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Burn induced nervous system morbidity among burn and non-burn trauma patients compared with non-injured people

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ABSTRACT

Objective: Burns cause acute damage to the peripheral nervous system with published reports identifying that neurological changes after injury remain for a prolonged period. To shed some light on potential mechanisms, we assessed injury etiology and patterns of nervous system morbidity after injury by comparing long-term hospital admissions data of burns patients and other non-burn trauma patients with uninjured people.

Methods: Linked hospital and death data of a burn patient cohort (n=30,997) in Western Australia during the period 1980-2012 were analysed along with two age and gender frequency matched comparison cohorts: non-burn trauma patients (n=28,647) and; non-injured people (n=123,399). The number of annual NS disease admissions and length of stay (LOS) were used as outcome measures. Multivariable negative binomial regression modelling was used to derive adjusted incidence rate ratios and 95% confidence intervals (IRR, 95% CI) and adjusted Cox regression models and hazard ratios (HR) were used to examine time to first nervous system admission after burn and incident admission rates.

Results: The most common peripheral nervous system condition identified in each cohort (burn, non-burn trauma, uninjured) were episodic and paroxysmal disorders followed by nerve root and plexus disorders and polyneuropathies/peripheral NS conditions. Significantly elevated admission rates for NS conditions (IRR, 95% CI) were found for the burn (2.20, 1.86–2.61) and non-burn trauma (1.85, 1.51–2.27), compared to uninjured. Peripheral nervous system admission rates after injury (IRR, 95% CI) were significantly higher regardless of age at time of injury for the burn (<15years: 1.97, 1.49–2.61; 15–45: 2.70, 2.016–3.55; ≥45 year: 1.62, 1.33–1.97) and non-burn trauma cohorts (<15years: 1.91, 1.55–2.35; 15–45: 1.94, 1.51–2.49; ≥45 year: 1.42, 1.18–1.72), when compared to the uninjured. Significantly higher rates of incident NS hospitalisations were found for the burn cohort vs. uninjured cohort for a period of 15-years after discharge (*0–5 years*: HR, 95% CI: 1.97, 1.75–2.22; *5–15 years*; HR, 95% CI: 1.44, 1.28–1.63). The non-burn trauma cohort had significantly higher incident nervous system admissions for 10 years after discharge (*0–30 days*: HR, 95% CI: 4.75, 2.44–9.23; *30 days to 1-year*

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HR, 95% CI: 2.95, 2.34–3.74; 1–5 *years*; HR, 95% CI: 1.47, 1.26–1.70; 5–10 *years*; HR, 95% CI: 1.34, 1.13–1.58).

Conclusions: Results suggest that injury patients are at increased risk of peripheral nervous system morbidity after discharge for a prolonged period of time. The time patterns associated with incident nervous system conditions suggest possible differences in underlying pathology and long-term patient care needs. Further research is needed to elucidate the underlying neuropathology.

1. Introduction

The skin is a sensory as well as protective organ, and burn injury has significant impacts on the extensive cutaneous innervation. Long after the burn has healed many patients report loss of cutaneous sensation or chronic pain indicating lasting changes to peripheral and potentially the central nervous system [1–3]. Recent research has demonstrated multiple changes to the nervous system after burn injury, from significant anatomical changes such as reduced skin innervation and elevated substance P positive fibres in the skin through to functional changes in cell activation and signal transduction[4–6]. In addition, our previous population-based research has reported significantly higher after burn hospital admission rates for nervous system conditions including episodic and paroxysmal disorders (includes epilepsy and recurrent seizures, migraine and headache symptoms, transient cerebral ischaemic attacks and sleep disorders) and nerve root and plexus disorders when compared with uninjured people [7]. However, no elevation in admission rates for peripheral nervous system disorders was found in this study.

Trauma close to skeletal structures and soft tissue may also cause acute physical nerve damage [8,9]. Nerve injury may also occur during surgical repair procedures that may frequently involve mechanisms of traction on soft tissue, extreme joint movement and screw implantation; however, in the majority of cases, nerves present neurapraxia and axonotmesis damage and recovery is frequently complete a few months after the initial trauma [10]. However, prolonged systemic inflammatory and immune responses triggered by non-burn trauma have been reported [11–13] that may potentially affect long-term NS morbidity and quality of life.

To date, limited data are available on the long-term NS morbidity of non-burn trauma patients. To better understand the relationship between burn injury, non-burn trauma and long-term nervous system morbidity, this whole-of-population study examined the effect of injury aetiology on nervous system after injury morbidity by comparing linked hospital admissions data of burns patients, other non-burn trauma patients and people with no record of an injury admission.

2. Methods

This study formed part of the Western Australia Population-based Burn Injury Project (WAPBIP) with human research ethic committee approvals from the Department of Health of Western Australia (DOHWA) and the University of Western Australia. Data were extracted from the Hospital Morbidity Data System (HMDS) and the Death Register and linked by the Data Linkage Branch of the DOHWA who then supplied de-identified data to the researchers [14]. WAPBIP data extraction and matching procedures have been previously published [15].

Linked hospital and death data for a burn patient cohort (n=30,997) in Western Australia during the period 1980–2012 and two age and gender frequency matched comparison cohorts, non-burn trauma patients (~1:1; n=28,647) and non-injured people (~4:1; n=123,399), were analysed. The non-burn trauma cohort excluded those with International Classification for Disease (ICD) codes for burns; effects of foreign bodies entering through orifices; injuries to nerves and spinal cord; poisoning; toxic effects of nonmedical substances (e.g. alcohol); and complications of surgical and medical care. The non-injured cohort included those with no record of an injury hospital admission during the study period.

Data included demographic factors (age, gender, indigenous status and geographic location) and indices of social disadvantage (Socio-economic Indices for Areas (SEIFA) [16]) and geographic remoteness (Accessibility Remoteness Index of Australia (ARIA+) [17]). Injury features for the burn and other non-burn trauma cohorts were classified using ICD codes. An indicator of existing comorbidity was derived using the Charlson comorbidity index which utilised hospital diagnoses ICD codes with a 5-year look back period [18,19]. Burn severity (total body surface area percent; TBSA %) was classified as minor <20%, severe ≥20% and unspecified. An indicator of injury severity was also generated using the International Classification for Injury Severity Score (ICISS) [20] based on survival probabilities for each recorded injury; for multiple injuries the ICISS score represented the product of respective injury survival probabilities. ICISS was classified using published cut-offs: minor ICISS ≥0.99; moderate ICISS >0.941 and <0.99; and, severe ICISS ≤0.941 [21,22].

The total number of years a person was at risk (person-years, PY) was estimated from the final discharge date for the burn and non-burn trauma cases to time of death or study end. This date was used for the respective frequency matched non-injury cohort. χ^2 tests were used to compare categorical variables with the level of significance at 5%.

Admissions for nervous system (NS) conditions were classified using principal diagnosis data and ICD Chapter 6 (ICD10: G00–G99) codes (ICD9 codes were mapped to ICD10). The annual number of admissions and summed length of stay (LOS) for combined (G00–G99) and selected subgroups of ICD classified nervous system conditions after burn (G40–G47: episodic and paroxysmal dosorders; G50–G59: nerve, nerve root and plexus disorders; and, G60-G64: polyneuropathies and other peripheral nervous system disorders) were examined. The admission of the index burn and non-burn trauma were not included in these outcome measures. Crude (observed) yearly admission rates were calculated for these variables. Incidence rate ratios (IRR) and 95% confidence intervals (CI) were generated using negative binomial regression adjusting for socio-demographic factors (gender, indigenous, 5-year age group, social disadvantage, remoteness), year of admission and health status variables (baseline comorbidity, previous nervous system disease admission). Analyses were undertaken on the total burn, non-burn trauma and uninjured cohorts as well as sub cohorts defined by gender and age at study start (<15, 15–45 and ≥45 years) and by decade of admission (adjusting for follow-up time). Analyses of selected injury subgroups with/without skin involvement were also undertaken for open wounds (included punctures, animal bites, cuts, avulsion, lacerations and traumatic amputations) and closed fractures.

Multivariable Cox proportional hazards models, adjusting for socio-demographic and health factors (listed above), were used to assess admission rates for first time (incident) hospital admissions for NS diseases after injury discharge (burn and non-burn trauma). Analyses were performed on cohort data excluding those with a prior admission for a NS condition. Members of the burn cohort with a record (prior/post) non-burn injury admission were also excluded to avoid potential confounding by systemic effects associated with non-burn trauma [13]. The proportional hazard assumption was tested [23] and if preliminary results showed non-proportionality, adjusted HRs were modelled for specified time periods directed by Aalen's linear hazards modelling [24].

Attributable risk percentages (AR%) were calculated using the adjusted hazard ratio (HR) [25] and these were used to estimate the proportions of incident admissions for nervous system conditions where injury was a component cause in the burn and non-burn trauma cohorts when compared with the non-injured cohort [26]. Statistical analyses were performed using Stata version 12 (StataCorp., LP, College Station, United States of America).

3. Results

3.1. *Cohort characteristics*

The median age at time of burn was 23 years (interquartile range (IQR), 7–39 years) and 68% were males. The non-burn trauma cohort and uninjured cohort had the same proportion of males (68%) and median age (23 years) as the burn cohort via frequency matching. Comparisons of socio-economic and health status variables for the three cohorts are shown in Table 1. The burn cohort had a higher proportion of indigenous Australians, those with lower socioeconomic status, and those from regional and remote areas. The burn cohort also had a larger proportion with pre-existing comorbidities, and a larger proportion with previous hospitalisations for nervous system conditions, when compared to the other cohorts. These variables were included in all regression models to adjust for potential confounding effects.

During the index admission 0.9% (n=283) burn patients died with a further 11.6% (n=3587) with record of death before the end of the study period. The proportion of the non-burn trauma cohort who died during their index admission was 0.6%, (n=165), while 9.4% (n=2679) died after discharge and before the end of the study period. The uninjured cohort had the lowest rate of deaths within the study period of the three cohorts (6.9%, n=8566). The median length of follow up was 15.6 years for the burn cohort (IQR: 7.2–24.3 years), 16.6 years for the non-burn trauma cohort (IQR: 8.5–24.9 years) and 16.1 years for the non-injured cohort (IQR: 8.1–24.6 years).

Full thickness burn sites were recorded for 14% (n=4390) of burn patients, 40% (n=12,307) partial thickness, 17% (n=5335) erythema burns and 31% (n=9708) had unspecified burn thickness sites recorded (patients could have multiple burn depths recorded). Severe burns (≥20% TBSA) were found in 2.9% (n=911) of the cohort, with 47.9% (n=14,854) with less severe burns (<20% TBSA). For the remaining 49.1% (n=15,232) the TBSA was unspecified and generally, these individuals had a burn admission earlier in the study period (ICD9 codes). Examination of median LOS (IQR) for those with unspecified TBSA, suggested that these were most likely less severe: unspecified TBSA 3 days (1–10), similar to that for those with <20% TBSA burns (4 days (1–10)). Individuals with severe burns generally had longer median LOS (25 days (12–48)). Burn sites were located on the head and neck (21%), trunk (23%), upper limbs and hands (42%), lower limbs and feet (34%), eyes (7%) and in the respiratory tract and other internal organs (2%). For 3% the site was unspecified (an individual could have multiple burn locations coded).

The non-burn trauma cohort included fractures (35%, n=9944), open wounds (22%, n=6359), contusions and superficial wounds (11%, n=3029), dislocations and sprains (6%, n=1650), internal organ injuries (4%, n=1062) and amputations (2%, n=568), with other or unspecified injuries accounting for the remaining 21% (n=6035). Within these more general ICD injury-type classifications (e.g. fractures which would include closed fracture of vault of skull without mention of intracranial injury, with concussion, unspecified), 9.7% (n=2765) of cohort members had traumatic brain injury coded as the primary reason (diagnosis) for the trauma admission.

3.2. *Admission rates*

There were 6,121 admissions (<15 years: n=742; 15–45 years: n=4001; ≥45 years: n=1378) with a primary diagnosis of a NS condition in the burn cohort occurring after burn discharge. This compared with 3,883 admissions (<15 years: n=751; 15–45 years: n=2242; ≥45 years: n=890) in the non-burn trauma cohort after index injury, and 7311 admissions (<15 years: n=1390; 15–45 years: n=3395; ≥45 years: n=2526) in the uninjured cohort after the matched event date. The number of individuals (%) in each cohort with a record of a nervous system hospital admission after study start: burn cohort n=2266 (7.3%); non-burn trauma cohort n=1724 (6.0%); and, uninjured cohort n=4445 (3.6%).

The breakdown of admission by specific sub-conditions for each cohort is shown in Table 2. Admissions for episodic and paroxysmal disorder comprised almost two thirds of nervous system admissions in the burn cohort compared with 45.7% in

Table 1 – Baseline demographic and pre-existing health status factors for those with a first burn hospitalisation, and age and gender frequency matched non-burn trauma cohort and non-injured cohort, Western Australia, 1980-2012.

Characteristics	No injury	Non-burn trauma N (%)	Burns N (%)	p-value
Total	123,399	28,647	30,997	
Demographic				
Aboriginality				
Yes	2993 (2.4)	2628 (9.2)	4481 (14.5)	<0.001
Social disadvantage quintiles[a]				
Quintile 1. (Most disadvantaged)	14,597 (12.0)	4854 (17.3)	6579 (21.6)	<0.001
Quintile 2.	28,339 (23.4)	9010 (32.1)	9878 (32.4)	
Quintile 3.	22,142 (18.2)	5785 (20.6)	6354 (20.8)	
Quintile 4.	21,671 (17.9)	4202 (15.0)	3833 (12.6)	
Quintile 5. (Least disadvantaged)	34,609 (28.5)	4226 (15.1)	3857 (12.6)	
Remoteness[b]				
Major city	88,278 (72.8)	15,763 (56.3)	15,810 (51.7)	<0.001
Inner regional	11,725 (9.7)	2967 (10.67)	3360 (11.0)	
Outer regional	11,653 (9.6)	4261 (15.2)	4958 (16.2)	
Remote	5897 (4.9)	2848 (10.2)	3434 (11.2)	
Very remote	3697 (3.0)	2178 (7.8)	3011 (9.8)	
Health status				
Any comorbidity (CCI ≥ 1)[c]	4691 (3.8)	1863 (6.5)	3131 (10.1)	<0.001
Previous nervous system admission[d]	1474 (1.2)	872 (3.0)	1732 (5.6)	
Injury severity category				
Low (ICISS ≥ 0.99)	123,399 (100)	19,646 (68.6)	17,917 (57.8)	<0.001
Medium (0.941 ≤ ICISS < 0.99)	0	7313 (25.5)	10,326 (33.3)	
High (ICISS < 0.941)	0	1688 (5.9)	2754 (8.9)	

[a] SEIFA socio-economic disadvantage quintiles; missing values 1.6% burn, 2.0% injury, 1.7% no injury.
[b] ARIA+ remoteness classification; missing values 1.4% burn, 2.2% injury, 1.7% no injury.
[c] Comorbidity based on derived Charlson Comorbidity Index (CCI) using 5-year look-back.
[d] Principal diagnosis hospitalisation for nervous system disease using 5-year look-back period.

Table 2 – Number of discharge admissions after burn (%) for nervous system conditions for the burns, non-burn trauma and no-injury cohorts, 1980-2012.

Nervous system (NS) conditions	Number of admissions N (%)		
	No injury	Non-burn trauma	Burns
Total	**7311 (100)**	**3883 (100)**	**6121 (100)**
Inflammatory diseases of CNS[b]	**98 (1.3)**	**40 (1.0)**	**77 (1.3)**
Systemic atrophies primary affecting CNS[b]	**79 (1.1)**	**26 (0.7)**	**42(0.7)**
Extrapyramidal and movement disorders	**172 (2.4)**	**98 (2.5)**	**117 (1.9)**
Other degenerative diseases of NS	**171 (2.3)**	**52 (1.3)**	**98 (1.6)**
Demyelinating diseases of the CNS[b]	**721 (9.9)**	**111 (2.9)**	**214 (3.5)**
Episodic and paroxysmal disorders	**2830 (38.7)**	**1773 (45.7)**	**3814 (62.3)**
Epilepsy and recurrent seizures[a]	*417 (5.7)*	*830 (21.4)*	*2589 (42.3)*
Migraine, other headache symptoms	*336 (4.6)*	*336 (4.6)*	*418 (6.8)*
Transient cerebral ischemic attacks and related syndromes	*503 (6.9)*	*303 (7.8)*	*201 (3.3)*
Sleep disorders	*1503 (20.6)*	*388 (10.0)*	*400 (6.5)*
Nerve, nerve root and plexus disorders	**2049 (28.0)**	**790 (20.3)**	**918 (15.0)**
Disorders trigeminal, facial and cranial nerve	*100 (1.4)*	*30 (1.4)*	*55 (0.9)*
Nerve root and plexus disorders	*27 (0.4)*	*29 (0.7)*	*48 (0.8)*
Mono-neuropathy upper/lower limbs	*1890 (25.9)*	*653 (16.8)*	*745 (12.2)*
Other mono-neuropathies	*31 (0.4)*	*78 (2.0)*	*70 (1.1)*
Polyneuropathies, peripheral NS disorders	**760 (10.4)**	**546 (14.1)**	**374 (6.1)**
Hereditary and idiopathic neuropathy	*149 (2.0)*	*12 (0.3)*	*7 (0.1)*
Inflammatory polyneuropathy	*405 (5.5)*	*397 (10.2)*	*276 (4.5)*
Other and unspecified polyneuropathies	*206 (2.8)*	*131 (3.4)*	*91 (1.5)*
Myoneural junction and muscle diseases	**32 (0.4)**	**207 (5.3)**	**23 (0.4)**
Cerebral palsy, other paralytic syndromes	**105 (1.4)**	**79 (2.0)**	**120 (2.0)**
Other disorders NS	**294 (4.0)**	**161 (4.1)**	**324 (5.3)**

the non-burn trauma cohort and 38.7% in the uninjured cohort. Over 40% of admissions in the burn cohort were for epilepsy and recurrent seizures, compared with 21.4% in the non-burn trauma and 5.7% of the uninjured cohort. A comorbid record of epilepsy/seizures in index admission data was found for 0.9% of the burn and 0.6% of the non-burn trauma cohorts, while 0.6% and 0.3% in the burn and non-burn trauma cohort, respectively, had records in both index and prior 5-year data. Among the uninjured cohort, 0.1% had a record of epilepsy/seizure during 5-years prior to study start.

Twenty percent of the admissions in the non-burn trauma cohort were for nerve root and plexus disorders compared with 28% in the uninjured and 15% in the burn cohort. Polyneuropathies and other peripheral NS disorders accounted for 14% of NS admission in the non-burn trauma cohort, 10.4% in the uninjured and 6.1% among those with burns.

In total, 38,159 days were spent in hospital by those in the burn cohort with a nervous system condition, with median length of stay (LOS) 1 day (IQR 0–3; 0 days = same day admission/discharge). This compared with 17,221 days in hospital in the non-burn trauma cohort (median LOS; 1-day IQR 0–2) and 38,297 days in hospital in the uninjured cohort (median LOS; 1-day IQR 0–2).

Observed (unadjusted) annual admission rates for combined NS conditions and by particular nervous system subcategories for burn vs. uninjured and non-burn trauma vs. uninjured are shown in Figs. 1 and 2, respectively. Results of adjusted negative binomial regression (IRR, 95% CI) comparing nervous system after burn admissions for the burn and non-burn trauma cohorts to the uninjured cohort are presented in Figs. 3 and 4.

Significantly elevated admission rates after burn were found for both the burn and non-burn trauma cohorts, regardless of gender and age sub groups analysed, when compared with the respective sub groups of the uninjured cohort. Assessment of nervous system disease admissions by decade of index injury admission for the burn and non-burn cohorts, when compared with the uninjured, showed a trend for decreasing nervous system admission rates with increasing decade years of index injury; however, overlapping of 95% CIs was evident. Likewise, while overlap of 95% CIs was found, the adjusted IRR was typically higher for the burn cohort than the non-burn trauma cohort, in comparison to the uninjured.

Adjusted admission rates for sub groups of nervous system conditions comparing the burn to the uninjured cohort found significantly higher rate of admissions after discharge for members of the burn cohort for episodic and paroxysmal disorders (IRR, 95% CI: 2.15, 1.77–2.60) and nerve, nerve root and plexus disorders (IRR, 95% CI: 1.23, 1.01–1.49); however, no significant difference was found for polyneuropathies and other peripheral nervous system disorders (IRR, 95% CI: 1.26, 0.44–3.60).

Comparing the non-burn trauma cohort with the uninjured cohort, those with non-burn trauma had higher rates of episodic and paroxysmal disorders (IRR, 95% CI: 1.98, 1.76–2.23) and nerve, nerve root and plexus conditions (IRR, 95% CI: 1.73, 1.51–1.98); however, no difference in polyneuropathies and other disorders of the peripheral nervous system (IRR, 95% CI: 0.51, 0.20–1.34) was found. These results (IRR, 95% CI) were similar when assessing those with open wounds vs. uninjured (*episodic and paroxysmal disorders*, 1.77, 1.41–2.23; *nerve, nerve root and plexus disorders*, 1.42, 1.14–1.77; *polyneuropathies and related conditions*, 0.37, 0.11–1.26) and those with closed fractures vs. uninjured (*episodic and paroxysmal disorders*, 1.74, 1.44–2.10; *nerve, nerve root and plexus disorders*, 1.63, 1.32–2.01; *polyneuropathies and related conditions*, 0.60, 0.22–1.66).

3.2.1. *First time admissions after discharge (incidence – survival analyses)*

Incident hospital admissions for nervous system conditions occurred in 4.7% (n = 931) of the burn cohort, 4.4% (n = 886) of the non-burn trauma cohort and 3.5% (n = 4224) of the uninjured cohort. Preliminary hazard ratio analyses showed non-proportionality and analyses were modelled for partitioned time windows. The burn cohort had significantly higher rates of first (incident) nervous system hospitalisations than the uninjured cohort for a period of 15-years after discharge (*0–5 years*: HR, 95% CI: 1.97, 1.75–2.22; *5–15 years*; HR, 95% CI: 1.44, 1.28–1.63). With respect to NS sub groups, significantly higher rate of first time admissions were found for the first 15 years after discharge for episodic and paroxysmal disorders (*0–5 years*; HR, 95% CI: 2.00, 1.69–2.36; *5–15 years*: HR, 95% CI: 1.58, 1.33–1.88) and for nerve, nerve root and plexus disorders (*0–5 years*; HR, 95% CI: 1.73, 1.38–2.16; *5–15 years*; HR, 95% CI: 1.34, 1.09–1.64); statistically significantly elevated first time admissions were not found

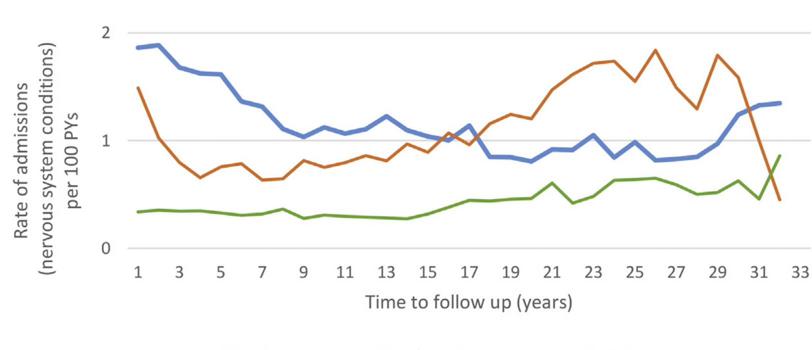

Fig. 1 – Unadjusted annual rates of hospital admissions (per 100 person years – PY) for nervous system conditions, burns and non-burn trauma compared with those with no injury, respectively.

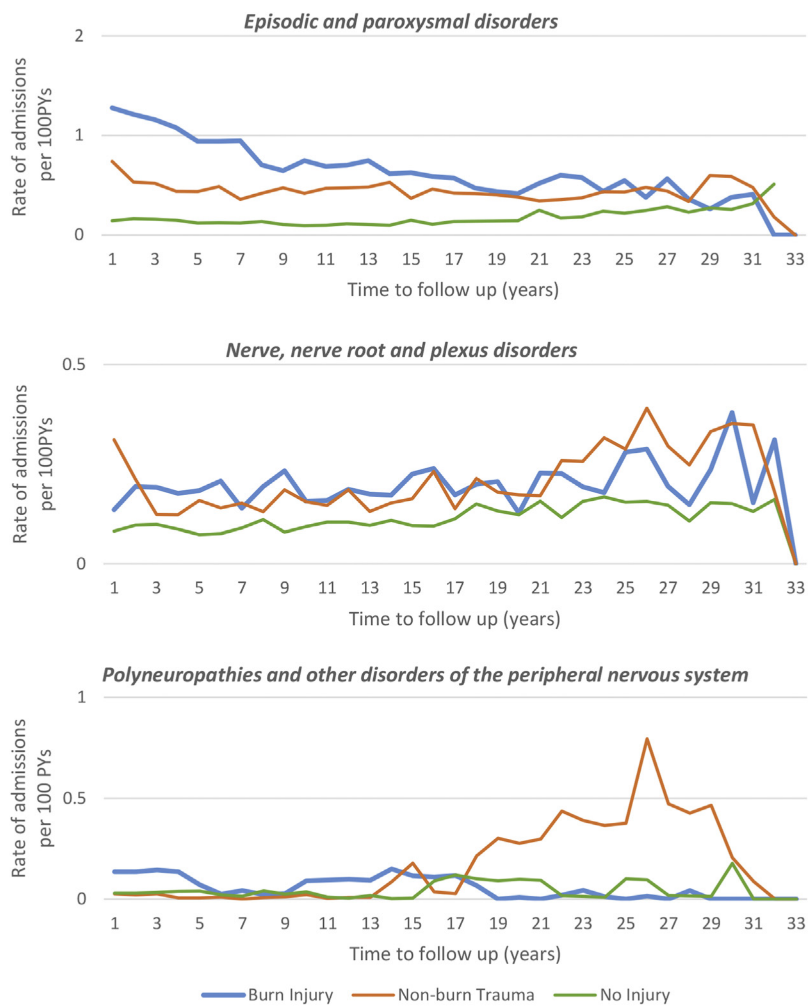

Fig. 2 – Unadjusted rates (per 100 person years– PY) of hospital admissions for nervous system sub-conditions, burns and non-burn trauma compared with no injury, respectively.

for polyneuropathies and other peripheral NS disorders (HR, 95% CI: 1.57, 0.92–2.67).

Comparison of the non-burn trauma cohort to the uninjured cohort, found those with non-burn trauma had significantly higher adjusted rates of incident NS admissions for 10 years after discharge. These rates were highest during the first 30 days after injury discharge (HR, 95% CI: 4.75, 2.44–9.23), decreasing with increasing time (*30 days to 1-year* HR, 95% CI: 2.95, 2.34–3.74; *1–5 years*; HR, 95% CI: 1.47, 1.26–1.70; *5–10 years*; HR, 95% CI: 1.34, 1.13–1.58; $\geq$*10 years*; HR, 95% CI: 1.01, 0.90–1.13). Adjusted Cox regression analyses for sub groups of NS conditions comparing non-burn trauma and the uninjured cohort are found in Table 3. Incident admission rates for episodic and paroxysmal disorders and nerve root and plexus conditions were 3- and 4-times higher, respectively, during the first year; while significantly elevated from 1 to 10 years, the magnitude was reduced to approximately 20–25% higher than the uninjured cohort.

In total, these results indicated that for 247 (26.5%) incident nervous system hospitalisations after burn and 203 (22.9%) incident non-burn trauma nervous system admissions, the respective injury was a component cause.

4. Discussion

This study revealed that injury patients with burn and other non-burn trauma experienced increased hospital admission rates for nervous system conditions for a protracted period after hospitalisation for the first (index) injury admission when compared with uninjured people randomly selected from the general population. These rates were significantly elevated regardless of gender, age at time of injury and decade of admission for both the burn and non-burn trauma cohorts. Typically, the adjusted IRRs were higher for the burn cohort than the non-burn trauma cohort when compared with the uninjured cohort, although the 95% confidence intervals overlapped.

With respect to incident or first-time admissions (after injury), differences in time patterns were observed. Compared to the uninjured cohort, members of the burn had statistically significantly elevated rates of first-time NS admissions for a period of 15 years for episodic and paroxysmal disorders and for nerve, nerve root and plexus disorders, with the highest rates found for the first 5-year period after discharge. The non-

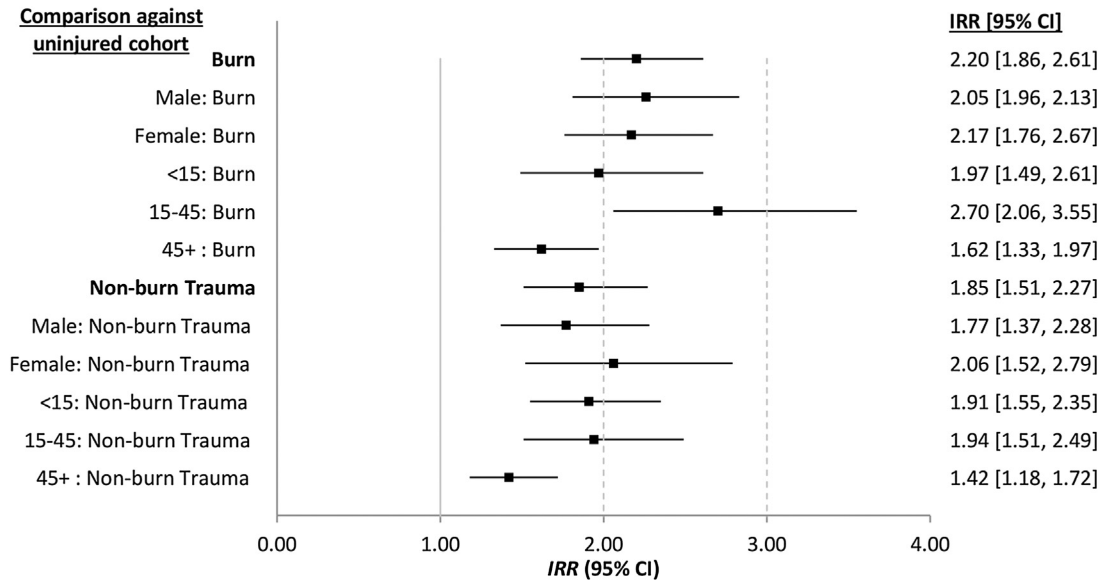

Fig. 3 – Adjusted incidence rate ratios (IRR) and 95% CI for hospital admissions for nervous system conditions comparing those with burns and other non-burn trauma with no injury and by sub groups defined by age and gender.

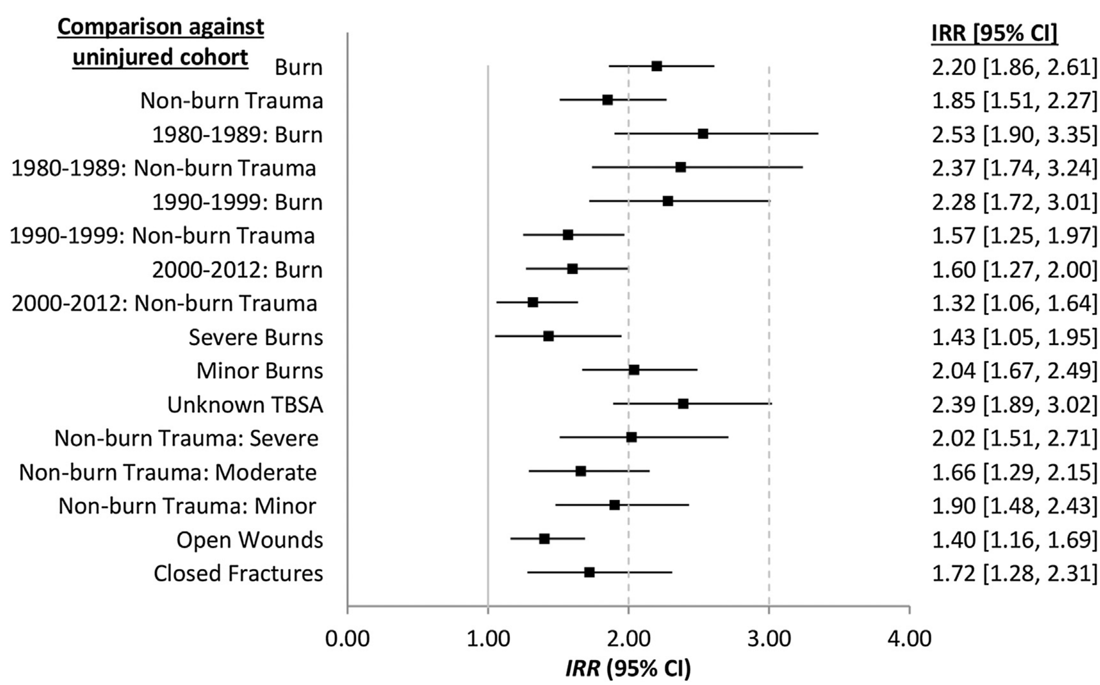

Fig. 4 – Adjusted incidence rate ratios (IRR) and 95% CI for hospital admissions for nervous system conditions comparing sub groups of the burn and non-burn trauma cohorts defined by decade of injury admission, severity of injury, and for sub-groups of non-burn trauma by injury type (open wounds; closed fractures), with no injury cohort.

burn trauma cohort had significantly higher incident NS admission rates for 10 years after discharge when compared with the uninjured cohort; however, the highest incident rates were observed during the first year after discharge. Interestingly, those with open wounds had significantly higher incident rates during the first year after discharge for both episodic and paroxysmal disorders (2.5-times higher) and nerve root and plexus conditions (4-times higher) than the uninjured, while incident rates were only significantly higher for nerve root and plexus disorders (2.7-times higher) for those with closed fractures, when compared with the uninjured. No significant differences in admissions for polyneuropathies/peripheral nervous system disorders were found for either the burn or non-burn trauma cohorts, when compared with the uninjured cohort.

The findings suggest that trauma is associated with elevated nervous system morbidity undergoing hospitalisation, with burn injury having the greatest and longest lasting

Table 3 – Adjusted hazard ratios (HR) and 95% CI for first time admissions for nervous system conditions after hospital discharge for non-burn trauma compared with the uninjured cohort.

Nervous system sub conditions	HR (95% CI)
Non-burn trauma (all types) compared to uninjured cohort	
Episodic and paroxysmal disorders	
0–1 year	2.76 (1.99–3.84)
1–10 years	1.25 (1.11–1.39)
10–33 years	1.03 (0.88–1.22)
Nerve, nerve root and plexus conditions	
0–1 year	3.71 (2.55–5.40)
1–10 years	1.20 (1.06–1.37)
10–33 years	1.06 (0.88–1.27)
***Polyneuropathies and other disorders of peripheral nervous system* 0–33 years**	1.72 (1.05–2.83)
Open wounds compared to uninjured cohort	
Episodic and paroxysmal disorders	
0–1 year	2.45 (1.31–4.58)
1–10 years	1.19 (0.95–1.48)
10–33 years	0.79 (0.55–1.13)
Nerve, nerve root and plexus conditions	
0–1 year	3.97 (2.02–7.82)
1–10 years	1.08 (0.82–1.43)
10–33 years	0.93 (0.63–1.37)
Polyneuropathies and other disorders of the peripheral nervous system	
0–33 years	2.08 (0.83–5.22)
Closed fractures compared to uninjured cohort	
Episodic and paroxysmal disorders	
0–1 year	1.50 (0.78–2.86)
1–10 years	1.05 (0.86–1.28)
10–33 years	1.03 (0.78–1.35)
Nerve, nerve root and plexus conditions	
0–1 year	2.73 (1.50–4.95)
1–10 years	1.04 (0.83–1.30)
10–33 years	0.98 (0.71–1.34)
Polyneuropathies and other disorders of the peripheral nervous system	
0–33 years	2.04 (0.98–4.27)

impact on susceptibility. This is similar to recent findings comparing the long-term cardiovascular impacts of burn and non-burn trauma [15] and may be indicative of the severity of burn injury compared to other trauma types in the extent and duration of its impact on long-term health. This is supported by the fact burn patients have poorer outcomes than predicted by the standard Injury Severity Score (ISS) [27]. Whilst the data here cannot identify a mechanism for linking trauma to nervous system morbidity, one possibility is that the immune response either causes acute damage to the nervous system that later presents as pathology or alternatively that the immune system itself is subject to sustained changes that lead to susceptibility to disease. There is evidence of sustained changes to immune function after burn injury and this evidence supports a greater impact on immune function of burn injury compared to non-burn trauma [13]. Others have also demonstrated that the greater the magnitude of the initial immune response the greater the subsequent downregulation of immune function which would also support burn injury having longer and more profound effects if mediated by immune system changes [28,29]. However, other mechanisms may also be important. Acute trauma, and in particular burns, can lead to profound metabolic, vascular and endocrine disruption [30,31], and even to changes in the microbiome which is increasingly being linked to disease, including of the central nervous system [32,33]. Therefore, further investigation is warranted to better understand a link between burn and non-burn trauma and subsequent neuropathology.

5. Strengths and limitations

This study used population-based linked hospital and death records with long follow up. The study included two comparator cohorts, non-burn trauma and people with no record of an injury admission, to provide an opportunity to assess nervous system conditions experienced by those with burns and non-burn trauma compared with uninjured people. Inclusion of a non-burn trauma cohort provided a chance to assess differences in nervous system health service patterns related to injury aetiology. To date, limited long-term data are available to access and published literature is sparse. In this study, nervous system morbidity was measured in terms of hospitalisations and as such may represent both incident and prevalent cases, including those for whom existing disease may be exacerbated by injury. More detailed prospective clinical data are required to shed light on any underlying pathways of neuropathology after burn and non-burn trauma.

In Australia, hospital and medical services are available to each person, and policies and criteria for hospital admission (admission and care type) are defined by respective State and Territory Governments' that admitting medical staff are required to comply. In addition, clinical information and hospital activity audits are undertaken regularly by the Department of Health Western Australia to assure accuracy of the data recorded in the health administrative databases. Most patients in Australia, including those with NS conditions, are managed in the community by general practitioners and specialists. As hospital morbidity data typically characterize the more serious diseases with admission for assessment and/or management, the results of this study may under-represent the magnitude of NS conditions experienced by burn and non-burn patients that are managed via primary and secondary care. Additional limitations of these study data include the lack of linked primary and pharmaceutical data that would shed light on the level of community-based health service used by the burn, non-burn trauma and uninjured subjects analysed in this study.

However, given these limitations, the analyses adjusted for cohort differences in the demographic factors, pre-existing health status and injury severity across the three cohorts. All models were adjusted for effects of geographic access to health services and also for social disadvantage using an Australian national census derived variable that has demonstrated high correlation with lifestyle risk factors (including alcohol, smoking, substance abuse, diet and activity) [34]. While all categories of injury severity examined (burn and non-burn) had significantly increased admission rates, a clear dose response association between injury severity and NS admission rates was not observed. This finding may in part be due to the small number of those hospitalised with severe injury (burns and non-burn trauma) in this Western Australian patient population and/or a 'healthy' survivor effect. An additional possibility is that survivors of severe injury received a higher level of medical care for a prolonged period after discharge that resulted in earlier diagnoses and management of secondary pathologies and reduced admissions. However, while this study has not been able to shed light on the underlying pathways of neuropathology after burn and non-burn trauma it does highlight the need for more detailed prospective clinical research to better understand the patterns of NS admissions observed after burn and non-burn trauma in this study, and patient health needs.

6. Conclusions

This study found that burn and other non-burn trauma patients have health service needs for nervous system conditions for a prolonged period after discharge from hospital for a first (index) injury, when compared with uninjured people. With respect to incident admissions for nervous system conditions after injury differences in time patterns were observed between patients with burns and non-burn trauma when compared to the uninjured cohort, with the highest rates found for the first 5-year period after discharge among burn patients compared with the first-year after non-burn trauma. Further investigation is required to better understand subsequent neuropathology after burn and non-burn trauma and the observed patient health needs.

Conflict of interest

All authors declare no conflicts of interest.

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Authors contribution

All authors have made contributions to the paper and authorized submission:

Janine Duke: conception of study design, data analysis support, interpretation, drafting of article and approved final manuscript as submitted.

Sean Randall, James Boyd: data analysis, interpretation, drafting of article, revisions and approved final manuscript as submitted.

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