of comorbidity and indices of socio-economic disadvantage, geographic remoteness and access to services. The socio-economic disadvantage index used in this study has been correlated with lifestyle risk factors including smoking, alcohol, nutrition and physical activity, associated with poorer health outcomes [34, 35] and is a risk factor for burns. [36, 37] Inclusion in the analyses of indices of social disadvantage and geographic distance to services geocoded to within a 200-household proximity of place of residence, while not optimal, did provide proxy measures of lifestyle and risk taking factors and a means to adjust for a level of residual confounding. Incomplete TBSA% data limited the full understanding of burn severity on long-term hospital use. The study represents both burn injury and diseases of the circulatory system serious enough to necessitate hospitalisation and the results may underestimate the extent of the impact of burn injury on cardiac health in the community. Regular quality and accuracy assessments of the Western Australia hospital morbidity data strengthen our findings [38] and it is expected that our results are generalisable to other populations with similar demographic characteristics and comparable health care systems to those of Australia.

Our findings of increased hospital admissions and prolonged length of hospital stay for diseases of the circulatory system, and long-term mortality due to circulatory system diseases in the burn injury cohort suggest that the initial burn injury has longer-term systemic impacts
on the heart and circulation. These findings have implications for the clinical management of burn injury and protocols for longer-term surveillance of burn patients after discharge, as well as the prevention of such injury.

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