Health Status Transitions Related to Traumatic Brain Injury.

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Abstract

For centuries, the study of traumatic brain injury (TBI) has been centred on historical observation and analyses of personal, social, and environmental processes, which have been examined separately. Today, however, computation implementation and vast patient data repositories are producing datasets of such volume and complexity as to challenge traditional scientific methodology. Drastically different approaches show great promise for research on TBI. We report a computational analysis of health status over time using population-wide health administrative data of patients with TBI. Our approach facilitates health status at injury event evaluation and classification, and unfolds health status trajectories, from that of preceding injury to the injury event itself, as they concern external causes of injury and injury severity. Taken together, the contrasting and interwoven aspects of health status on a time continuum can influence injury event trajectories and should be considered in TBI risk analysis for the improvement of diagnosis, treatment, and prevention.

Main body

Introduction

Health status has been traditionally considered to encompass different dimensions, and has been defined by the World Health Organization as "a state of complete physical, mental, and social wellbeing, and not merely the absence of disease or infirmity"[1]. A recent discussion has highlighted the limitations of this definition, and suggested that health status is rather a dynamic process that reflects a person's change, which is consistent with the life course perspective within an environment, and that the past influences the present[2,3].

Research on the dynamic component of health status in traumatic brain injury (TBI), which refers to structural and/or physiological disruption of brain function due to an external force[4], is rapidly developing in various contexts[4–6]. Recently, the view of TBI has shifted from that of an injury event, to a condition with lifelong consequences for both morbidity and mortality[5,6]. Furthermore, it has been proposed that TBI may not be a cause, but rather an effect of multiple disorders associated with risk of falls and adverse behaviours, including epilepsy, stroke, and substance-related disorders, among others[5-8]. With this in mind, recent advances have focussed on the preventability of TBI following a head injury event and adverse TBI consequences[6,9], which may be related to a wide range of risks within health status preceding the injury event, as well as risk of an injury event itself [10,11].

The promulgation of TBI as a disease process rather than an event has enhanced the implementation of health transition following the TBI event; however, the health status transition from the time preceding injury to an injury itself remains unclear, and the challenge of considering how health statuses of individual patients unfold differently over time remains. Some health-related conditions are chronic in nature and require continuous management[13–15] at the time a person sustains an injury; in these situations, the disorder (i.e., cardiovascular, metabolic, and neurologic disorders) is more likely to be

captured in the injury surveillance data, as these are considered in TBI management and care[16]. Other health-related conditions are temporal in nature (e.g., sprains and strains, acute intoxication, abuse), and may not be noted in the injury event, but may increase the probability of an injury as a result of falls, such as among those with poor balance or confusion, thus reflecting changes at both the physiological and psychosomatic levels[17,18]. To complicate matters, the majority of patients discharged directly from the emergency department (ED) receive a diagnosis of "concussion, S06.0" with non-specific complaints of headaches, dizziness, balance issues, and sensitivity to noise and light[18–21]. While the Glasgow Coma Scale (GCS) allows for a well-defined designation of TBI severity in more severe injury events that include a loss of consciousness and post-traumatic amnesia, this scale lacks sensitivity for milder injuries, such as concussion[22]. The GCS is also less able to explain progressive symptom evolution from a relatively minor external physical force in patients who present with multiple disorders that require concurrent treatment at the time of the injury event[23,24]. Furthermore, disorders often coalesce with each other, as well as with age-related factors and social adversities, which creates a vastly complex web of possible correlations to account for in the study of health status transition in TBI.

One method to increase confidence in the characterisation of health status transitions is to use data mining and multiple testing methods, to apply these to longitudinal health status data of patients with TBI both preceding and at the time of TBI diagnoses, and to compare these data with those of patients without TBI who are individually matched to TBI patients by sex, age, place of residence, and income level. This would allow health status to be studied in relation to the difference between the cohorts, and at two time points.

Here, we present a new analysis of existing data characterising health status transitions in 235,003 unique patients with a diagnosis of TBI sustained in falls, motorvehicle collisions (MVC), when struck by/against an object, in sport-related activity, or due to assault. We analysed the results using the following seven-level analysis and validation process: (1) determining TBI and the reference (non-TBI)

event windows; (2) multiple testing to detect a set of definable health status patterns in TBI vs. non-TBI diagnoses; (3) factor analysis of health status patterns that are significantly related to TBI vs. non-TBI events; (4) a conditional logistic regression model and correlation matrix and hierarchical clustering using correlation-based distance to group health statuses at the TBI event; (5) health status transitions from the time preceding TBI to the TBI event, grouping all factors from each period into a single heatmap using agglomerative hierarchical clustering; (6) interpretation of factors preceding and at the TBI event that are clustered together, to examine how many meaningful dimensions can be distinguished; and (7) internal validation of the results at each level analysis. Using this process, we confirmed that health status preceding injury is reflected in the injury event health status, and we provide evidence that health status preceding injury can explain the external cause of TBI and contribute to injury severity. These results provide a means by which to connect information on health status transitions in TBI and associated risks, from the time preceding injury to the injury event itself.

Methods

Population and health status data

We accessed the data from the Institute for Clinical Evaluative Sciences[25], which collects and stores health administrative data on publicly funded services provided to residents of Ontario, Canada, including information on acute care hospitalisations and ED visits. With nearly 14 million residents, Ontario is Canada's most populous province, comprising 43% of Canada's population[26]. Universal health care covers all medically necessary healthcare services at the point of care. The standardised discharge summary includes patient demographics, and main and associated diagnoses according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, (ICD-10) Canadian Enhancement classification codes[27]. The ICD-10 codes consist of a combination of alphanumeric characters that characterise broad diagnosis categories. Each code is designed as an alphanumeric code and arranged hierarchically, with the code length ranging from 3–6 characters. The

first three characters designate the category of the diagnosis, which is the same as the World Health Organisation's ICD-10 international standard for reporting diseases and health conditions[28]. The health service records data are linked deterministically at the individual level through a unique, encoded identifier based on name, sex, date of birth, and postal code. By applying unique de-identified identifiers, the health status trajectory of each patient can be tracked over time.

We used a previously established cohort of patients discharged between the fiscal years 2007/2008 and 2015/2016 from acute care (identified in the Discharge Abstract Database) and from the ED (identified in the National Ambulatory Care Reporting System) with a diagnostic code for TBI (ICD-10 codes S02.0, S02.1, S02.3, S02.7, S02.8, S02.9, S04.0, S07.1, and S06)[6]; these patients comprised the TBI cohort in the present study. Patient demographics, main and associated diagnosis, condition, problem or circumstance data[27] were collected for each individual patient. We selected a 10% random sample of patients discharged from acute care hospitals or the ED during the same study period for a reason other than TBI, and individually matched these to patients with TBI by sex, age, place of residence (urban vs. rural), and income quintile; these patients comprised the reference population[6]. The index date for patients with TBI was their first occurrence of TBI over the study period, whereas, for the reference population, the index date was the midpoint of the ED or acute care visits. Data from 235,003 unique patients with TBI (and a same number of reference patients) were randomly split into training (50%; n = 117,689), validation (25%; n = 58,798), and testing (25%; n = 58,516) datasets. All analyses were completed and reported using the testing dataset, and the training and validation datasets were used for internal validation.

TBI event, injury severity, mechanism, and context

We found that the incidence of TBI over the study period (index date) followed a certain trend, whereby the number of hospital visits surrounding the TBI index date appeared to plateau 30 days before and after the index date, and remained largely unchanged thereafter (Figure 1). Therefore, this 61-day period was defined as the TBI event window. This methodology was repeated on the reference

population. We followed previously published severity classifications[29,30] to assign TBI injury severity. External causes of injury were determined using Centers for Disease Control and Prevention major external cause of injury group codes (E codes), which were divided into falls, struck by/against object, MVC, assaults, and sports-related injury[31].

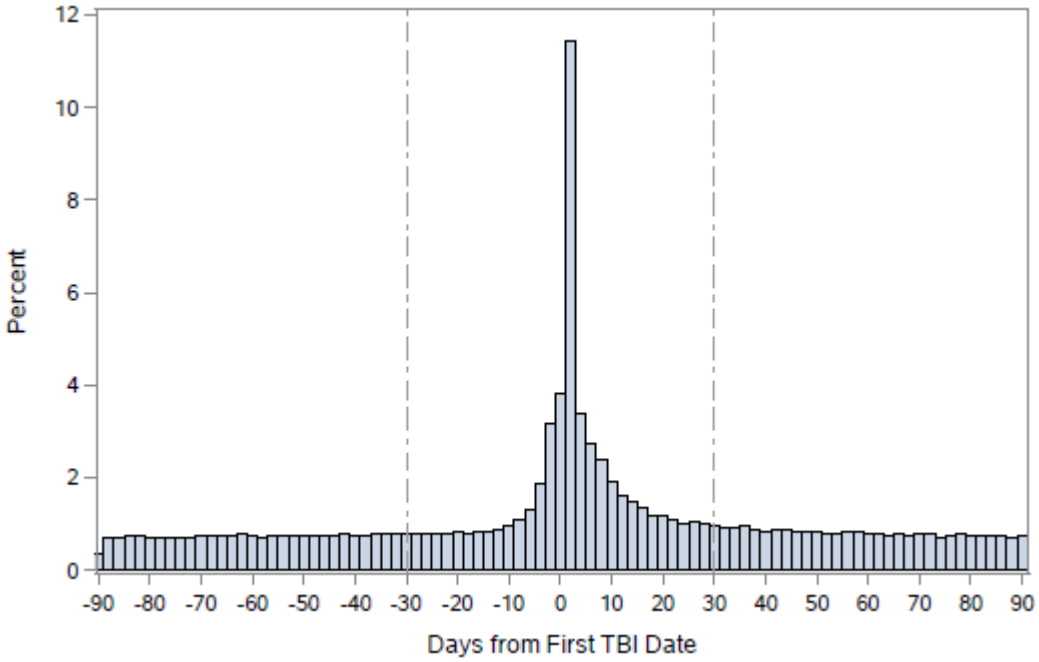

Figure 1. Number of hospital visits surrounding the TBI index date.

Health status preceding the injury event

We evaluated the health status preceding a TBI event reported by previous studies[6,32,33]. From all the possible ICD-10 codes classifying patients' main and associated diagnoses, a previous data mining and validation study identified 43 factors that were significantly overrepresented in patients with TBI compared to reference patients (individually matched based on sex, age, place of residence, and income quintile) within the 5 years preceding their TBI event. For details, please see the study[6].

Health status at the injury event

To identify health status at the TBI event and to gain insight into its observed correlations, we conducted an analysis with all ICD-10 codes depicted across the 10 and 25 diagnoses fields of the National Ambulatory Care Reporting System and the Discharge Abstract Database, respectively, for patients with TBI and reference patients at the index date. We converted all 2,600 codes into binary variables, except for provisional codes for research and temporary assignments, U98 and U99. The first three characters (one alphabetic and two numeric) of the ICD-10 comprised 2,600 distinct codes that defined specific diagnoses. These 2,600 binary ICD-10 code variables were tested for significant correlations with TBI diagnosis codes using a matched McNemar test with correction for multiple testing[34]. The Benjamini-Yekutieli method was applied to acquire a set of codes controlled at a False Discovery Rate (FDR) of 5%[35,36]. We identified ICD-10 codes that were associated with a TBI event, for which we then calculated odds ratios (ORs) to compare with the reference population. To eliminate measurement artifacts, the procedure was first performed using the training dataset, and then repeated using the validation dataset[37]. Only codes that were significant in both the training and validation sets were retained for further analysis.

To gain insight into the dimensionality structure of individual diagnoses codes, we performed factor analysis using principal components methods[38]. The optimal number of factors was determined by the breakpoint on the scree plot, eigenvalue, the greatest cumulative proportion of variance accounted for, and via a conditional logistic regression looped through all possible factors covering the largest area under the receiver operating characteristic curves[39] (Supplementary Figure 1, Supplementary Table 2). The conditional logistic regression model was built using binary factor-based scores40. Patients were assigned a score of one if they possessed any of the ICD-10 codes contained in the factor definition; otherwise, they were assigned a zero. These factor-based scores were used to calculate ORs and 95% confidence intervals from a conditional logistic regression model[40] on the association between each factor and TBI, controlling for sex, age, rurality, and income in the testing dataset. To visualise the results of the factor analysis and conditional logistic regression model, a Pearson's correlation matrix

was generated for all significant factors[41], and hierarchical clustering was performed on similar group factors using correlation-based distance[42] to identify groups of people with similar current-associative factors for TBI. To aid in the visualisation of clusters in the heatmap, clustering was performed using Ward (minimum variance) linkages[43]. The algorithms for these agglomerative clustering methods have been described elsewhere[43].

Health status transitions

To further expand our understanding of health status transitions from the time preceding TBI to the TBI event, we clustered all factors from each period into a single heatmap, when values of factors representing each time period were correlated. This was done using a Fisher transformation, which converted the correlations into "z-like statistics"[44]. Next, factors preceding TBI were pooled into separate "injury severity" and "mechanisms of injury TBI" event groupings. To determine the consistency of observed patterns, heatmaps were generated and compared between the training, validation, and testing dataset, with an FDR-corrected alpha set at 0.05. All correlations with adjusted p-values greater than 0.05 were set to 0 on the heatmaps, leaving only significant correlations with an FDR < 0.05. All analyses were conducted using SAS software (version 9.410, SAS Inc., Cary, NC) and R (version 3.4.1.11, R Foundation for Statistical Computing; www.r-project.org). Figures were created using R (ComplexHeatmap and Wordcloud, R Foundation for Statistical Computing; www.r-project.org).

Results

Of the 58,516 patients in the testing dataset, 57% were male and 43% were female. The most common TBI mechanisms were falls (n = 26,480 [45%]) and being struck by/against an object (n = 20,845 [36%]). Of all injuries, 25% were sports-related and 10% were sustained in a MVC. Assaults accounted

for 7% of TBIs. Injury severity was not established in 25,036 [43%] patients; most of these cases were recorded as concussion without a specified length of unconsciousness (ICD-10 code S06.0; Table 1 and Supplementary Table 3).

Table 1. Characteristics of patients with a first traumatic brain injury-related visit in the emergency department or acute care and matched reference patients.

Variables	**Patients with TBI (N=58,516)**	**Reference patients (N=58,516)**
Sociodemographic characteristics		
Sex, n (%)		
Male	33,379 (57)	33,379 (57)
Female	25,137 (43)	25,137 (43)
Age at injury (years), mean (SD)	36.23 (25.33)	36.24 (25.32)
Income quintile, n (%)		
Q1 (lowest)	11,465 (20)	11,465 (20)
Q2	11,540 (20)	11,540 (20)
Q3	11,494 (20)	11,494 (20)
Q4	12,182 (20)	12,182 (20)
Q5 (highest)	11,835 (20)	11,835(20)
Rurality	9,084 (16)	9,084 (16)
TBI-related characteristics		
TBI main diagnosis, n (%)	51,705 (88)	NA
Injury severity, n (%)		
Unspecified	25,036 (43)	NA

Mild	20,461 (35)	NA
Moderate	2,166 (4)	NA
Severe	10,853 (19)	NA
Type of first healthcare entry, n (%)		
Emergency Department	48,142 (82)	NA
Acute Care	4,147 (7)	NA
Emergency & Acute*	6,227 (11)	NA
External Cause of Injury, n (%)		
Sports injury	14,472 (25)	NA
Assault	4,359 (7)	NA
Falls	26,480 (45)	NA
Motor vehicle accidents	5,808 (10)	NA
Struck by/against	20,845 (36)	NA
Other	6,791 (12)	NA
Missing	166 (0)	NA

Abbreviations: n/a= not applicable; TBI = traumatic brain injury; SD = standard deviation. Data given as mean (standard deviation) or n (%). *A patient had a transfer to either location on the same day.

The matched McNemar tests were performed on the training dataset for 2,600 ICD-10 codes. The Benjamini-Yekutieli multiple testing recognised 273 diagnoses codes that were specific to TBI (i.e., had an OR >1). These codes were re-tested on the validation dataset, and 226 (83%) of them were internally validated (Supplementary Tables 3 and 4; Supplementary File 1). Factor analysis was applied to the training dataset. Of the 226 codes included in the analysis, 164 (73%) individual codes met the

factor loading cut-off of 0.2 (Supplementary Figure 2). For details on frequencies, ORs, and factor loadings of codes that met the factor analysis cut-off and codes that did not meet the cut-off, see Supplementary Tables 4 and 5, respectively. Using the breakpoints on the scree plots and the interpretability, 35 factors were selected. Factor 9 (asphyxiation, suicide) had low frequencies in the reference population (<6) and was excluded from further analyses. The remaining 34 factors were studied further. Figure 2 presents each factor by injury severity share.

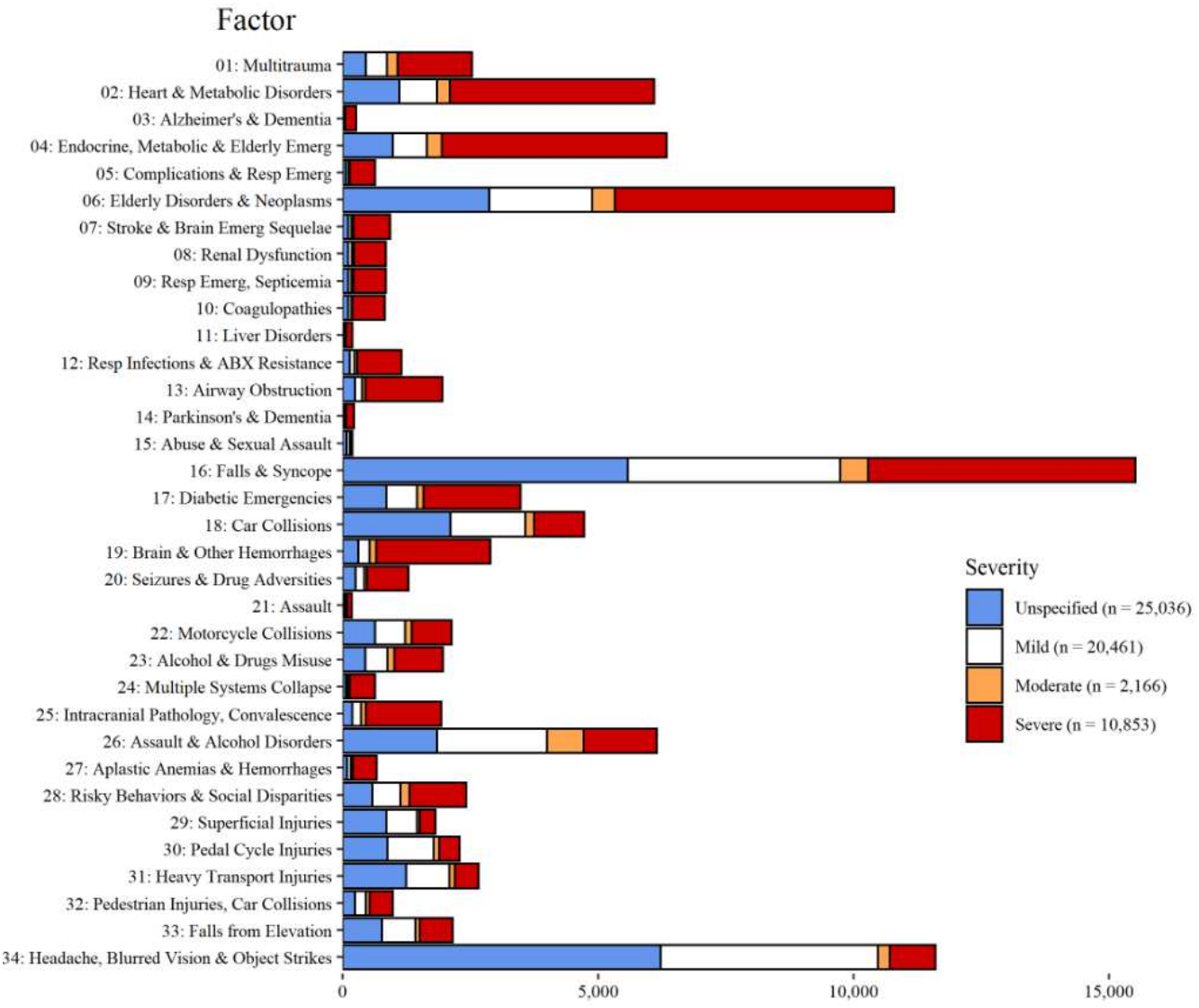

Figure 2. Health status factors and injury severity share in patients with TBI in Ontario, Canada 2002–2016. Total number of each health status factor in TBI event across the sample set (n=58,516). Data are shown for each injury severity, coloured by mild, moderate, severe, and unspecified.

Table 2 presents the descriptions, frequencies, ORs, and ICD-10 codes included for each of the 34 factors. Supplementary Table 4 presents factor loading and detailed description of each factor.

Table 2. Factor analyses with ICD-10-CA codes loading, disease category and effect size (OR and 95% CI).

Factor number	**Short description**	**Category**	**ICD-10 codes**	**Frequency in cohorts**		**OR [95% CI]**
				TBI	Ref	
Factor 1	Multitrauma	Emergency Medicine	S36, S27, S37, T06, T79, S42, S26, S72	2,535	749	3.49 [3.21-3.79]
Factor 2	Heart & Metabolic Disorders	Cardiology	E78, I10, I48, Z95, I50, Z92, E03, E11	6,095	3,787	1.97 [1.88-2.07]
Factor 3	Alzheimer's & Dementia	Neurology	F00, G30	267	79	3.41 [2.65-4.39]
Factor 4	Endocrine, Metabolic & Elderly Disorder	Emergency Medicine/Geriatrics	I10, E87, E83, E22, F05, Z75, N17, F06, B96, I95, R41	6,338	2,873	2.85 [2.70-3.00]
Factor 5	Complications & Respiratory Disorders	Emergency Medicine	J95, Y84, J15	638	204	3.14 [2.68-3.68]
Factor 6	Elderly Disorders & Neoplasms	Geriatrics	S72, F05, Z75, R41, F03, Z51, R29, W05, R26, W19, C79, Z74, W06	10,793	2,275	6.92 [6.54-7.31]
Factor 7	Stroke & Brain Emerg Sequelae	Neurology/Physical Medicine and Rehabilitation	G81, R47, I63, I69, R13	929	322	2.96 [2.61-3.37]
Factor 8	Renal Dysfunction	Nephrology	N17, Z99, N18, N08	845	439	2.00 [1.77-2.25]
Factor 9	Respiratory Emergencies, Septicaemia	Emergency Medicine	N17, J17, A41, J96	844	378	2.32 [2.05-2.63]
Factor 10	Coagulopathies	Haematology	Z92, Y44, D68	826	183	4.65 [3.95-5.48]
Factor 11	Liver Disorders	Gastroenterology	K70, R18, K72, B18	198	71	2.79 [2.13-3.66]
Factor 12	Respiratory Infections & ABX Resistance	Infectious Diseases	B96, B95, U82, A49, L89	1,147	570	2.09 [1.88-2.31]
Factor 13	Airway Obstruction	Emergency Medicine	Z51, R13, J96, L89, J69, W80	1,956	771	2.70 [2.48-2.95]

Factor 14	Parkinson's & Dementia	Neurology	F02, G20, G31	221	50	4.42 [3.25-6.01]
Factor 15	Abuse & Sexual Assault	Family medicine/ Psychiatry/Trauma	T74, Y07, Y05, Y06	196	15	13.07 [7.73-22.09]
Factor 16	Syncope & Falls	Emergency Medicine/Mechanism	I95, W19, R55, W18, W01	15,516	3,106	6.79 [6.49-7.11]
Factor 17	Diabetic Emergencies	Emergency Medicine	E11, N08, E14, R73, G63	3,479	2,426	1.54 [1.45-1.63]
Factor 18	Car Collision	External cause of injury	V43, V49, V48, V89, V47, T14, Z04, V58	4,723	711	7.14 [6.58-7.75]
Factor 19	Brain & Other Haemorrhages	Neurology	Z51, C79, I61, I60, G91, I62, G06, I67, Z54	2,887	744	4.24 [3.90-4.62]
Factor 20	Seizures & Drug Adversities	Neurology/ Pharmacology Emergencies	Y46, G40, T42, R56, G41, R27	1,284	288	4.56 [4.00-5.19]
Factor 21	Assault	External cause of injury	X99, S21, S11, S15	178	33	5.39 [3.72-7.82]
Factor 22	Motorcycle Accidents	External cause of injury	S42, V28, V29, V27, V23, V86, V22	2,133	674	3.27 [3.00-3.58]
Factor 23	Alcohol & Drugs Misuse	Psychiatry	Y90, R78, F10	1,960	435	4.66 [4.19-5.18]
Factor 24	Multiple Systems Collapse	Emergency Medicine /Neurosurgery	G93, Z52, D65, E23, I46	629	76	8.28 [6.53-10.51]
Factor 25	Intracranial Pathology, Convalescence	Emergency Medicine/Physical Medicine and Rehabilitation	S72, Z51, C79, I62, Z54, Z50	1,925	363	5.75 [5.11-6.46]
Factor 26	Assault & Alcohol Disorders	Psychiatry/ Population and Community Health/ Mechanism	F10, Y04, Y09, Y00, H05, H11, H53, Y08	6,151	762	9.30 [8.58-10.09]
Factor 27	Aplastic Anaemias & Haemorrhages	Haematology/ Neurology	D46, D61, D69, D64	659	455	1.46 [1.29-1.65]
Factor 28	Risky Behaviours & Social Disparities	Family Medicine/ Psychiatry/Population and Community Health	B18, F10, F14, F11, Z59, Z91, Z72, Z21	2,417	694	3.64 [3.34-3.97]
Factor 29	Superficial Injuries	Emergency Medicine	S30, S40, S70, S20, S10, S39	1,813	894	2.06 [1.90-2.23]
Factor 30	Pedal Cycle Injuries	External cause of injury	V18, V19, T00, V13, V17	2,292	514	4.64 [4.21-5.13]

Factor 31	Heavy Transport Injuries	External cause of injury	V43, V44, V54, S19	2,661	298	9.53 [8.42-10.79]
Factor 32	Pedestrian Injuries, Car Crashes	External cause of injury	S15, V03, V09, T08, T02, I72	982	92	10.89 [8.78-13.52]
Factor 33	Falls from Elevation	External cause of injury	W17, W13, W11, W12	2,147	296	7.59 [6.70-8.59]
Factor 34	Headache, Blurred Vision & Object Strikes	Neurology/ Mechanism	R51, F07, G44, W22, Z02, W20	11,604	2,079	6.80 [6.45-7.16]

Abbreviations: ABX = antibiotics; CI= confidence interval; OR= odds ratio; TBI = traumatic brain injury; SD = standard deviation. Frequencies given as numbers.

Health status transitions

Heatmaps of factors preceding TBI and factors of the TBI event are presented in Figure 3.

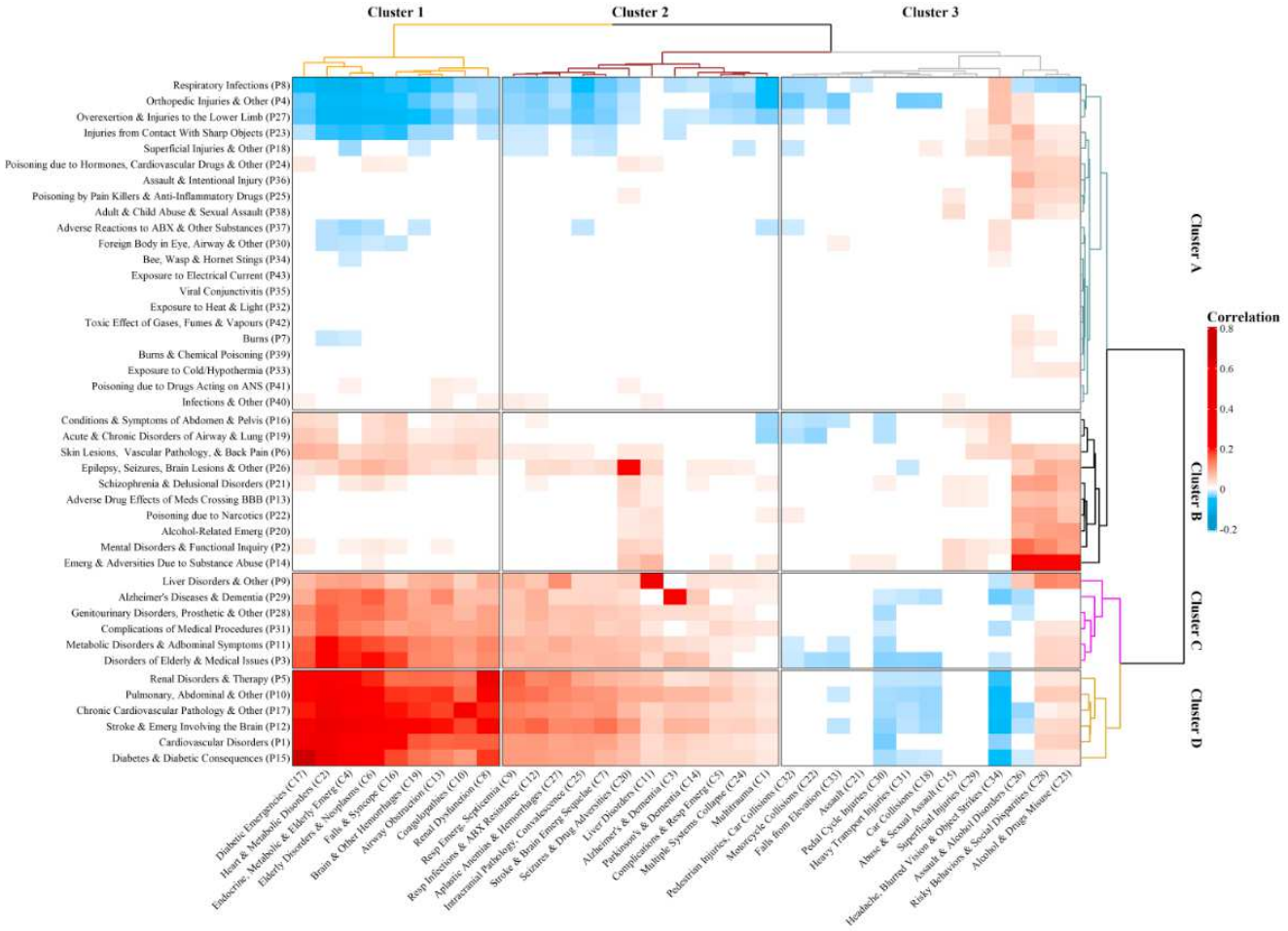

Figure 3. Cluster analysis and heatmap across 43 factors preceding TBI (y-axis) and 34 factors at the TBI event (x-axis). On the left y-axis, preceding injury-clusters (Clusters A-D) are annotated for

reference with the text. On the upper x-axis, TBI event-clusters (Clusters 1-3) are likewise annotated. Annotations are presented as guidelines and are not definitive. Only factors that were internally validated in the testing and validation datasets are presented. In the heatmap, each colour represents a set of binned ranks in the heatmap, with blue colours representing negative correlations and red colours representing positive correlations, adjusted for FDR. White fields represent non-significant correlations after adjustment for FDR.

To determine the consistency of the observed patterns, heatmaps were generated and compared between the training, validation, and testing datasets (Supplementary Figures 2 and 3). Combined clusters were distinguished by the type of health status factor. Most of these clusters were characterised by system-level dysfunctions, morbidity due to drug poisoning or overdose, and social disparities patterns. The strongest positive correlations between health status at the injury event and health status preceding TBI were between Cluster 1 and Cluster D (i.e., multiple body system pathology) and Cluster 2 and Cluster C (i.e., advanced age-related brain pathology). The multiple body system pathology was composed of endocrine system pathology, i.e., diabetes and diabetic emergencies (Factor C17 and Factors P15), cardiovascular system pathology (Factor C2 and Factor P1), alterations in renal and urinary tract function (Factor C8 and Factor P5), and brain haemorrhages and stroke (Factor C19 and Factor P12). The advanced age-related brain pathology consisted of liver disorders (Factor C11 and Factor P9), Alzheimer's disease and dementia (Factor C3 and Factor P29), and aplastic anaemias and haemorrhages and liver disorders (Factor C27 and Factor P9), among other advanced neurological sequalae. Cluster B preceding TBI (i.e., poisons, drug overdose, social adversity) was strongly associated with multiple pathologies at the injury event (Clusters 1-3), including seizures and drug adversities (Factor C20 and Factor P26) and illnesses due to poisons and drug overdose (Factor C23 and Factor P9; Factor C26 and Factor P13). Weaker correlations were observed between multiple body system pathology and advanced age-related brain pathology at the injury event and Cluster A preceding injury (i.e., young age-related concerns), assault and intentional

injury (Factors P28 and P36 and Factor C26), overexertion and superficial injuries, exposure to environmental adversities (i.e., burns, cold/hypothermia, exposure to heat/light), and lifestyle and adverse drug effect preceding injury (Factors P18, P7, P33, and C23 and C28). Despite visual similarities of Cluster C and D, which were characterised by multiple body system pathology and advanced age-related brain pathology, respectively, they were more dissimilar than Clusters A (i.e., young age-related concerns) and B (i.e., poisons, drug overdose, social adversity).

Health status preceding injury explains injury severity and external causes of injury

Many of the health status factors preceding TBI showed a significant association with TBI severity, thereby probably contributing to the GCS score at the time of injury. For example, severe TBI and age at injury was characterised by a strong link to Clusters C and D (i.e., multiple body system pathology and advanced age-related brain pathology, Figure 4), which comprised metabolic disorders (Factor P9, P11, P15), neurological disorders (Factor P12), cardiovascular pathology (Factor P1 and P17), Alzheimer's disease and dementia (Factor P29), and disorders of older people (Factor P3), while respiratory infections, MSK injuries, and overexertion in Cluster A (i.e., young age-related concerns, Factors P8, P4, and P27) preceding TBI were negatively correlated with severe TBI. A reverse health status association was observed for the mild and unspecified TBI severity, whereas moderate TBI severity showed positive correlations with the cluster of disorders associated with poisoning due to narcotics, substance abuse, and liver pathology preceding injury (Factors P22, P14, and P9). This clustering analysis was performed separately for the training, validation, and testing datasets, and consistent patterns in the clustering of health status factors with injury severity were observed across each dataset.

External causes of injury were also distinguished by combined clusters of health status factors preceding TBI. Falls were characterised by a strong positive correlation with Clusters C and D (i.e., multiple body system pathology and advanced age-related brain pathology), mimicking the clusters

associated with severe TBI, and a strong negative correlation with Cluster A (i.e., young age-related concerns), mimicking the clusters associated with mild and unspecified TBI severity. In contrast, struck by/against an object showed a strong positive correlation with Cluster A, and negative correlations with Clusters C and D.

A few patterns of a weak negative correlations were observed between health status preceding TBI and MVC as an external cause of injury, whereas sport-related and assault-related causes of injury showed distinct positive correlations with health status preceding TBI. Meaningful observations included clustering of respiratory infections preceding injury with orthopaedic injuries and overexertion (Cluster A, Factors P8 with P4 and P27) in sport-related injury, and preceding injury poisoning by drugs and other substances, assault and abuse, and injuries from contact with sharp objects (Cluster B, Factors P23, P24, P36, and P38) with assault-related TBI.

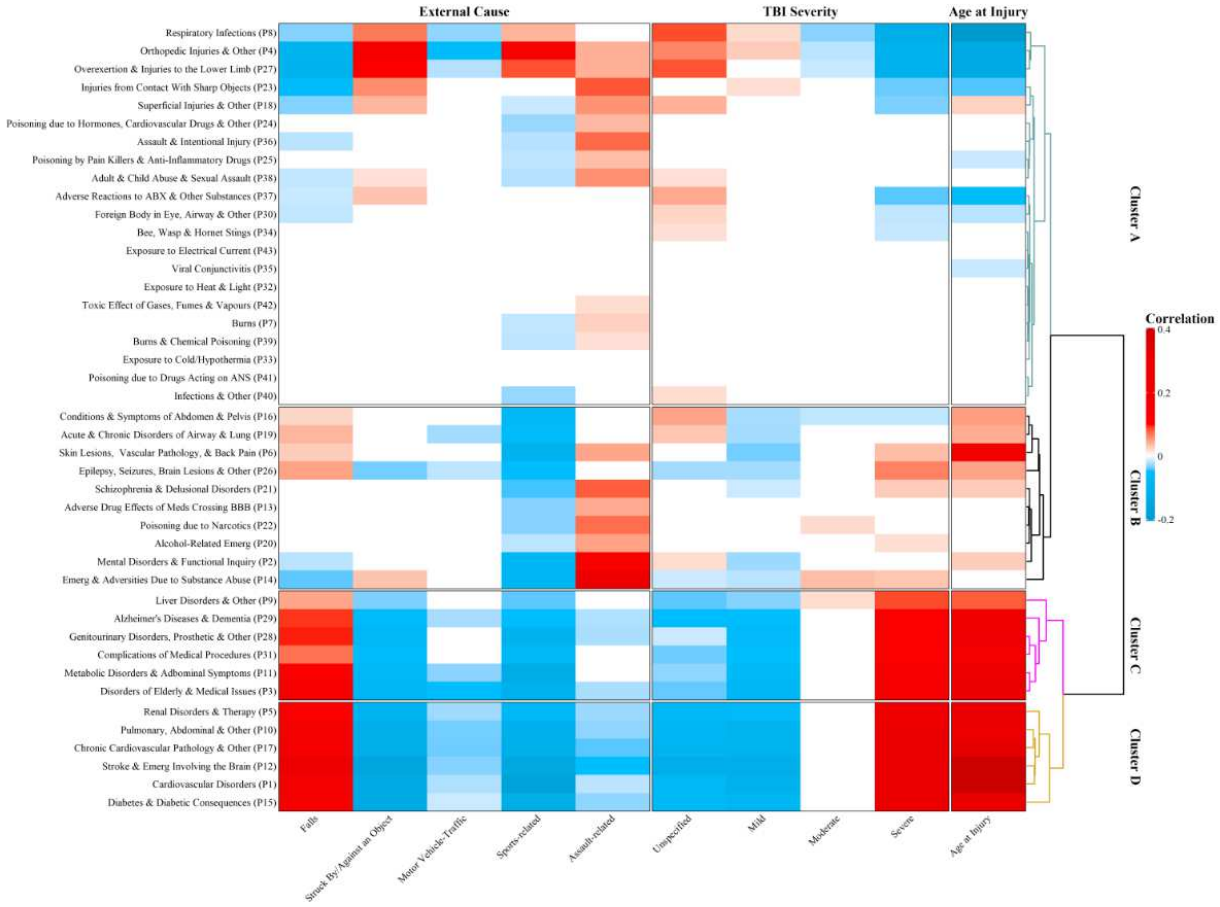

Figure 4. Cluster analysis and heatmap across 43 factors preceding TBI (y-axis) and mechanism, context of injury and TBI severity (x-axis). On the right y-axis, sample-based clusters are observed. Annotations are presented as guidelines and are not definitive. Only factors that were internally validated in the testing and validation datasets are represented. In the heatmap, each colour represents a set of binned ranks in the heatmap, with blue colours representing negative correlations and red colours representing positive correlations, adjusted for FDR. White fields represent non-significant correlations after adjustment for FDR.

Discussion

In this paper, we have described a method for aligning health status transition in TBI, a disorder of significant public health concern and a major cause of disability worldwide[4,45]. The methods presented here describe an innovative non-hypothesis-driven approach for detecting health status at injury events and then combining health status results preceding the injury; this offers an explanation for the challenges associated with injury diagnosis, classification, and surveillance, which can be confounded by population health heterogeneity and epigenetic ambiguity[46]. With these challenges in mind, we conducted an impartial and interpretable assessment of health status transitions in TBI accounting for 2,600 individual diagnoses encoded using the ICD-10[3] in a retrospective cohort of people of all ages, biological sex, socioeconomic standing, and place of living who had non-differential access to healthcare. We internally validated our results and found them to be robust. We believe that the presented method to study health status transitions in TBI will spur the development of additional methods and prove useful for future analyses on health status transition after the injury event.

Our results demonstrate that the transition in health status from the time preceding injury to the injury event involves a precise sequence of events. We observed both unnoticeably carrying transitions, whereby the person's health status preceding injury was not a constituent of the health status captured in the TBI event (i.e., exposures to gases and fumes, electrical currents, sharp objects, machinery, as shown by non-significant associations), as well as transitions when the health status preceding injury

was contained in the assessment of the injury event. Such transitions include cardiovascular, endocrine, metabolic, and neurological disorders, and disorders of the elderly, were not resolute with time, and which were significantly reflected in the TBI event's external cause of injury and injury severity. Together, these results suggest that attention to the health status transition patterns in TBI emerge along with the projection of comorbidity, which is consistent with previous reports[47-52].

Our results suggest that many disorders and social adversities preceding injury are reflected in external causes of injury and injury severity. Disorders clustering within the same external cause of injury and injury severity, as highlighted here, illuminate TBI as an event that is constructed within the context of health and social statuses, both formative and reflective[6,53]. For example, we observed that clusters composed of cardiovascular and metabolic disorders, stroke, dementia, and disorders of the elderly preceding TBI were strongly associated with falls and severe TBI. While the above disorders, individually, have long been known to be implicated in the risk of falls[54-56], we demonstrated their formative links, both with other disorders and with TBI diagnosis. The association of Clusters C and D with TBI severity found here has significant diagnostic relevance. In this regard, both the depth and duration of coma following the injury event have been considered as an injury severity indicator using the GCS score[57]. While it has been previously suggested that GCS scores can be affected by intoxication, hypoxia, and hypotension, among other things[58-60], the health status and age of patients presenting with these signs are not currently accounted for when determining injury severity. This has both clinical and policy implications, as there is a continuing debate over use of the GCS score in trauma patients of all ages, including preverbal children, to determine the time to extubation[61], sedate[62], and withdraw life support[63], as well as intensive care stay duration[64], rehabilitation[65], discharge destination[66], resource utilisation[67], and litigation[68].

A large number of TBIs in our sample (43%) did not have an established injury severity; most of these events were coded as concussions without a specified length of unconsciousness (S06.0 codes). The links between MSK illnesses preceding injury event and unspecified TBI severity sustained in a sports-

related context have been described previously[6]; however their clustering on young age-related disorders (i.e., respiratory infections and adverse reaction to antibiotics (Factors P8 and P37), overexertion (Factor P27), adult and child abuse and assault (Factor P38), and foreign body in eye or airway (Factor P30) preceding injury) highlight the limitations of establishing level of responsiveness according to three aspects – eye-opening, motor, and verbal responses – in compromised person-environment and healthcare interactions, as well as to a greater probability of an unwitnessed injury event in such interactions.

Finally, our results provide a basis for using pre-injury health status as an integral part of precision medicine and injury surveillance. We found clusters of factors associated with severe injury and those with mild injury severity and concussion. Factors clustering on moderate-to-severe TBI are composed of system-level disorders, poisons, and drug overdose, and those associated with mild TBI and unspecified injury severity (i.e., concussion codes) are composed of MSK-related injuries and respiratory illnesses. The external cause of injury, especially falls and struck by/against an object, nearly clustered in accordance to the severity, with falls linked to patients with system-level and neurological disorders and severe TBI, and being struck by/against an object linked to superficial injuries, overexertion, orthoepic injuries, and mild TBI and concussions[69,70]. Notably, MVCs showed very few associations, all negative, the most significant of which, across clusters, were orthopaedic injuries, seizure disorders, and disorders of older people; these conditions linked to obstacles to, or lack of authorisation to operate a machinery[71-73].

As presented in this research, we developed a feasible method to deal with big data and complex clinical and public health topics in TBI simultaneously, which can be applied to other complex disorders and injuries. We have shown that it is possible to convert 2,600 diagnoses encoded within the ICD-10 structure into 226 TBI event-specific diagnoses, and then further reduce these diagnoses to 34 factors that collectively explain the TBI event's significantly shared variance with factors preceding TBI. We created a procedure for visualised cluster analysis and heatmaps to accurately trace health

status transitions and to detect and localise the clusters associated with the transitions. Encouraged by meaningful observations, we adapted and extended the analyses to external causes of injury and injury severity, and provided evidence that health status five years preceding an injury event is reflected in the injury event, as TBI-event health status and factors were implicated in the cause of injury and injury severity designation. Depending on the cluster and its formation, we anticipate that our analyses could offer new important information on injury severity in the case of falls and being struck by/against an object, and assault-related injury surveillance.

Despite the scientific and technological advances captured in this work, there are still questions to be addressed in future research. The data-driven approach we developed and the results are based on ED and hospital records; there are still persons with TBI who may choose to be treated at a primary care facility within the healthcare system, which could be an additional source for coding injury and morbidity data. Primary care data should be explored in the future, given that hospital data tends to be efficient and does not always strive for completeness[27,28]. This is important for assault-related injury surveillance, as the E-codes do not capture the victim/perpetrator relationship, i.e., TBIs due to intimate-partner violence. In Ontario, a code is mandatorily assigned only when the condition or circumstance exists at the patient's visit and is significant to the patient's treatment or care[28]. In the future, we plan further investigation and external validation of health status preceding injury, especially for circumstances not reflected in the TBI event window, but which were implicated in the external cause and severity of the injury, linking them to recovery and functional trajectory. Finally, we used the first three characters in the ICD-10, which designate the category of the diagnosis at the time preceding an injury event[74]. By using the whole sequence of codes instead of the first three characters, more data can be preserved for model testing, training, and validation; however, this necessitates a higher computing power to run the analyses[74]. In summary, advances in data-driven analysis reveal a remarkable extent of meaningful associations in health status in the time preceding and following a TBI

event. Predicting health status transitions governing external causes of injury and injury severity is our next important question with compelling injury surveillance and public health ramifications.

Ethical approval and informed consent

Approval: The study protocol was approved by the ethics committees at the clinical (Toronto Rehabilitation Institute-University Health Network) and academic (University of Toronto) institutions.

Accordance: All methods were carried out in accordance with the relevant guidelines and regulations.
Informed consent: This research utilised encrypted administrative health data with no access to personal information. No humans were directly involved in this study.

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Author Contributions

AC, TM, VC and MDE conceived the original concept and initiated the work. MDE designed and optimized statistical analyses for this work. AT and MS carried out the analyses with the support of MDE. TM optimized reporting. All authors discussed the results biweekly and further steps for analyses and interpretation. TM wrote the manuscript. All authors read the paper and commented on the text.

Additional Information

Competing interests

The authors declare no financial and non-financial competing interests.

Availability of materials and data

ICES is an independent, non-profit research institute funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). As a prescribed entity under Ontario's privacy legislation, ICES is authorized to collect and use health care data for the purposes of health system analysis, evaluation and decision support. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario. The dataset from this study is held securely in coded form at the Institute for Clinical Evaluative Sciences (ICES). While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from

the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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Figures

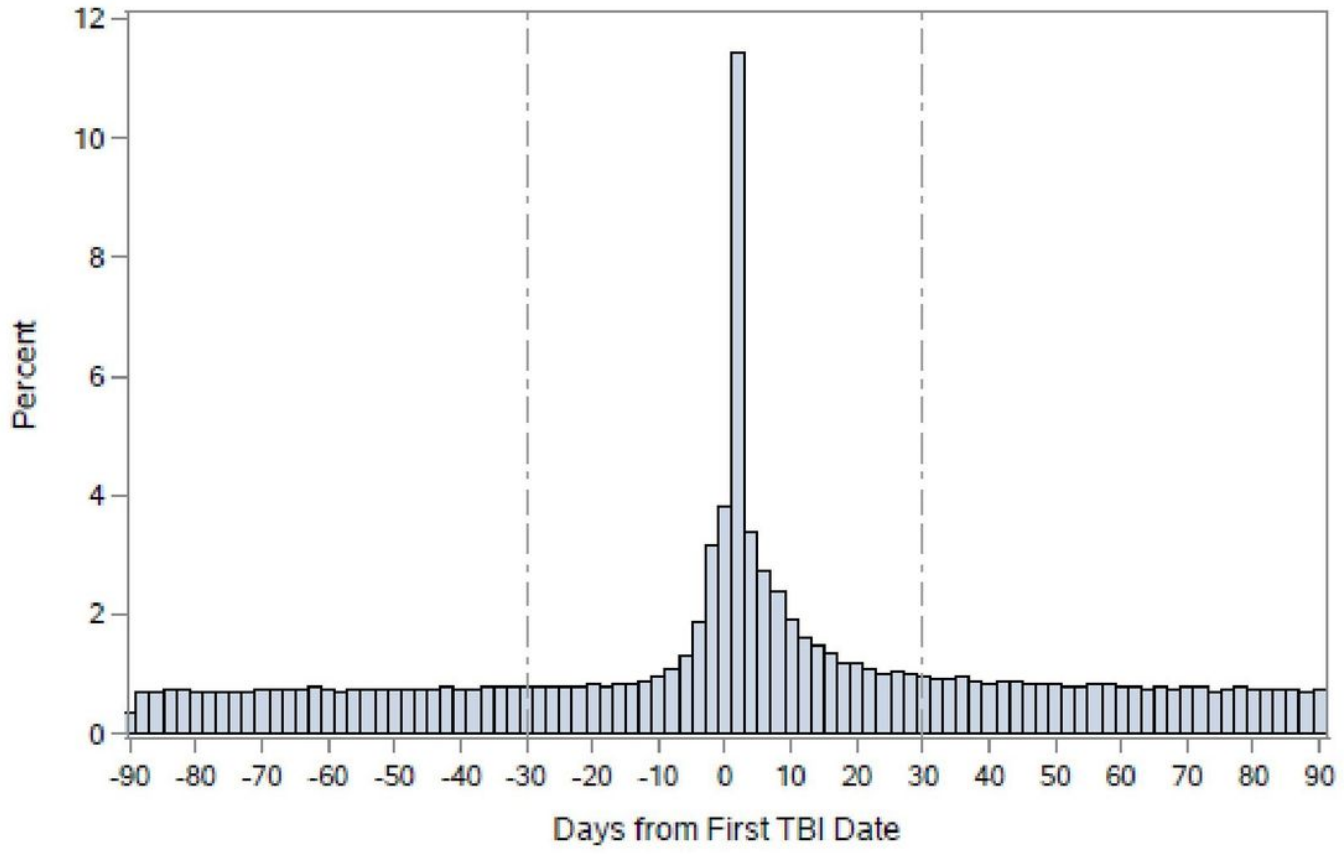

Figure 1

Number of hospital visits surrounding the TBI index date.

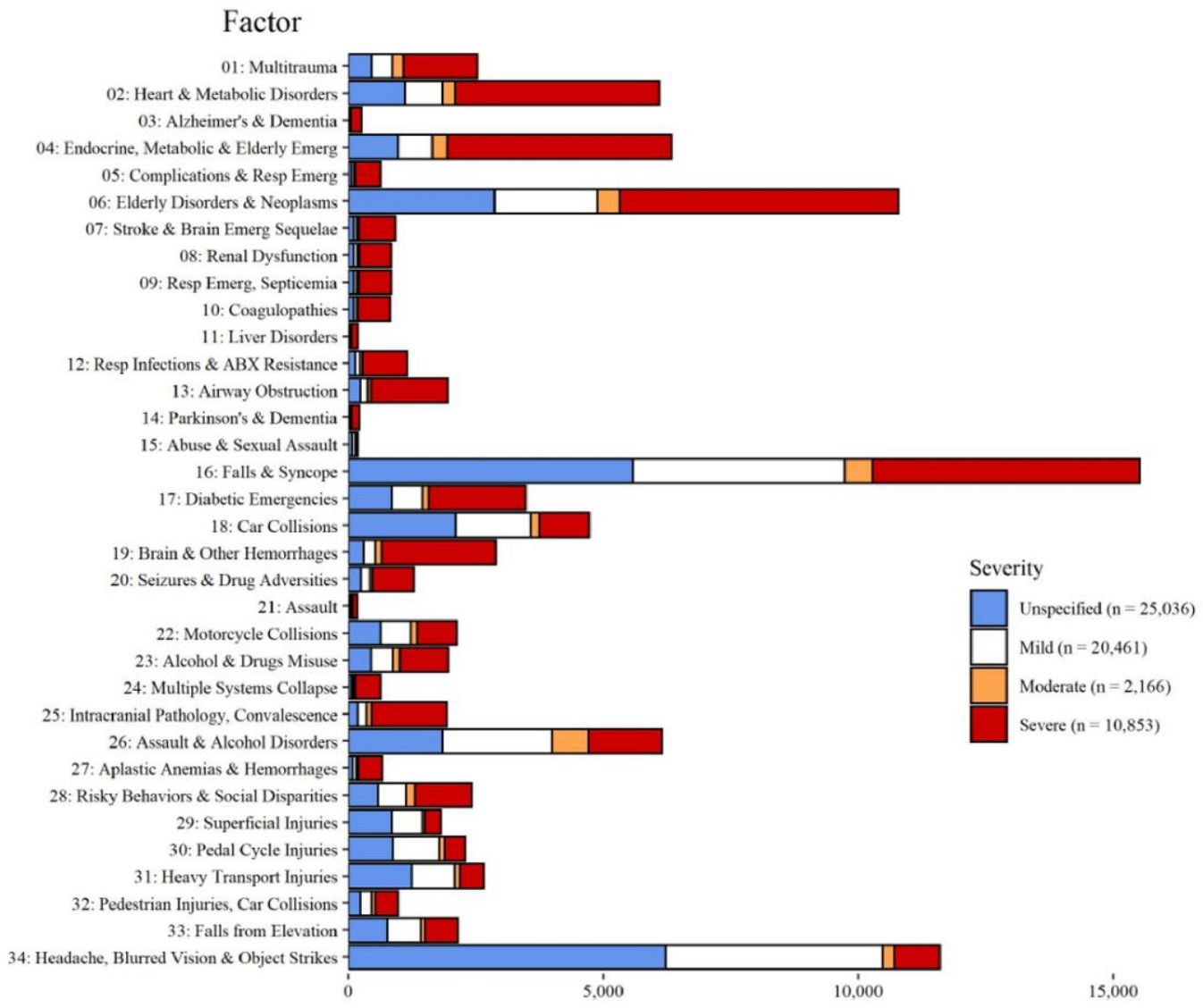

Figure 2

Health status factors and injury severity share in patients with TBI in Ontario, Canada 2002– 2016. Total number of each health status factor in TBI event across the sample set (n=58,516). Data are shown for each injury severity, coloured by mild, moderate, severe, and unspecified

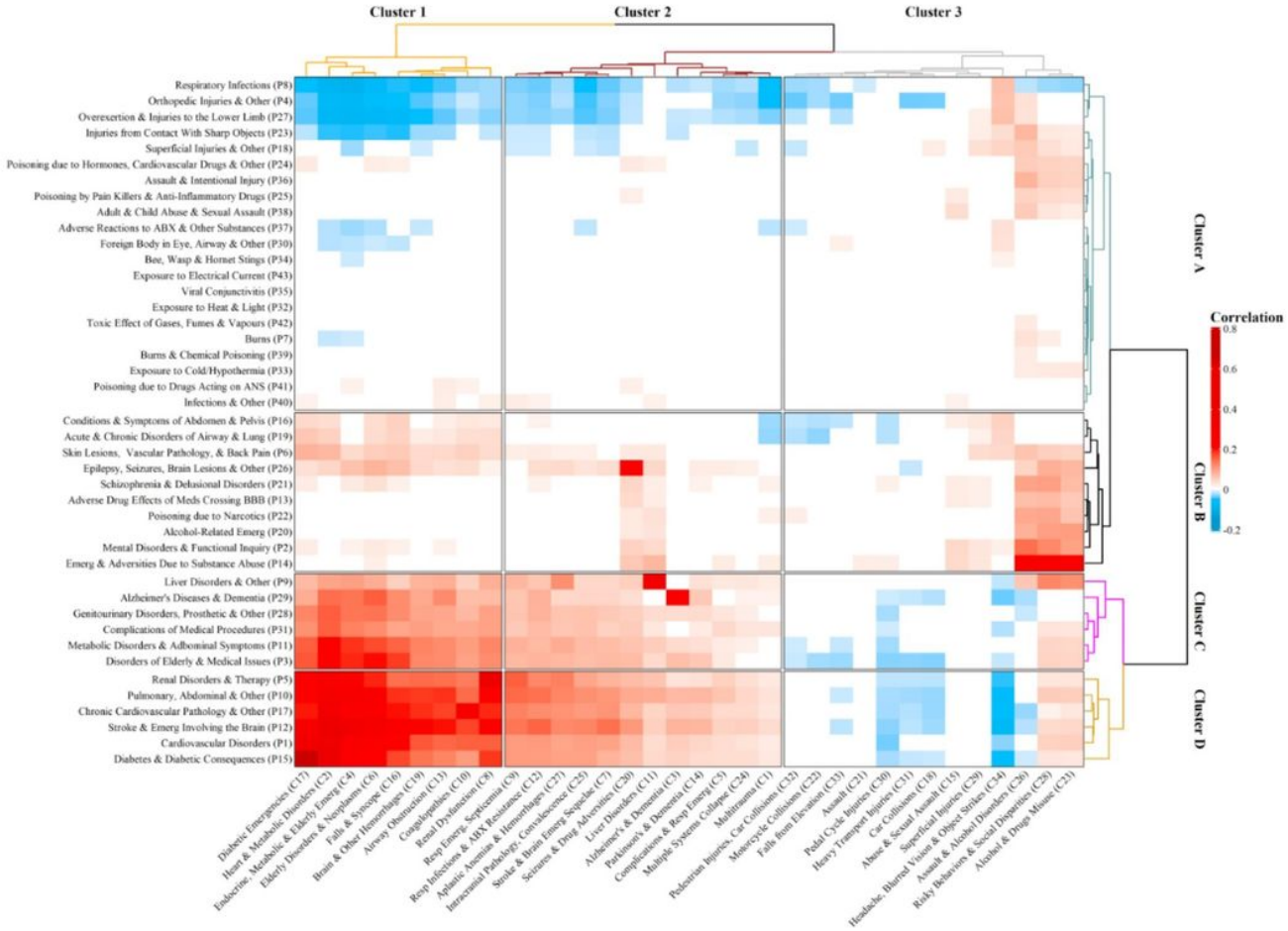

Figure 3

Cluster analysis and heatmap across 43 factors preceding TBI (y-axis) and 34 factors at the TBI event (x-axis). On the left y-axis, preceding injury-clusters (Clusters A-D) are annotated for reference with the text. On the upper x-axis, TBI event-clusters (Clusters 1-3) are likewise annotated. Annotations are presented as guidelines and are not definitive. Only factors that were internally validated in the testing and validation datasets are presented. In the heatmap, each colour represents a set of binned ranks in the heatmap, with blue colours representing negative correlations and red colours representing positive correlations, adjusted for FDR. White fields represent non-significant correlations after adjustment for FDR.

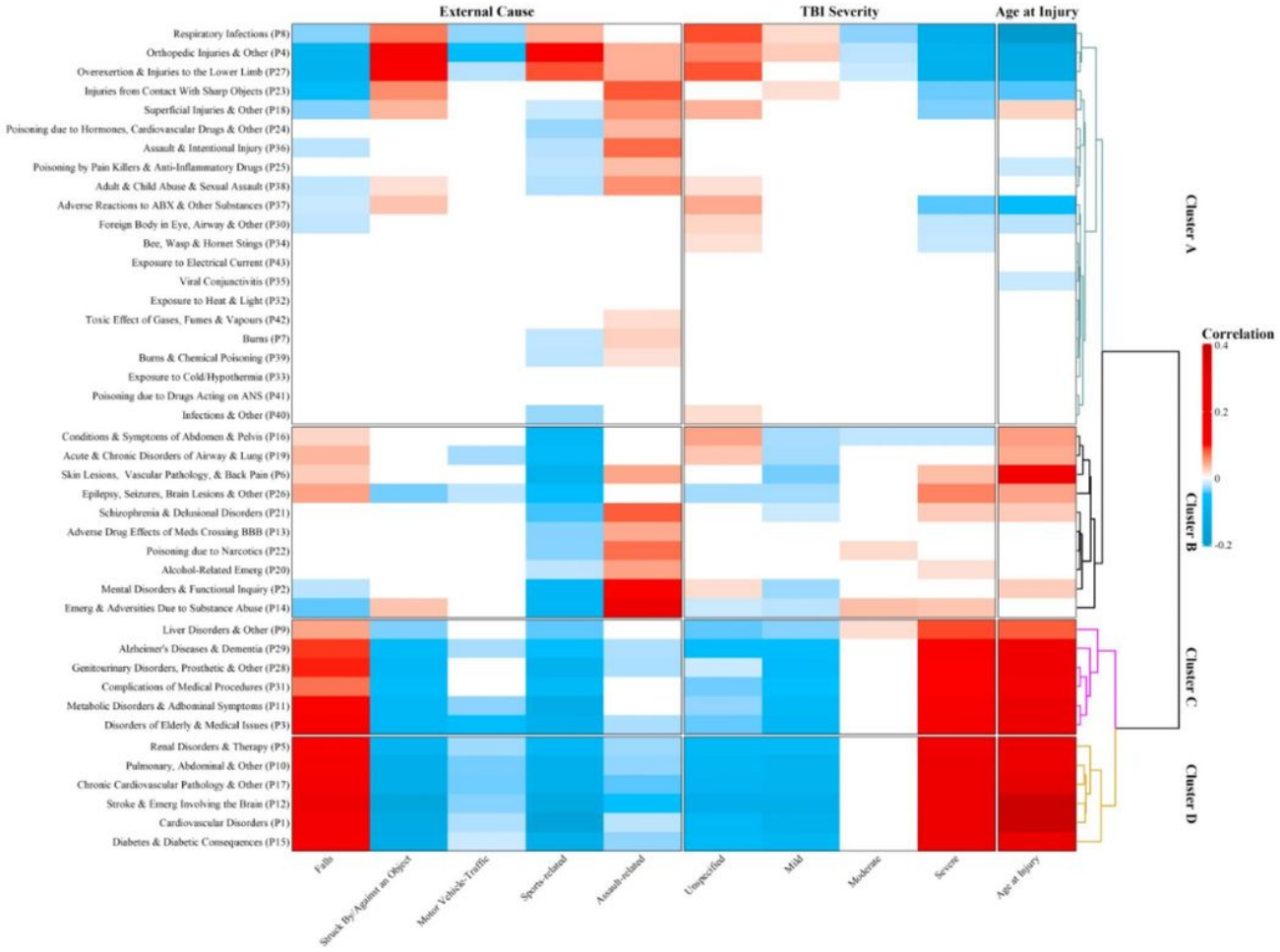

Figure 4

Cluster analysis and heatmap across 43 factors preceding TBI (y-axis) and mechanism, context of injury and TBI severity (x-axis). On the right y-axis, sample-based clusters are observed. Annotations are presented as guidelines and are not definitive. Only factors that were internally validated in the testing and validation datasets are represented. In the heatmap, each colour represents a set of binned ranks in the heatmap, with blue colours representing negative correlations and red colours representing positive correlations, adjusted for FDR. White fields represent non-significant correlations after adjustment for FDR.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary12042021.pdf