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Acute burn injuries associated with long-term mortality

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Are Acute Burn Injuries Associated With Long-Term Mortality? A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Emerging evidence suggests that the pathophysiological impact of acute burn injuries may have chronic health consequences. We conducted a systematic review and meta-analysis to investigate the association between burn injuries and long-term mortality in patients surviving to initial discharge from hospital.

Methods: Medline and Embase databases were searched on 22 October 2021. Studies were eligible for inclusion if they compared long-term mortality amongst burn survivors to non-injured controls from the general population. When the same output metrics related to mortality were reported, meta-analyses were undertaken using a random effects model. Risk of bias was assessed using the Joanna Briggs Institute (JBI) critical appraisal tool.

Results: Following an extensive literature search, six studies (seven articles) were identified for inclusion. They were predominantly based in high-income countries, with each comparing burns' survivors to matched non-injured controls from the general population. The four studies included in the meta-analysis had a combined unadjusted odds ratio of 2.65 (1.84 – 3.81; 95% confidence interval) and adjusted mortality rate ratio of 1.59 (1.31 – 1.93; 95% confidence interval). Thus, burn survivors demonstrated greater mortality rates when compared to their non-injured counterparts. Similar findings were illustrated in the remaining studies not included in the meta-analysis, with the exception of one study which found no significant difference between the two groups.

Conclusions: Our review suggests that acute burn injuries are associated with greater long-term mortality rates (unadjusted and adjusted). The underlying mechanism is unclear and further work is required to establish the role of certain factors such as biological ageing processes, to improve outcomes for burn patients.

Key words: burns; mortality; life expectancy; long-term; survival; chronic

INTRODUCTION

As a common traumatic cause of morbidity and mortality, an estimated 11 million people seek medical attention for burn injuries annually [1]. Recent trends demonstrate a temporal reduction in the length of inpatient stay, burn severity and mortality, with 180,000 annual global deaths now attributed to burns [2,3]. Developments in health and social care have improved the provision of preventative measures and the acute management of these injuries [4]. However, evidence over the past decade suggests that the pathophysiological insult of this acute injury may have chronic physical and psychological consequences [5].

The long-term effects of burn injuries have been described across multiple organ systems [5]. Population studies have illustrated an increased risk of certain diseases in burns' survivors ranging from musculoskeletal and endocrine conditions to disorders of the cardiovascular system [5–8]. The incidence of cancer amongst burn survivors is also significantly greater when compared to their non-injured counterparts [9]). Furthermore, several studies have proposed a relationship between acute burn injury and long-term mortality [10,11]. However, there are currently no systematic reviews solely assessing this association, with other reviews to date predominantly addressing long-term morbidity.

We conducted a systematic review and meta-analysis to investigate the association between burns, long-term mortality and life expectancy in burns' survivors who were discharged from hospital following their initial injury, with no restriction on the age of the patient at time of injury.

METHODS

Our review protocol was prospectively registered on PROSPERO (CRD42021282696). The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [12] provided a reporting framework for this article.

Literature search

A comprehensive literature search was performed using the MEDLINE (Ovid 1946 to 2021 October 22: including In-Process, In-Data-Review & Other Non-Indexed Citations) and Embase (Ovid 1974 to 2021 October 22) databases. Variations of the terms "burn", "long-term" and "mortality" and appropriate subject headings (MeSH and Emtree) were combined with the Boolean operators "OR" and "AND". Search fields were limited to the "Title" and "Abstract". There were no language restrictions. The full search strategy is described in Appendix 1. Following the removal of duplicate hits, two investigators (HKNK and KCL) independently screened the title and abstracts, shortlisting articles for retrieval. The full-text articles were then reviewed in parallel against the inclusion and exclusion criteria. The reference lists of appropriate articles were also screened for eligible studies. Any discrepancies were discussed by the investigators, before agreeing on the studies to be included in this review.

Inclusion and exclusion criteria

Cohort studies (retrospective or prospective) assessing long-term all-cause or disease-specific mortality of burns' survivors following discharge from hospital, relative to their counterparts with no burn injury, were included. Those reporting failure to reach life expectancy and subsequent years of lost life, were also eligible. There were no restrictions placed on the type, mechanism or severity of burn injury or patient age.

Studies investigating short-term mortality (less than one month post-discharge) only or without an appropriate (non-injured) control or comparator group were not eligible for inclusion. Furthermore, articles only reporting long-term morbidity or accidental deaths were excluded. Editorials and case reports were also excluded.

Data extraction

Data were extracted from eligible studies by two independent investigators (HKNK and KCL) using a pre-designed template. This included details of the first author, year of publication, study design, country of study, type of injury, comparator or control cohort, number of subjects, age of subjects, duration of follow-up and mortality outcome measures including rate and hazard ratios.

Statistical analysis

Quantitative analyses were performed using the Comprehensive Meta-Analysis (CMA) software, version 3.3.070 (Biostat Inc., Jersey, USA). Odds ratios were calculated using raw data on deaths in the burns and control cohorts. Where adjusted mortality rate ratios were reported, they were converted to log rate ratios and standard error values using the Revman5 calculator (Cochrane, UK) prior to analysis on CMA. Random effects were applied for all meta-analyses, given the heterogeneity of the study populations. Subgroup analyses were undertaken for sex (male and female) and burn severity (severe and minor) where data were reported on the appropriate subset of papers in the included articles. The Q-test was used to identify differences between categories of subgroups, with significance defined as a p-value of <0.05.

Quality assessment of studies

The Joanna Briggs Institute (JBI) critical appraisal tool for cohort studies was used to assess the quality of evidence presented in the studies [13]. This consists of a checklist of questions, based on study methodology and other areas where a risk of bias may arise, such as the identification and adjustment for confounding factors and attrition rates. Findings from each study were described, however sensitivity analyses were not possible.

RESULTS

Summary of literature search

The initial literature search returned 3,244 hits. Following de-duplication, the titles and abstracts of 2,204 records were screened. No additional papers were identified from the reference lists of appropriate articles. A total of 20 articles were shortlisted for retrieval and review of their full texts against the inclusion and exclusion criteria. A further 13 papers were then excluded for a variety of reasons such as the lack of an appropriately matched comparator or control cohort. Therefore, six studies (seven articles) were included in this review [10,11,14–18] **(Figure 1)**.

Study characteristics

A summary of study characteristics and outcomes is detailed in **Table 1**. All studies were retrospective in nature and predominantly from North America and Australia. Although all types of burn aetiologies were considered (such as flame, electrical, scalds and chemical), one study only investigated patients with burn injury affecting at least 10% total body surface area (%TBSA) [10]. Patients of different age groups were assessed (from children [11] to adults [10,14–18]), and the duration of follow-up ranged from one to thirty-three years.

Study outcomes

Reported outcome measures included: relative risk of death before reaching estimated life expectancy [14], hazard ratio [10] and mortality rate ratio [11,15–17]. Four articles were based on subpopulations of the Western Australian Population-based Burn Injury Project (WAPBIP), with two papers reporting different outcomes on the same cohort: mortality secondary to cardiovascular disease [15] and all-cause mortality [17]. After adjusting for confounding variables, such as patient demographics, socioeconomic status and pre-existing co-morbidities, significantly greater all-cause [11,16,17] and cardiovascular disease-specific [15] mortality rate ratios were demonstrated, when burn victims were compared to non-injured controls. Similar significant findings were seen in Canadian [10] and Swedish [14] populations, with regards to all-cause mortality and relative risk of not reaching estimated life expectancies, respectively. One study reported no statistically significant acceleration in mortality rate when burn survivors were compared to the rest of the general population [18].

Four articles [10,11,15,16] reported causes of death, with common causes ranging from cancer [10,11,16] and cardiovascular disease [10,11,15,16] to trauma [10,11,16] and psychiatric disorders [10,11,16]. However, there was considerable variation between studies regarding the conditions that burns' patients were at highest risk of dying from [10,11,15,16]. Similar disparities were observed when patients were divided into subgroups according to burn severity, based on the %TBSA affected [11,16,17]. One study found that major burns (≥20% TBSA) were associated with a higher mortality rate ratio, than that of minor burns (<20%TBSA) [11]. However, the opposite was demonstrated when assessing older patients from the Western Australian population, with significantly greater mortality rates observed in minor burns' victims [16,17].

Meta-analysis

Raw data on the total number of deaths during follow-up were reported in four articles [10,11,16,17]. Using these figures, the unadjusted odds ratio of long-term mortality among burn survivors was 2.648 (1.839 – 3.813; 95% confidence interval), thus greater odds of death in burn survivors compared to non-injured controls **(Figure 2a)**. Three articles reported all-cause adjusted mortality rate ratios [11,16,17], accounting for similar confounding factors. When combined, the rate ratio was 1.592 (1.312 – 1.933; 95% confidence interval), thus greater mortality rates amongst burn survivors relative to non-injured controls **(Figure 2b)**. However, no statistically significant difference was demonstrated when comparing individuals based on the severity of burns or sex **(Table 2)**.

Quality assessment of studies

A majority of the studies (four studies, five articles) were of relatively high methodological quality, recruiting participants from the same population, whilst also identifying and adjusting for confounding factors and ensuring complete follow-up [10,11,15–17]. Studies that were of low or moderate quality lacked clarity in how exposure was measured and failed to address participants lost to follow up and so were at risk of attrition bias [14,18]. Furthermore, the follow-up periods were relatively short when compared to those of other studies. A summary of the responses from the JBI critical appraisal tool is illustrated in **Table 3**.

DISCUSSION

Recent trends demonstrate a reduction in the incidence, severity and in-hospital death rate associated with burn injuries [2,3]. This is particularly true of high-income countries, with the burden of disease predominantly in low- and middle-income countries [1]. Therefore, with the relative rise in proportion of non-fatal events, it is important to consider the potential long-term sequelae of acute burn injuries. Our review and meta-analysis suggests that burn injuries are associated with greater long-term mortality rates, when compared to non-injured members from the general population. With the exception of a single study [18], all other studies demonstrated significantly greater rates of all-cause [11,16,17] and disease-specific [15] mortality, including premature death [14]. This was confirmed when combining the effects between studies (unadjusted and adjusted), although there was a high degree of heterogeneity and variability in the length of follow-up. The remaining paper showed comparable survival between burn victims and the general population [18]. However, this study was published more than three decades ago with a high attrition rate of more than 23%, short follow-up times (maximum of 5.5 years) and insufficient adjustment for confounding factors. Additionally, a British study showed no significant difference between age of death and predicted life expectancy in elderly burns' patients [19]. However, this study lacked a comparator or control cohort and hence did not meet the inclusion criteria for this review.

The relationship between burn severity and long-term survival remains unclear, with no significant association demonstrated in the meta-analysis. A study in children under 15 years old, found a positive correlation between burn severity and long-term mortality [11]. In contrast, analysis of the adolescents, adults and geriatric patients from the same population revealed higher adjusted mortality rate ratios in minor burns, relative to the non-injured cohort, than that of major burns [16,17]. This may suggest a potential age-dependent effect of burn severity on life expectancy. One may also argue that this does not support a cause and effect relationship.

However, data on burn severity (%TBSA) were missing in more than half of the deaths of the burns' cohorts, thus such conclusions cannot be definitively made. In a more recent study of 365 critically ill American adult burn survivors, a similar observation was made [20]. The group was divided into two based on %TBSA (severe: ≥20% vs. minor: <20%). Five years following discharge from hospital, the mortality rate was lower in those who had burns affecting ≥20% TBSA. The authors suggested that this may have been due to patients in the severe burns subgroup being relatively younger, as they demonstrated that advanced age is an independent risk factor for five-year mortality [20]. It has also been proposed that patients who are discharged from hospital following major burn injury represent a physiologically robust cohort with a greater reserve, hence their ability to survive the initial insult [17,20].

The various causes of death may explain the apparent reduction in long-term survival of burn victims but some may argue this heterogeneity may not support a direct cause and effect relationship between burns and long-term mortality. In many instances, causes include disorders of different organ systems [10,15]. Burn injuries have been associated with the long-term acquisition of several conditions [5] such as cancer [21], diabetes [7], musculoskeletal pathology [6], gastrointestinal disease [22], cardiorespiratory disorders [15,23] and neurological conditions [24]. Although burns initially affect the skin, it has long been recognised that such injuries are associated with systemic consequences. Jeschke and colleagues compared a cohort of paediatric patients who had suffered severe burns to non-injured controls over a period of three years. The hypermetabolic and hyperinflammatory state of the burn victims, as determined by factors such as stress hormones and acute phase proteins respectively, appeared to persist throughout the study period [25]. This may subsequently result in a dysfunctional immune system, manifesting as increased susceptibility to chronic conditions, affecting multiple organ systems, later in life and hence premature deaths [5].

Major trauma, including burn injuries, may lead to a reduction in long term survival [26]. An association between major trauma and an acceleration in the ageing process has been proposed [27]. Biological age is believed to be a better indicator of morbidity than chronological age and can be assessed using telomere length and epigenetic analysis. Telomeres are repetitive sequences of DNA located at the end of chromosomes where they have a protective function. In fully differentiated adult cells, which lack telomerase, telomere length shortens with each cell cycle and so correlates with cellular age [28]. Epigenetics refers to the study of indirect DNA modifications, independent to the alteration of the nucleotide sequence. DNA methylation is an example of such modification which subsequently regulates gene expression, the extent of which may be used to determine biological age in the so-called epigenetic clock [29]. A number of meta-analyses have shown that childhood psychological trauma and/or subsequent post-traumatic stress disorder (PTSD) is associated with advanced biological ageing as determined by telomere length attrition [30–32] and DNA methylation [32,33]. A study of military veterans has reported increased biological age, estimated by DNA methylation, for those who sustained a physical injury but not post-traumatic stress disorder [34]. Thus, physical trauma and resultant psychological stress may accelerate the biological ageing process and in turn lead to earlier acquisition of degenerative disorders and subsequent death. This may underpin the rise in long-term mortality observed following burn injuries but has not yet been explored in the literature.

Mental illness and traumatic injuries were found to be amongst the common causes of death in the burns' cohort of some studies [10,11,16]. Gueler and colleagues compared long-term outcomes in adults with a self-inflicted burn to those with a non-self-inflicted burn. In the former cohort, long-term suicidal ideation and mortality was significantly worse relative to their counterparts [35]. Self-harm is often the consequence of a psychiatric disorder. Thus, even if burn victims survive to discharge from hospital, the increased risk of a shortened lifespan, may be attributable to inadequate optimisation of their mental health. Public health policy must address health and social care shortcomings in order to effectively manage such patients.

Strengths and limitations

To our knowledge this is the first systematic review to exclusively assess the association between acute burn injury and long-term mortality. Previous reviews have predominantly addressed the risk of acquiring chronic physical and psychological disorders following initial injury, with some consideration of mortality [5,6,36]. We completed a comprehensive search with broad terms used across two relevant databases, whilst also screening reference lists of selected papers, to ensure maximum coverage of the available literature.

However, this review is limited by the relatively small number and characteristics of the included studies. Firstly, they were all retrospective in nature, thus are prone to missing chart data due to inconsistent documentation and/or loss of records. Additionally, pooled quantitative analyses were only performed on a limited number of studies predominantly from the WAPBIP due to the heterogeneity in reported outcome measures. Furthermore, four of the articles were based on subpopulations of the WAPBIP [11,15–17], with the others also from high-income countries [10,14,18]. Therefore, the findings may not be generalizable across all populations, particularly low and middle-income countries, who have a greater burden of burn injuries [1]. Two studies did not explicitly adjust for potential confounding factors such as social deprivation and prior health status [14,18]. Thus, any difference in long-term mortality observed in these studies may be attributable to such factors as burn patients often reside in more rural locations, are of a lower socioeconomic class and suffer from prior health conditions [11]. The remaining studies collected and adjusted for similar variables, however, the severity of pre-existing co-morbidities were often not reported, a further limitation of retrospective studies [10,11,15–17]. Future studies should be prospective in nature, undertaken in a variety of countries and adjust for confounders such as age, co-morbidities and socioeconomic status. This will facilitate the collection of a complete data set and allow the comparison between burns of different severities after adjustment for confounding variables, assessing for a direct dose-response relationship.

CONCLUSIONS

It is widely recognised that burn injuries have chronic consequences across several organ systems. This review suggests that such injuries are also associated with greater long-term mortality rates. Further research is required to address the limitations of the included studies in order to confirm this finding and establish the underlying mechanism and the role of certain factors such as acceleration of biological ageing processes. This will help tailor the provision of health and social interventions aimed at improving outcomes for burn patients.

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FIGURE AND TABLE LEGENDS

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram of literature search.

Figure 2. Forest plots of long-term mortality in burns' survivors relative to non-injured controls using (a) unadjusted odds ratio and (b) adjusted mortality rate ratio.

Table 1. Summary of the characteristics and outcomes of included studies.

Table 2. Subgroup analyses of long-term mortality of burns' survivors relative to non-injured controls.

Table 3. Quality assessment of included studies.