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Comorbidity in adults with traumatic brain injury and all-cause mortality: a systematic review

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ABSTRACT

Objectives Comorbidity in traumatic brain injury (TBI) has been recognised to alter the clinical course of patients and influence short-term and long-term outcomes. We synthesised the evidence on the effects of different comorbid conditions on early and late mortality post-TBI in order to (1) examine the relationship between comorbid condition(s) and all-cause mortality in TBI and (2) determine the influence of sociodemographic and clinical characteristics of patients with a TBI at baseline on all-cause mortality.

Design Systematic review.

Data sources Medline, Central, Embase, PsycINFO and bibliographies of identified articles were searched from May 1997 to January 2019.

Eligibility criteria for selecting studies Included studies met the following criteria: (1) focused on comorbidity as it related to our outcome of interest in adults (ie, ≥18 years of age) diagnosed with a TBI; (2) comorbidity was detected by any means excluding self-report; (3) reported the proportion of participants without comorbidity and (4) followed participants for any period of time.

Data extraction and synthesis Two independent reviewers extracted the data and assessed risk of bias using the Quality in Prognosis Studies tool. Data were synthesised through tabulation and qualitative description.

Results A total of 27 cohort studies were included. Among the wide range of individual comorbid conditions studied, only low blood pressure was a consistent predictors of post-TBI mortality. Other consistent predictors were traditional sociodemographic risk factors. Higher comorbidity scale, scores and the number of comorbid conditions were not consistently associated with post-TBI mortality.

Conclusions Given the high number of comorbid conditions that were examined by the single studies, research is required to further substantiate the evidence and address conflicting findings. Finally, an enhanced set of comorbidity measures that are suited for the TBI population will allow for better risk stratification to guide TBI management and treatment.

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Strengths and limitations of this study

- This systematic review is the first systematic review that investigated the relationship between comorbidity, sociodemographic and clinical characteristics and all-cause mortality in populations with traumatic brain injury (TBI).
- The Quality in Prognosis Studies tool was used to evaluate the quality of the available evidence.
- We acknowledge heterogeneity in the included studies, which demonstrate a great deal of variations in the populations studied, forms and types of comorbidities examined and the timing of mortality outcome. As such, meta-analyses were not performed.
- Further studies on the effect of comorbidity on mortality throughout the life course in patients with TBI are necessary.

INTRODUCTION

A traumatic brain injury (TBI), defined as 'an alteration in brain function or other evidence of brain pathology, caused by an external force',[1] is a major public health concern and a leading cause of death and disability across the world.[2] Globally, TBI is among the top three neurological conditions accounting for disability.[2] Specifically, approximately 50–60 million new TBI cases are estimated to occur annually.[2] Over 200 per 100 000 individuals with TBI are admitted to European hospitals each year, with an average in-hospital case fatality rate of 3%; in the USA, the average rate is 6.2%, and estimates indicate that 1%–2% of the population live with disability caused by TBI.[3] Among those who survive, injury-related physical and cognitive impairments are often lifelong. In addition to experiencing disabilities, the challenges of adjusting to changing roles and responsibilities postinjury may result in exacerbation of pre-existing conditions or expedition of the development of new disorders and clinical clusters (ie, comorbidities), including but not limited to anxiety, mood, pain and cognitive disorders, thereby increasing the associated direct and indirect medical costs.[4–6]

Comorbidity in TBI has long been recognised to alter the clinical course of patients by affecting selection of both early

and long-term healthcare services postinjury, and hence influencing short-term and long-term outcomes.[7–9] Recent timely initiatives have recommended that an assessment of comorbidities be included among the TBI population, which is extremely important, as the presence of comorbidity or multiple comorbidities in patients with TBI is common and has shown to be associated with all-cause mortality.[10–13] In addition to comorbidities, advanced age and male sex have also been found to be associated with elevated TBI-related mortality rates.[14 15] While a number of previous research studies have highlighted the types and number of comorbidities among patients with TBI,[10] there remains a paucity of evidence synthesis on the effects of different comorbid conditions on early and late mortality post-TBI, taking into account distribution of comorbidity across the age span and among sexes.

To address the highlighted research gaps, the primary objective of this systematic review was to: (1) examine the relationship between comorbid condition(s) and all-cause mortality in TBI and (2) determine the influence of sociodemographic and clinical characteristics of patients with a TBI at baseline on the development of adverse or beneficial outcome (ie, mortality or survivorship) across time.

METHODS

The systematic review was conducted based on a previously peer-reviewed protocol registered with the International Prospective Register of Systematic Reviews and published in an open access journal.[16] The presentation of the findings was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.[17]

Search strategy

Due to the extensive number of studies identified within the searched databases, shifts in clinical classifications and TBI definitions during the past 20 years, and the limited empirical evidence regarding the impact of searching and inclusion of earlier works on systematic review findings,[18] our search for relevant articles covered publication period from May 1997 to January 2019 within the following databases:

1. MEDLINE (including Medline in Process and other non-indexed citations, ePubs and Medline Daily).
2. Embase.
3. Cochrane Central Register of Controlled Trials.
4. PsycINFO.

Please see published protocol and online supplementary file 1 for specifics on data searches and MeSH (Medical Subject Headings) terms used.[16]

Inclusion and exclusion criteria

Studies that were included met the following criteria: (1) focused on comorbidity as it related to our outcome of interest in adults (ie, ≥18 years of age) diagnosed with a TBI on the basis of predefined definitions within the study; (2) comorbidity was detected by any means excluding self-report; (3) reported the proportion of participants without comorbidity and (4) followed participants for any period of time. Studies that fell into either of the following categories were excluded: (1) evaluated children or adolescents (ie, <18 years of age), (2) >50% of participants had pre-existing TBIs or severe comorbidity at baseline assessment and the subgroup with incident comorbidity could not be extracted independent of pre-existing cases. Furthermore, the following study designs/formats were excluded: letters to editors, reviews without data, case reports or public reports, conference abstracts articles with no primary data, studies that focus on therapeutic interventions and theses.

Data extraction: selection and coding

Two researchers (CX and SH) independently screened study titles and/or abstracts and reviewed full texts of manuscripts to determine fulfilment of the inclusion criteria. Discrepancies in opinion were resolved through discussion with a third researcher (TM). A previously developed standardised form was used to assess study quality and synthesise study results from the included articles.[19] Extracted information included the following: (1) study design, (2) study setting, (3) information of the study population and baseline characteristics, (4) attrition rates, (5) details of the definition(s) of TBI and comorbidity, (6) definition of outcome and timing of measurements, (7) the statistical approach used, (8) predictor variables included in the statistical model and (9) information for the assessment of the risk of bias. Two reviewers (CX and SH) extracted the data independently, and third reviewer (TM) directed the process, reviewed the quality of data extraction, and mediated a resolution in cases of disagreement by performing a separate assessment, and through follow-up discussions with two reviewers.

Risk of bias (quality) assessment

The quality of each study was evaluated independently by two reviewers (CX and SH) using the Quality in Prognosis Studies tool to assess risk of bias in studies of prognostic factors.[20] The assessment of each study quality consisted of the following steps: (1) assessment of seven categories of potential bias sources, including study participation, study design, study attrition, prognostic factor, outcome measurements, confounding measurement and account, as well as, analyses; (2) grading the presence of potential biases in each category as 'yes,' 'partly,' 'no,' or 'unsure' and (3) summarising the overall level of potential bias for each study where '++' was assigned when all seven quality criteria were fulfilled (allowing one 'partly' in each bias category); '+' was assigned when four to six criteria were fulfilled; '−' was assigned when fewer than four criteria were fulfilled (ie, at least one 'yes' in each category). A retrospective cohort study design is weaker than a prospective, and therefore, '++' rating (if achieved) was degraded to '+'. Studies assigned '++' were referred to as 'high-quality studies',

studies assigned '+' were referred to as 'moderate quality studies" and studies assigned '-' were referred to as 'low-quality studies'. Details on the process of quality assessment are presented in online supplementary tables 1 and 2. Disagreements between the two reviewers were mediated by a third reviewer (TM), who assessed the study's quality independent of the two reviewers and followed up with a discussion.

Data synthesis

The included studies were synthesised through tabulation and qualitative description.[21] There was a plan to investigate the pooled effect on our outcome of interest for each group of comorbid disorders (a meta-analytical component of this review), if the data permitted. However, the high heterogeneity among the included studies, concerning study methodology (design-prospective and retrospective cohort), method of assessment of comorbidity, duration of follow-up, etc), population (age, sex, TBI severity, comorbidity type and severity and medication regimen, etc), as well as study settings (acute care, rehabilitation and community) ruled out meta-analysis.

Patient and public involvement

Patients and the public were not involved in this review.

RESULTS

The searches yielded a total of 11 396 records, from which 9100 records remained after the duplicates were removed. Of the 9100 records, 179 met the criteria for a full-text screen, of which 65 studies were included for the quality assessment. 38 of the studies were of 'low' quality and were excluded. Reasons for study exclusion with specific risk of biases are reported in online supplementary table 2. These studies were penalised because of biases on multiple levels, four or more out of seven criteria of biases. A total of 27[22–48] studies, all of 'moderate' quality, were included for data analysis (figure 1).

Study characteristics

A summary of the included studies is presented in Table 1, online supplementary tables 3 and 4. Among the 27 studies, 14 were population based[23 25 26 28 29 33–37 40 41 44 45] and 13 were clinical studies.[22 24 27 30–32 38 39 42 43 46–48] Of the 14 population-based studies, all but one used a retrospective cohort design.[29] Of the 13 clinical studies, four used a prospective cohort methodology[22 27 39 43] and nine used a retrospective cohort methodology.[24 30–32 38 42 46] With respect to TBI severity, 10 studies included patients of all TBI severities,[29 32 33 35–37 39 41 43 46] six studies included moderate and severe TBI cases,[24 30 38 45 47 48] and one study included patients with mild TBI.[22] The

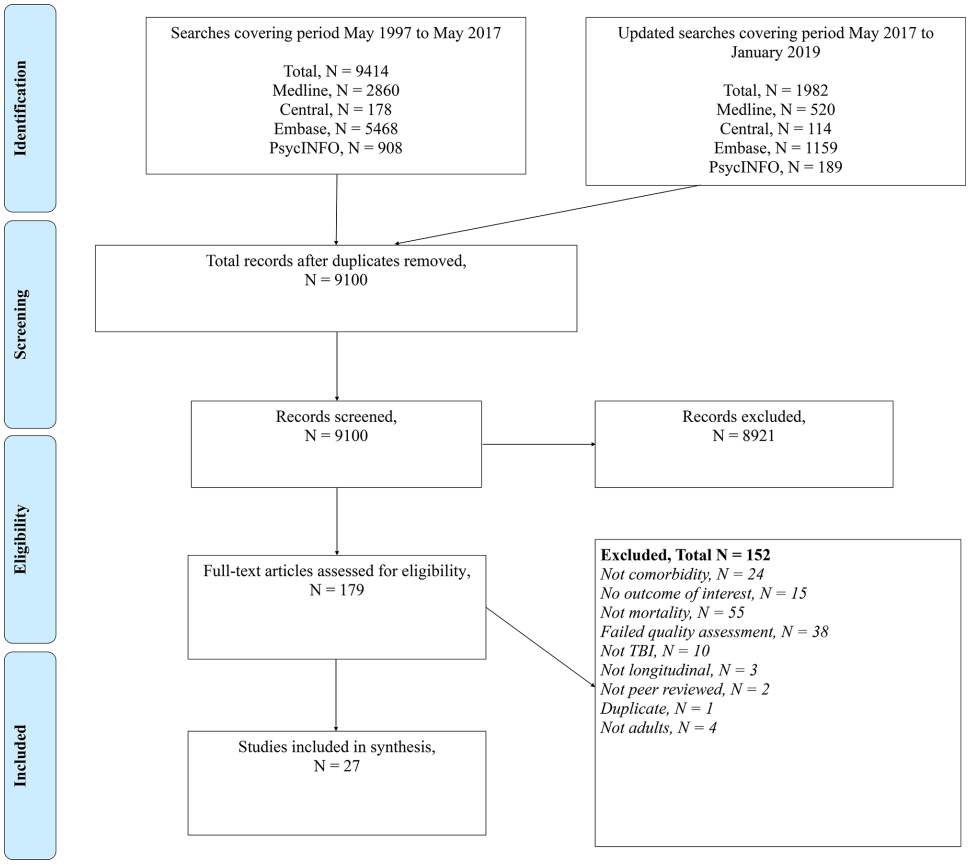

Figure 1 PRISMA diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TBI, traumatic brain injury.

Table 1 Findings of all included studies

AuthorDateCountrySample byDesignInclusion criteria (IC)Exclusion criteria (EC)	PopulationSample sizeAge (mean (SD), range), yrsSex (%M)Time since injury (TSI) Injury severity (IS)±SD	Follow-up periodAssessment time points/N assessed	Comorbidity definition Measurement used/ assessment criteria Frequencies (%), scores (mean±SD, median Q_3-Q_1)	Outcome definitionSources	Analyses MethodologyResultsAdjusted	Adjustment NotesLimitations
Ahmadi *et al*[22] 2015USAProspective longitudinalClinicalIC: Veterans w alteration in mental state; GCS score≥12; LOS≤30 mins; PTA≤24 hours; no CT abnormality; no lesions/trauma-related neurologic, psychosomatic deficitEC: Subjects w CAD, schizophrenia, mood, substance abuse, other mental Ds	mTBI n=85Age: 58±9Sex: 100% MTSI: NRIS: Mild	Mean±SD: 31±14mosNR	**CAC**, marker of atherosclerotic burdenDual-source 64-slice CTCAC, density of>130 HU CAC score: 199 (18-590)**PTSD,** based on DSM IV codes,PCL-M, CAPSmTBI: 36.5%	**CV mortality**Social Security Death Index, primary care physician, VHA EMR	**RR (95% CI); all p<0.005** *CV mortality compared to controls, subj w/out TBI:* CAC 1–100: 2.25 (1.93–2.63CAC 101–400: 4.93 (4.33–5.61CAC 400+:7.06 (6.24–7.97) *Other models:*TBI: 2.89 (2.69–3.11TBI & PTSD: 3.41 (2.01–5.68TBI & CAC: 3.53 (2.85–6.57TBI & PTSD & CAC: 5.01 (4.12–7.72)	Age; gender; DM; HPT; HCl; family history of CHD; smoking status; PTSD**RR (95% CI)** NRNote: mTBI is a predictor of presence & sev. of CAC (p<0.01)Limitations: only males/veterans, baseline assessment post-TBI NR
Aiolfi *et al*[48] 2017USARetrospective longitudinalClinicalIC: adult patients (≥16 years old); severe blunt TBI; meet BTF criteria for ICP monitoring EC: transferred from other hospitals; dead on arrival	N=13 188Median age (IQR): 52 (32-71)Sex: 71.1% MTSI: NRISAIS$_{head}$ 3: 11.2%AIS$_{head}$ 4: 35.5%AIS$_{head}$ 5: 53.4%	Duration: 30 dNR	**Presence of any comorbidity** NR**Hypotension** Systolic BP<90 mmHgPresence of any comorbidity: 49.3%Hypotension: 3.4%	**All-cause in-hospital mortality** TQIP database	Multivariate logistic regression**OR (95% CI)** Overall comorbidities: 1.042 (0.952–1.14); p=0.374Hypotension: 2.336 (1.877–2.906); p<0.001	Age, gender, race, injury mech, AIS, ICP placement**OR (95% CI); all p<0.05 unless NS** Age≥65 years: 2.895 (2.621–3.198)Gender (ref: F): NSRace (ref: except white): NSFall: 1.645 (1.456–1.859)MVC: NSAIS (ref: 3)4: 2.063 (1.621–2.625)5: 13.728 (10.913–17.269)Limitations: usual limitations of data-bank based studies
Baguley *et al*[45] 2012AustraliaRetrospective longitudinalPopulation-basedIC: age 16–70 at time of injury; TBI; primary BIRP admission; discharged aliveEC: secondary admissions	N=2545Age: 35±14Sex: 81% MTSI: NRIS: GCS Score<9; PTA length>1 day	Median: 9.3 years; IQR, 7.4 years; Range, 2.0–19.5 yrsNRR	Hx of **epilepsy**, **psychiatric ds**, **alcohol/ drug misuse**Recorded psychiatric admission, medications, psychologist/psychiatrist, drug/alcohol referral or a record of units/ dayEpilepsy: 3%Psychiatric Ds: 15%Alcohol/ drug misuse: 29%	**All-cause mortality** NDI and NCIS	Cox regression model**HR (95% CI)**Epilepsy: 2.11 (1.35–3.3); p=0.001Alcohol/drug misuse: 2.39 (1.1–2.91); p<0.001	Sex; age; discharge destination, admission and discharge FIM scores; occurrence of aspiration pneumonia; LOS**HR (95% CI); all p<0.05 unless NS** Sex (ref: F): 2.24 (1.38–3.62)Age (ref: 16–20)21–25: NS26–35: NS36–45: 2.01 (1.07–3.8)≥46: 3.25 (1.80–5.87)Limitations: only more severe TBI
Bosarge *et al*[24] 2015USARetrospective longitudinalClinicalIC: HbA and admission glucose levels; Head AIS>3EC: GCS>8	N=626Age: NDN: 38.6±18.6DN: 59.1±13.2SIH: 37.9±18.3 DH: 59.2±16.2Sex: NDN: 76.7% MDN: 38.5% M SIH: 73.0% M DH: 75.0% MTSI: NRIS: ISS NDN: 28.9±11.7DN: 30.5±15.4SIH: 34.4±14.3DH: 30.5±14.9	Median (IQR): NDN, 11 (2-22) d; DN, 13 (10-22) d; SIH, 3.5(1-21) d; DH, 6.5 (1–29) dNR	**Hyperglycemia** Serum glucose≥200 mg/dL DM: Hx;≥6.5% Hb1AcDH: glucose≥200 mg/dL in pts w DMSIH: absence of DM; glucose≥200 mg/dL NDN: 68.5%DN: 2.1%SIH: 24.3%DH: 5.1%	**All-cause mortality** Trauma registry	Cox regression model**HR (95% CI)** NDN: 0.67 (0.51–0.88)DN: 0.27 (0.07–1.12) DH: 0.63 (0.37–1.08)SIH: Ref	Age; sex; ISS; RTS; lactic acid>2.5 mmol/ L**HR (95% CI)** NRLimitations: no causative relationship btw hyperglycemia and mortality; SIH and DH not mutually exclusive

Continued

Table 1 Continued

Author Date Country Sample by Design Inclusion criteria (IC) Exclusion criteria (EC)	Population Sample size Age (mean (SD), range), yrs Sex (%M) Time since injury (TSI) Injury severity (IS)±SD	Follow-up period Assessment time points/N assessed	Comorbidity definition Measurement used/ assessment criteria Frequencies (%), scores (mean±SD, median Q_3-Q_1)	Outcome definition Sources	Analyses Methodology Results Adjusted	Adjustment Notes Limitations
Brandel *et al*[23] 2017 USA Population-based Retrospective longitudinal IC: tSDH EC: cSDH	OSHPDN=51 429 Age: 67.63±21.4 Sex: 58.74% MNISN=137 125 Age: 68.97±19.34 Sex: 56.62% MTSI: NRIS: NR	NR	**Psychiatric dx,drug/substance use/ abuse** ICD-9 codes **CCI** OSHPD Depression: 8% Bipolar ds: 0.87% Psychosis: 0.98% Schizophrenia: 0.87% Anxiety: 1.93% CCI>0: 49.69% NIS Depression: 7.86% Bipolar Ds: 0.99% Psychosis: 0.98% Schizophrenia: 0.83% Anxiety: 2.34% CCI>0: 48.05%	**All-cause in-hospital mortality** OSHPD discharge disposition codes; HCUP codes	Multivariate logistic regression **OR (95% CI); all p<0.05 unless NS** *OSHPD* Depression: 0.64 (0.52–0.78) Bipolar ds: 0.45 (0.21–1) Psychosis: NS Schizophrenia: NS Anxiety: 0.37 (0.21–0.65) Alc. abuse: 0.65 (0.49–0.86) Tobacco abuse: 0.64 (0.48–0.85) Depressant, stimulant, cannabis abuses: all NS Alc. dependence: 0.47 (0.29–0.77) Depressant, stimulant, cannabis dependence: all NS CCI=1: 1.27 (1.12–1.44) CCI=2: 1.44 (1.24–1.68) CCI=3: 1.67 (1.4–2) CCI=4: 1.97 (1.57–2.48) CCI=5: 1.86 (1.36–2.56) CCI=6: 2.87 (2.29–3.6) *NIS* Depression: 0.61 (0.51–0.72) Bipolar ds: NS Psychosis: 0.38 (0.2–0.7) Schizophrenia: NS Anxiety: 0.5 (0.35–0.72) Alc. Abuse: 0.77 (0.63–0.94) Tobacco abuse: 0.61 (0.49–0.75) Depressant, stimulant, cannabis abuses: all NS Alc. dependence: 0.6 (0.4–0.91) Depressant, stimulant dependence: both NS CCI=1: 1.18 (1.07–1.3) CCI=2: 1.44 (1.27–1.63) CCI=3: 1.69 (1.44–1.99) CCI=4: 2.2 (1.76–2.75) CCI=5: 2.13 (1.46–3.11) CCI=6: 3.8 (3.1–4.66)	Race; sex; age; insurance status; hospital region & setting; survival risk ratios; admission from LTC; craniotomy; LOC duration; yr of hospitalization; mech of injury; no. of ds; prior psychiatric history **OR (95% CI); all p<0.05 unless NS** *OSHPD* Age: 1.04 (1.04–1.04) Sex (F): 1.1 (1.02–1.18) Injury mech (ref: Unknown) Fall; MVA; misc: all NS LOC (ref: none/brief) Prolonged, return to normal: 2.65 (1.8–3.91) Unspecified/prolonged; w/o return to normal: NS Race (ref: White) Black; Hispanic; Asian/Pacific Islander; American India/Alaska Native: all NS Insurance status (ref: Medicare/private) Medicaid; uninsured: all NS *NIS* Age: 1.02 (1.02–1.03) Sex (F): 0.77 (0.71–0.83) Injury mech (ref: Unknown) Fall: 0.57 (0.49–0.67) MVA: 1.22 (1.08–1.38) Misc: 0.48 (0.35–0.65) LOC (ref: none/brief) Prolonged, return to normal: 1.6 (1.23–2.1) Unspecified/prolonged; w/o return to normal: 1.71 (1.54–1.88) Race (ref: White) Black: 0.85 (0.73–1) Hispanic: 0.77 (0.66–0.89) Asian/Pacific Islander; American India/Alaska Native; Other: All NS Insurance status (ref: Medicare/private) Medicaid: NS Hospital location (ref: rural) Urban: NS Limitations: lack of clinical data Note: mental illness may be over diagnosed in acute care or unrecognized in unconscious TBI pts
Cheng *et al*[25] 2015 Taiwan Retrospective longitudinal Population-based matched case-control IC: 20–80 years old; TBI surgery, LCEC: NR	N=7296 Age TBI w LC, 54.42±12.78 TBI w/o LC: 54.59±13.49 Sex: TBI w LC, 83.51% MTBI w/o LC, 83.8% MTSI: NRIS: NR	Mean: 1 year NR	**LC (alc., non-alc., coexistence);** ICD-9 codes 1 year look-back window LC: 25% Alc. LC: 16.9% Non-alc. liver: 60.8% Coexistence LC: 22.3%	**1 year all-cause mortality** NHIRD	Cox regression model **HR (95% CI), all p<0.05** LC (all): 1.75 (1.61–1.9) Alc. LC: Ref Non Alc.: 1.24 (1.04–1.48) Coexistence: 1.51 (1.25–1.83) **Approx. % increase in 1 year mortality, all p<0.05 unless NS** LC+HF: 7% LC+HPT: −5% LC+renal failure: 21% LC+DM; LC+MI; LC+stroke: all NS	Age; gender; length of ICU classification; length of ventilation; HPT; DM; MI; stroke; HF; renal diseases; HBV; HCV **HR (95% CI), all p<0.05 unless NS** Age (ref: 20–35) 35–50: 1.32 (1.06–1.64) 50–65: 1.65 (1.32–2.05) 65–80: 2.1 (1.67–2.63) Gender (ref: M): NS Limitations: only included TBI pts who underwent surgery
Colantonio *et al*[26] 2008 Canada Retrospective longitudinal Population-based IC:>15 years old; ICD-9 codes for head injury EC: NR	N=2721 Age: mean NR Sex: 70.9% MTSI: NRIS: AIS<3: 38.1% AIS=3: 28.1% AIS>3: 33.8%	Mean: 1 year NR	**Comorbid conditions (mental health & other dx)** Discharge abstract codes from OTR 0 comorbidity: 79.6% 1 comorbidity: 13.7% 2 comorbidities: 6.7% Psychiatric comorbidity: 8.1%	**1 year all-cause post-acute mortality** RPDB	Poisson multivariate model **RR (95% CI), p<0.0001** 0 comorbidity: Ref 1 comorbidity: 1.27 (1.01–1.6 ≥2 comorbidities: 2.08 (1.61–2.68)	Age; maximum head AIS; injury mechanism; discharge status **RR (95% CI), all p<0.05** Age (ref: 15–19) 20–24: 0.25 (0.08–0.79) 25–29: 0.55 (0.24–1.24) 30–34: 0.7 (0.33–1.5) 35–39: 0.61 (0.3–1.25) 40–44: 0.66 (0.33–1.31) 45–49: 0.43 (0.21–0.86) 50–54: 0.28 (0.14–0.57) 55–59: 0.23 (0.12–0.46) 60–64: 0.33 (0.17–0.62) 65–69: 0.26 (0.14–0.49) 70–74: 0.17 (0.09–0.32) 75–79: 0.25 (0.13–0.46) 80–84: 0.22 (0.12–0.41) 85–89: 0.14 (0.07–0.27) 90+: 0.22 (0.1–0.49) Max AIS (ref: 1, 2 or 3) 4 or 5: 1.37 (1.14–1.64) Injury mech. (ref: MVC) Fall: 1.33 (1.09–1.64) Other: 1.36 (0.98–1.91) Note: variables not significant in univariate analyses not included in multivariate model Limitations: No GCS or functional measures
Dams O Connor *et al*[27] 2016 USA Prospective longitudinal Clinical IC:≥65 years old; no prior TBI w LOC; no dementia EC: NR	N=76 Age: 75.3±6.5 Sex: 32% MTSI: NRIS: Saw doctor: 81% LOC≥10 mins: 16% Hospitalized≥1 night: 33%	Average (range): 7.5 (1–18) yrs Every 2 years	**Medical conditions; alc. problems** Self-reported CD: 14%	**All-cause mortality** Follow-up visits	Multivariate model **HR (95% CI)** CD: 2.4 (1.21–4.75); p=0.01	Age; education; sex; ADL score Notes: Other comorbid variables not mentioned in multivariate model Limitations: no TBI w/o LOC; no younger adults

Continued

Table 1 Continued

AuthorDateCountrySample byDesignInclusion criteria (IC)Exclusion criteria (EC)	PopulationSample sizeAge (mean (SD), range), yrsSex (%M)Time since injury (TSI) Injury severity (IS)±SD	Follow-up periodAssessment time points/N assessed	Comorbidity definition Measurement used/ assessment criteria Frequencies (%), scores (mean±SD, median Q_3-Q_1)	Outcome definitionSources	Analyses MethodologyResultsAdjusted	Adjustment NotesLimitations
Donohue *et al*[28] 2007USARetrospective longitudinalPopulation-basedIC:≥65 years old; admitted for 1st time head injury in 1999EC: NR	N=21 044Age:≥65Sex: 47.3%TSI: NRIS: AIS max≥3	NRt_1: At discharget_2: 30 d p/d t_3: 6 mos p/dt_4: 1 yr p/d	**CCI** Injury discharge recordCCI=0: 59%CCI=1: 27.1%CCI=2: 9.4%CCI≥3: 4.5%	**1 year all-cause mortality** Medicare provider analysis and review and denominator files	Logistic regression model **OR (95% CI)** CCI=0: refCCI=1: 1.32 (1.23–1.42)CCI=2: 2.03 (1.83–2.25)CCI≥3: 3.5 (3.04–4.03)	Sex; age; AIS max; prolonged LOC**OR (95% CI)** Age (ref: 65–74)75–84: 1.75 (1.61–1.9)85+: 3.59 (3.29–3.92)Sex (ref: F): 1.32 (1.24–1.41)AISmax (ref: 3)4: 1.29 (1.21–1.38)5: 11.94 (8.89–16.11)Prolonged LOC: 1.48 (1.14–1.93)Limitations: NR
Griesdale *et al*[38] 2009CanadaRetrospective longitudinalClinicalIC: severe TBI (GCS≤8)EC: died win 12 hours; non-traumatic etiology; high cervical spine injury	N=170Age: 38±16.9Sex: 77.6% MTSI: NRIS: APACHE II: 23.4±4.7Median best GCS in 12 hours (IQR): 6 (5–7)	Median (IQR): 39 (18-58) dNR	**SIH** Serum glucose≥200 mg/dL or 11.1 mmol/L**Hypoglycemia** Serum glucose≤80 mg/dL or 4.4 mmol/L ≥1 hyperglycemia event: 64.7%≥1 hypoglycemia event: 48.2%	**All-cause in-hospital mortality** ICU database	Multivariable logistic regression **OR (95% CI)** Hypoglycemia: NSSIH: 3.6 (1.2–11.2); p=0.02	Age; APACHE II score; GCS; admission yr; craniotomy; ext ventricular drain; mannitol; systolic BP<90 mmHg or arterial PPO<70 mmHg; increase intracranial pressure; mean morning glucose**OR (95% CI)** NRLimitations: residual confoundingNote: not overlook effects of hypoglycemic events on brain
Harrison-Felix *et al*[29] 2012USAProspective longitudinalPopulation -basedIC: mild to severe TBI;≥16 years old; present in acute care<72 hrs p/i; receive both acute care and rehab in TBIMS centres; provide consentEC: NR	N=8573Age: 39±18.4Sex: 73.8% MTSI: NRIS: GCS: 9.4±4.5LOC: 8.5±14.1 dPTA: 33.9±34 d	Median (range): NR (1d – 20.3 years) after inpatient rehab dischargeNR	**Pre-injury drug use; SCI** Measurement; frequencies; scores: NR	**All-cause mortality** Death certificate; SSDI	Cox regression model **RR (95% CI)** SCI: 0.48 (0.26 to 0.88)Pre-injury drug use: 1.33 (1.04–1.7)	Age; sex; race; marital status; employment status; yr of injury; injury cause; LOC d; FIM & DRS scores at rehab discharge**RR (95% CI)** Age at injury: 1.04 (1.04–1.05)Sex (ref: M): 0.59 (0.48–0.72)Race (ref: White)Hispanic: 0.51 (0.33–0.81)Other: 0.87 (0.36–2.13) Black; Asian: all NSMarital status (ref: married)Divorced/widowed: 1.35 (1.11–1.64)Never married: NSEmployment status (ref: competitively employed) Unemployed: 1.52 (1.15–2.01)Retired: 1.72 (1.34–2.21)Other: 2.14 (1.5–3.07)Student: NSInjury mech. (ref: vehicular)Falls: 1.65 (1.33–2.05)Violence: 1.47 (1.11–1.95) Pedestrian; sports; other: all NSDays of unconsciousness: 0.99 (0.98–0.99) Limitations: only included pts in inpatient rehab
Han *et al*[46] 2017KoreaRetrospective longitudinalClinicalIC: traumatic acute SDHEC: non-surgical; surgery performed>48 hrs p/i;<15 years old;>65 years old	N=318Age: 47.8±12.7Sex: 75.5% MTSI: NR IS: GCS: 7.77±1.8	Duration: 30 dNR	**Diabetes** Use of antidiabetic medications; medical records**HPT** Use of anti-HPT medications; medical records**Smoking; drinking** Former and current smokers/drinkers**SIH** Glucose>200 mg/L; absence of diabetes or diabetic medicationFrequencies; scores: NR	**30 d in-hospital mortality** Medical charts	Cox regression model **HR (95% CI)** Diabetes: 2.28 (1.2–4.32); p<0.05SIH: 1.55 (0.86–2.78); p=0.145	Age; gender; midline shift; GCS; tSAH; TICH; IVH; EDH; skull fracture; bilateral acute SDH; re-operation; antithrombotics use**HR (95% CI), p<0.05 unless NS** Age (per 1 year increase): NSGender (ref: M): NSGCS (per 1 increase): 0.59 (0.52–0.68)Limitations: only 2 hospitals; no Hb1Ac to determine diabetes
Jovanovic *et al*[39] 2016SerbiaProspective longitudinalClinicalIC: all pts in ICU in 2013; TBI (isolated or w≥1 extracranial injury and required MV)EC:<18 years old; gastric aspiration; previous antibiotic therapy; recent hospitalization; nursing home/extended care residence; home therapy; malignancy	N=177Median age (IQR): 50 (37)Sex: 80.2% MTSI: NRIS: median (IQR)APACHE II: 15 (9)GCS: 8 (6)ISS: 20 (20)AIS_{head}≥3: 67.2%AIS_{face}≥3: 25.4%AIS_{thorax}≥3: 22%$AIS_{abdomen}$≥3: 9%$AIS_{extremity/pelvis}$≥3: 24.3%AIS_{spine}≥3: 2.3%	Duration: 28 dNR	**No. of comorbidities; cardiac disease** Measurement: NR0 comorbidity: 53.7%1 comorbidity: 28.2%2 comorbidities: 10.7% ≥3 comorbidities: 7.3%Cardiac disease: 28.2%	**28 d all-cause mortality** Medical documents	Logistic regression**OR (95% CI)** Comorbidities : NSCardiac disease: NS	Age; sex; GCS; Rotterdam CT score; type and no. of injuries; injured body regions; AIS; ISS; APACHE II**OR (95% CI)** NRLimitations: NR
Liao *et al*[40] 2012TaiwanRetrospective longitudinalPopulation-basedIC: TBI btw 2005-2008EC: NR	N=16 635Age: NRSex: 55.1% MTSI: NRIS: NR	NR	**Mental ds** ICD-9-CM codes**HPT; diabetes; ischaemic heart disease; HLD; stroke; epilepsy; renal dialysis** Measurement: NRMental Ds: 32.84%HPT: 22.5%Diabetes: 10.6%Ischaemic heart disease: 8.7%HLD: 5.7%Stroke: 5.9%Epilepsy: 2.3%Renal dialysis: 0.3%	**All-cause in-hospital mortality** NHIRD	Multivariate logistic regression **OR (95% CI)** Mental ds: 1.15 (0.95–1.4)Stroke: 1.39 (1.06–1.82)Renal dialysis: 5.62 (3.55–8.9) Ischaemic heart disease: 1.06 (0.82–1.37) HPT: 0.87 (0.7–1.08)Diabetes: 1.31 (1.04–1.66)HLD: 0.86 (0.6–1.22)Epilepsy: 1.14 (0.65–1.99)	Age; sex; urban residence; low income status; **OR (95% CI), p<0.05 unless NS** Age (ref: 20–29)30–39: 1.51 (0.9–2.54)40–49: 2.41 (1.51–3.84)50–59: 3.71 (2.37–5.8)60–69: 4.37 (2.74–6.99)≥70: 13.3 (8.75–20.2)Sex (ref: F): 2.02 (1.65–2.47) Urbanization (ref: low)Moderate; high; very high: all NSLimitations: suicide not included; underestimate mental Ds

Continued

Table 1 Continued

AuthorDateCountrySample byDesignInclusion criteria (IC)Exclusion criteria (EC)	PopulationSample sizeAge (mean (SD), range), yrsSex (%M)Time since injury (TSI) Injury severity (IS)±SD	Follow-up periodAssessment time points/N assessed	Comorbidity definition Measurement used/ assessment criteria Frequencies (%), scores (mean±SD, median Q_3-Q_1)	Outcome definitionSources	Analyses MethodologyResultsAdjusted	Adjustment NotesLimitations
Marino *et al*[30] 2006ItalyRetrospective longitudinalClinicalIC: ICP monitoring;>48 hours ICU stay;>14 years old; GCS<12; clinical/radiologic documentationEC: NR	N=89AgeNo cerebral infarct: 34.4±17.7Cerebral infarct: 34.2±17.2SexNo cerebral infarct: 83.3% MCerebral infarction: 88.2% MTSI: NRIS: median (IQRNo cerebral infarct GCS: 7 (5–7)Cerebral infarct: 7 (4–8) No cerebral infarct ISS: 26 (20-30)Cerebral infarct ISS: 25 (20–29.5)SAPS II No cerebral infarct: 30.87±9.1Cerebral infarct: 36.4±10.7	Mean±SDNo cerebral infarct: 17.2±5 dCerebral Infarct: 16.8±6.9 dNR	**Cerebral Infarction** Dx using criteria from neuropathologic studies Cerebral infarct: 19.1%	**ICU all-cause mortality** Medical records	Multivariate logistic regression **OR (95% CI); p<0.05** Cerebral infarction: NS	Age; GCS; Admission brain CT (Marshall scale); pupillary light reflex; intracranial HPT; cerebral hypoperfusion; systolic hypotension**OR (95% CI), p<0.05 unless NS** GCS score: 0.76 (0.57–1.02)Age: all NSNote: other clinically relevant variables in model not specifiedLimitations: small sample size; overfitting
Nguyen *et al*[31] 2014USARetrospective longitudinalClinicalIC: TBI; urine toxicology screenEC:<15 years old; died; DNR or wdrawn care≤24 hours of admission	N=446Age: 49.4±21.7Sex: 78.3% MTSI: NRISISS: 20.8±10.9AIS_{head}≥4: 53.4%	NR	**THC exposure** Toxicology screenTHC(+) defined as>50 ng/mLTHC(+): 18.4%	**All-cause mortality** Medical records	Multivariate logistic regression **OR (95% CI)** THC(+): 0.224 (0.051–0.991); p<0.05	Age; gender; AIS; injury mechanism; ethnicity; alc.; ISS**OR (95% CI), p<0.05 unless NR** Age≥45: 2.17 (1–4.4)AIS head≥4: 10.9 (3.8–31.3)Other variables NRLimitations: positive screen does not correlate w active/chronic drug use
Peck *et al*[32] 2014USARetrospective longitudinal ClinicalIC: acute ICHEC: transferred from another hospital; preinjury anticoagulant/antiplatelet agent therapy status unknown	N=322AgeP/d death: 80.2±10.8Survivors: 74.2±11.8SexP/d death: 41.3%MSurvivors: 51.7%MTSI: NRISP/d death GCS: 14±2.1Survivors GCS: 14±2.3P/d death ISS: 18±5.8Survivors ISS: 18±6.1	Median (IQR)P/d deaths: 149 (26-505) dSurvivors: 410 (160-845) dNR	**Charlson comorbidities** ICD-9-CM codesP/d deaths: 1.59±1.95Survivors: 0.76±1.23	**P/d all-cause mortality** California Death Statistical Master File; County of San Diego Office of Vital Records and Statistics death certificate registry	Cox regression model **HR (95% CI)** Charlson comorbidity count: 1.98 (1.48–2.69); p<0.001	Age; preinjury coagulants; discharge condition; discharge equivalence**HR (95% CI), p<0.05 unless NS** Admission age: 1.04 (1.01–1.06)Note: sex not included as NS in univariate analysisLimitations: specific comorbid conditions not examined
Scheetz[33] 2015USARetrospective longitudinalPopulation-basedIC:>65 years old; same level fall; TBIEC: treated and discharged from ED	N=3331Age: 81.1±8.1Sex: 47.4%MTSI: NRISMild: 3.5%Moderate-severe: 74.5%Undetermined: 5.9%Not classified: 16.1%	Mean duration: 6.1 dNR	**Chronic diseases** Diseases present>12 mos; places limits on self-care, independent living and social interactions; need healthcare resourcesNo. of chronic conditions: 4.5±2.2	**In-hospital all-cause mortality** New York State Inpatient Databases Healthcare Cost and Utilization Project	Logistic regression **OR (95% CI)** HPT: 0.75 (0.59–0.96)Cancer, lymphoma: 2.79 (1.23–6.3)Cancer, metastatic: 2.34 (1.22–4.47)Cancer, solid tumor: 2.11 (1.13–3.95)Congestive HF: 1.55 (1.13–2.12) Coagulation ds: 2 (1.32–3)Diabetes w & w/o complication: NR	Age; gender; weight loss; TBI dx; LOS; pts location relative to geographic size**OR (95% CI)** Age (continuous): 1.03 (1.02–1.05)Mayo (moderate to severe): 2.61 (1.6–4.25) LOS: 0.53 (0.37–0.76)Limitations: cannot determine severity of some TBI dx; generalizability
Selassie *et al*[41] 2011USARetrospective longitudinalPopulation-based IC: TBI resulting in hospital admission btw 1998 and 2009EC: pts coded as late effects of TBI; repeat admissions for same event	N=41 395Age: 43.7±25.4Sex: 64.4% MTSI: NRIS: AIS_{head} 2: 41.3%AIS_{head} 3: 19.1%AIS_{head} 4–6: 39.7%ISS<16: 22.7%ISS 16–24: 19.5%ISS 25–75: 57.9%	Win 120 d after TBINR	**Sepsis** ICD-9-CM codes**Elixhauser Comorbidity Scale** 5 groups based on risk profiling, literature support and similarities w underlying pathologySepsis: 1.0%Liver-renal: 1.1%Neurological-stroke: 2.9%Diabetes-metabolic: 10.4%HD: 10.6%Others: 25.9%	**All-cause mortality in acute care** South Carolina hospital discharge dataset	Cox regression model **HR (95% CI), all p<0.005** Sepsis: 1.34 (1.11–1.61)Liver-renal: 1.65 (1.29–2.12)Neurologic-stroke: 1.53 (1.32–1.78)Diabetes-metabolic: 1.36 (1.23–1.51) HD: 1.36 (1.21–1.53)Other: 0.81 (0.73–0.9)	Age; gender; race; insurance status; AIS_{head}; ISS; trauma facility level; place of residence**HR (95% CI), p<0.05 unless NS** Age (ref:≤24)25–44: NS 45–64: 1.16 (1.04–1.3)≥65: 1.89 (1.63–2.19)Gender (ref: F): NSRace (ref: White)Black: NSInsurance Status (ref: commercial)Uninsured: 1.29 (1.15–1.45)Medicare; indigent care/ Medicaid: all NSAIS head (ref: 2)3: 2.08 (1.73–2.5)4–6: 4.97 (4.21–5.87)ISS (ref:<9)9–15: NS16–75: 2.52 (1.91–3.31) Place of residence (ref: urban)Rural: NSLimitations: no GCS scores; dx codes may be influenced by reimbursement
Shandro *et al*[42] 2008USARetrospective longitudinalClinicalIC: 18–84 years old; arrived alive in hospital; moderate-severe injuryEC: dead<30 mins of arrival; delayed treatment>24 hours;>65 years old w a 1st dx of hip fracture; burns; does not speak English or Spanish; non-USA residents	N=1529AgeBAC 0: 47.8±32.3BAC 1–100: 37.8±26.6BAC 101–230: 40.3±28.7BAC>230: 44.8±25.4SexBAC 0: 63%MBAC 1–100: 86.3%MBAC 101–230: 84.9%MBAC>230: 84.6%MTSI: NRISBAC 0 NISS: 37.3±21BAC 1–100 NISS: 41.4±20.1BAC 101–230 NISS: 38.8±19.8BAC>230 NISS: 40.7±24AIS_{max}=4: 54%AIS_{max}=5–6: 46%$AIS_{head\ max}$=4: 55%$AIS_{head\ max}$=5–6: 45%	Duration: NRt_1: At discharget_2: 3 mos p/d t_3: 12 mos p/d	**BAC** Specimens drawn during ED phase of careMultiple imputation method used for missing dataBAC 0: 64%BAC 1–100: 9.5%BAC 101–230: 16.9%BAC>230: 9.5%	**All-cause mortality** Proxy or NDI	Multivariate logistic regression **OR (95% CI)** In-hospital deathBAC≤100: 1.18 (0.53–2.59) BAC 100–230: 0.89 (0.55–1.46)BAC>230: 0.58 (0.27–1.25)90 d deathBAC≤100: 1.1 (0.54–2.24)BAC 100–230: 0.82 (0.5–1.34)BAC>230: 0.56 (0.27–1.2)365 d deathBAC≤100: 1.09 (0.53–2.25)BAC 100–230: 0.85 (0.55–1.32)BAC>230: 0.64 (0.3–1.37)	Age; gender; NISS; insurance status; race; injury mechanism; midline shift; ED/pre-hospital shock; GCS motor; CCI; AIS_{max}; $AIS_{head\ max}$ **OR (95% CI)** NRLimitations: no assessment of preinjury alc. dependence; incomplete dataNotes: lab studies shown neuroprotective effects of alc.

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Table 1 Continued

AuthorDateCountrySample byDesignInclusion criteria (IC)Exclusion criteria (EC)	PopulationSample sizeAge (mean (SD), range), yrsSex (%M)Time since injury (TSI) Injury severity (IS)±SD	Follow-up periodAssessment time points/N assessed	Comorbidity definition Measurement used/ assessment criteria Frequencies (%), scores (mean±SD, median Q_3-Q_1)	Outcome definitionSources	Analyses MethodologyResultsAdjusted	Adjustment NotesLimitations
Shafi *et al*[34] 2005USARetrospective longitudinalPopulation-based IC: admission to level 1 or 2 trauma center; blunt mechanism of injury; 18–45 years oldEC:≥1 d admission delay; death≤1 d; pts w missing data	N=30 742Age (SEM): 29.92 (0.0461)Sex: 73.1%MTSI: NRIS: mean (SEMISS: 15.01 (0.068) RTS: 6.986 (0.009)	Mean (SEM): 6.98 (0.069) dNR	**Hypotension** Defined as systolic BP of≤90 mmHgHypotension: 4.4%	**All-cause in-hospital mortality** NTDB	Multivariate logistic regression **OR (95% CI)** Hypotension: 4.1 (3.45–4.86)	Age; gender existing medical conditions; hospital complications; ED GCS**OR (95% CI)** NRLimitations: no info on BP after ED; cannot make causal relationship
Shibahashi *et al*[47] 2017JapanRetrospective longitudinalClinicalIC: talked after TBIEC:<16 years old; systolic BP<40 mmhg; AIS≥3 on other body regions	N=24 833Median age (IQR) Survivors: 66 (48-78)Deaths: 77 (67-84)Sex: 67% MTSI: NR ISMedian GCS (IQR) Survivors: 14 (14-15)Deaths: 13 (12-14)Median ISS (IQRSurvivors: 16 (10-17)Deaths: 20 (16-25)	Median (IQR): 8 d (2-20) dNR	**DM; stroke; malignancy; congestive HF; chronic kidney disease; pulmonary disease; LC; hematologic dx; hypotension** NR DM: 11.8%Stroke: 7.4%Malignancy: 2.6%Congestive HF: 2.2%Chronic kidney disease: 1.8%Pulmonary disease: 1.5%LC: 0.9%Hematologic dx: 0.39%Hypotension: 1.5%	**All-cause in-hospital mortality** Japan Trauma Data Bank	Multivariable logistic regression**OR (95% CI)** DM: 1.02 (0.83–1.24)Stroke: 0.86 (0.67–1.11)Malignancy: 1.25 (0.87–1.79) Congestive HF: 1.82 (1.31–2.51)Chronic kidney disease: 2.76 (1.96–3.89)Pulmonary disease: 1.44 (0.94–2.22)LC: 4.05 (2.56–6.4)Hematologic dx: 5.23 (2.87–9.55) Hypotension: 2.42 (1.41–4.15)	Hospital admittance; age; sex; GCS; RTS; ISS; head CT; cerebrum/cerebellum/ skeletal injuries**OR (95% CI)** Age (year): 1.05 (1.04–1.05)Sex (ref: F): 1.5 (1.27–1.77)GCS: 0.75 (0.67–0.83)ISS: 1.12 (1.1–1.14)RTS: NSLimitations: patients older than previous studies
Spitz *et al*[43] 2015AustraliaProspective longitudinalClinicalIC:>15 years old; primary dx TBI; admitted to inpatient head injury rehab programEC: NR	N=3341Age: 35.7±17.6 at injurySex: 72%MTSI: NRISmTBI: 8.5%Moderate TBI: 21.7%Severe TBI: 69.9%GCS 3–8: 55.4%GCS 9–12: 15.1%GCS 13–15: 29.5%	Mean±SD: 13.2±8.1 yearsNR	**Pre-morbid medical history** (Psychological dx; excessive/problem drinking; head injury; stroke)Medical files Head injury: 5.2%Stroke: 1.5%Excessive alc. use: 18%Treatment for mental problem: 15.1%	**All-cause mortality** NDI & NCIS	Cox regression model **HR (95% CI), all p<0.05** Stroke: 2.17 (1.12–4.2)Excessive alc. use: 2.04 (1.44–2.9)Treatment for mental problem: 1.66 (1.14–2.43)	Age; gender; preinjury employment/ relationship status; back and chest injury**HR (95% CI), p<0.05 unless NS** Age (as it increases): 1.06 (1.05–107) Gender (ref: M): 1.51 (1.08–2.11) Unemployed: 1.62 (1.12–2.37) Limitations: generalizability; only in rehab; heterogeneous follow up scheduleNotes: neoplasms less common in TBI pts
Selassie *et al*[35] 2014USARetrospective longitudinalPopulation-basedIC: pts w TBI defined by CDCEC: pts coded as late effects of intracranial injury; repeated encounters w same dx	N=33 695Age: 42.8±25.3Sex: 64.1%MTSI: NRISSevere (AIS 4–6): 34.7%Moderate (AIS 3): 19.6%Mild (AIS 2): 45.7%	Median (IQR): 53 (22-90) mosNR	**HD; liver-renal diseases; cancer, HPT; diabetes & metabolic illnesses; neurological diseases & stroke; mental health problems** ICD-9-CM codes based on Elixhauser Comorbidity Index classification HD: 9.8%Liver-renal disease: 1%Cancer: 1.3%HPT: 14.8%Diabetes & metabolic illness: 9.6%Neurological disease & stroke: 2.6%Mental health problem: 6%All other conditions: 4.6%	**All-cause mortality** South Carolina statewide hospital discharge dataset; Division of Vital Records	Cox regression model **HR (95% CI); all p<0.01** HD: 2.13 (1.93–2.34Liver-renal diseases: 3.25 (2.71–3.89)Cancer: 2.64 (2.24–3.1) HPT: 1.43 (1.3–1.57)Diabetes: 1.89 (1.7–2.11)Neurological disease & stroke: 2.07 (1.77–2.42)Mental health problem: 1.59 (1.38–1.83)All other conditions: 1.64 (1.42–1.89)	Age; sex; TBI severity; race; insurance status; trauma facility level; concomitant injuries**HR (95% CI), p<0.05 unless NS** Age (as it increases): 1.05 (1.04–1.05) Sex (ref: M): 0.77 (0.73–0.82)TBI severity (ref: AIS=2AIS=3: 1.19 (1.1–1.29)AIS=4–6: 1.24 (1.16–1.32)Race (ref: White)Other: 0.68 (0.55–0.83)Black: NSInsurance status (ref: commercial)Uninsured: 1.27 (1.11–1.45)Indigent care/Medicaid: 1.67 (1.48–1.87)Medicare: 1.54 (1.4–1.69) Limitations: missed pts who died out of state; omission of conditions not helpful to reimbursement
Schiraldi *et al*[44] 2015USARetrospective longitudinalPopulation-basedIC: primary dx TBI; hospitalizationEC:<18 years old	N=92 159Age: 54±23Sex: 59%MTSI: NRIS: ICDISS: 0.82±0.2	Mean±SD: 12±21 dNR	**CCI** Deyo's adaption of CCI to administration dataCCI 0: 55.1%CCI 1:23.5%CCI 2: 11.5%CCI>3: 9.9%	**All-cause mortality** MarketScan database	Multivariate analyses **OR (p-value)** CCI 1: 1.27 (<0.0001)CCI 2: 1.55 (0.5244) CCI>3: 2.71 (<0.0001)	Age; gender; ICDISS; insurance type**OR (p-value)** Age (yr increment): 1.02 (<0.0001) Gender (ref: M): 0.8 (<0.0001)ICDISS (unit increase): 0.01 (<0.0001)Insurance (ref: commercial)Medicaid: 1.29 (<0.0001) Medicare: NSLimitations: no GCS; no specific comorbidities
Thompson *et al*[36] 2012USARetrospective longitudinalPopulation-basedIC:≥55 years old; blunt head injuryEC: NR	N=196Age: 69.3±10Sex: 70.9%TSI: NRISISS: 25.6±9GCS: 9.9±4	Mean±SD: 21.6±24 dNR	**Elixhauser Comorbidity Index; HPT; alc. abuse; cardiac arrhythmias; CAD; diabetes; CPD; MI; RA; other neurological problem; anemia**Elixhauser score: 1.7±1pati: 41.4%Alc. Abuse: 25.3%Cardiac arrhythmias: 11.1%CAD: 9.9%Diabetes: 9.3%CPD: 8.6%MI: 7.4%RA: 7.4%Other neurological: 6.2%Anemia: 5.6%	**In-hospital all-cause mortality** University's TBIR	Multivariate logistic regression **RR (95% CI); p<0.001** MI: 14.3 (2.1–97.1)CAD: NSElixhauser comorbidity index: NSAll other comorbid conditions: NR	Age; sex; injury severity**RR (95% CI)** NR Limitations: predominantly White sample; multiple comparisonsNotes: wide CI for MI suggest unreliable estimate

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Table 1 Continued

Author Date Country Sample by Design Inclusion criteria (IC) Exclusion criteria (EC)	Population Sample size Age (mean (SD), range), yrs Sex (%M) Time since injury (TSI) Injury severity (IS)±SD	Follow-up period Assessment time points/N assessed	Comorbidity definition Measurement used/ assessment criteria Frequencies (%), scores (mean±SD, median Q_3-Q_1)	Outcome definition Sources	Analyses Methodology Results Adjusted	Adjustment Notes Limitations
Utomo *et al*[87] 2009 Australia Retrospective longitudinal Population-based IC: ≥65 years old; head injury of AIS≥4; no injury to any other body region w AIS>1; btw July 2005 & June 2007	N=428 Age: ≥65 Sex: 54.7%MTSI: NRISMild (GCS 13–15): 75.1%Moderate (GCS 9–12): 11.5%Severe (GCS 3–8): 13.5%AIS_{head} 4: 58.6%AIS_{head} 5: 41.4%	Median (IQR): 6.9 (3.3–12.9) dNR	**CCI**CCI 0: 46.3%CCI 1: 29.2%CCI 2 to 6: 23.8%	**In-hospital all-cause mortality** VSTR	Multivariate logistic regression **OR (95% CI); p-value**CCI: NS	Age; AIS_{head}; systolic BP; GCS; brainstem injury; ICP monitoring; transferred from 1 hospital to another**OR (95% CI), p<0.05 unless NS** Age (ref: 65–74)75+: 2.89 (1.3–6.44)GCS (ref: 13–15)9–12: 6.75 (3.27–13.9)3–8: 24.1 (10.7–54.3)Brainstem injury (yes): .98 (2.15–29.7)All other variables NRLimitation: no subgroup analyses Note: CCI may not be sensitive to describe relationship between comorbidity and mortality

AIS, Abbreviated Injury Scale; APACHE II, Acute Physiology and Chronic Health Evaluation II; Adj, adjusted; Alc, alcohol; BAC, blood alcohol concentration; BIRP, brain injury rehabilitation programme; BP, blood pressure; Btw, between; CAC, coronary artery calcium; CAD, cardiovascular disease; CAPS, Clinician Administered PTSD Scale; CCI, Charlson Comorbidity Index; CD, cerebrovascular disease; CDC, Centers for Disease Control and Prevention; CES-D, Centers for Epidemiologic Studies Depression Scale; CHD, coronary heart disease; CPD, chronic pulmonary disease; CV, cardiovascular; D, day(s); DH, diabetic hyperglycaemia; DM, diabetes mellitus; DN, diabetic normoglycaemia; DNR, do not resuscitate; DRS, Disability Rating Scale; DSM IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; Ds, disorder(s); Dx, diagnosis; ED, emergency department; EDH, epidural haematoma; EMR, electronic medical records; FIM, functional independence measure; GCS, Glasgow Coma Scale; HBV, hepatitis B virus; HCI, hypercholesterolemia; HCUP, healthcare cost and utilisation project; HCV, hepatitis C virus; HD, heart disease; HF, heart failure; HLD, hyperlipidaemia; HPT, hypertension; HU, hounsfield units; HbA1c, haemoglobin A1c; Hrs, hours; Hx, history; ICD-9, International Classification of Diseases – 9th Rev; ICD-9-CM, International Classification of Diseases – 9th Rev, Clinical Modification; ICISS, International Classification of Diseases Injury Severity Score; ICP, intracranial pressure; ICU, intensive care unit; ISS, Injury Severity Scale; IVH, intraventricular haemorrhage; LC, liver cirrhosis; LOC, loss of consciousness; LOS, length of stay; LTC, long-term care; MI, myocardial infarction; Mech, mechanism; Misc, Miscellaneous; NCIS, National Coroners Information System; NDI, National Death Index; NDN, non-diabetic normoglycaemia; NIS, Nationwide Inpatient Sample; NISS, New Injury Severity Score; NR, not reported; NS, not significant; NTDB, National Trauma Data Bank; OIF, Operation Iraqi Freedom; OSHPD, California Office of Statewide Health Planning and Development; OTR, Ontario Trauma Registry; POL-M, PTSD Checklist-Military; PPO, partial pressure of oxygen; PTSD, post-traumatic stress disorder; P/d, postdischarge; P/i, postinjury; Pts, patients; RA, rheumatoid arthritis; RPDB, Registered Persons Data Base; RR, relative risk; RTS, Revised Trauma Scale; Ref, reference; SAPS II, Simplified Acute Physiology Score; SCI, spinal cord injury; SDH, subdural Haematoma; SIH, stress-induced hyperglycaemia; SSDI, Social Security Death Index; Sev, severity; Subj, subjects; TBI, traumatic brain injury; TBIMS, traumatic brain injury model systems; TBIR, traumatic brain injury repository; THC, tetrahydrocannabinol; TICH, traumatic intracerebral haematoma; Unadj, unadjusted; VHA, Veteran Health Administration; VSTR, Victorian State Trauma Registry; cSDH, chronic subdural haemorrhage; mTBI, mild traumatic brain injury; tSAH, traumatic subarachnoid haemorrhage; tSDH; traumatic subdural haemorrhage; w, with; w/o, without.

remaining 10 studies did not report information on TBI severity.[23 25–28 31 34 40 42 44]

Studied outcomes varied across the included studies. Eleven studies examined long-term (>30 days follow-up) all-cause mortality,[25–29 31 32 35 42 43 45] 15 studies examined short-term (≤30 days follow-up and/or in-hospital) all-cause mortality[23 24 30 33 34 36–41 44 46] and 1 study examined long-term cardiovascular mortality.[22]

Comorbidity in patients with TBI has been measured using vario

hods including the Charlson Comorbidity Index (CCI),[23 28 32 37 44 49] Elixhauser Comorbidity Index (ECI)[35 36 41 50] and chronic comorbidity scores determined through pharmacy records.[27] Two studies reported the association between comorbidity load and mortality by examining the number of comorbid conditions.[26 39] A single study examined the relationship between the presence of any comorbidity and mortality.[48] With respect to comorbidity groups and types, studies examined a wide range of mental and physical conditions. A full list of the comorbidities can be found in table 1.

Relationship of baseline clinical characteristics and outcome

Select sociodemographic characteristics and outcome

Among the studies that included age within their final multivariate models, 14 found a significant relationship between increasing age and both short-term and long-term mortality,[23 25 28 29 31–33 35 37 40 41 43–45 47 48] two studies did not identify any significant relationship[30 46] and one study found an increased rate ratio of long-term mortality for the younger age groups compared with the older age groups (≥50 years of age).[26] Effect sizes varied greatly as shown in table 1. The remaining eight studies did not report their findings on the association between age and mortality.[22 24 27 34 36 38 39 42]

With respect to sex, seven studies found a reduced risk of both short-term[40 44 47] and long-term mortality[28 29 35 45] and one study found an increased risk of long-term mortality among females.[43] Six studies did not find any significant association between sex and mortality rates[25 31 35 40 46 48] and a single study demonstrated conflicting findings.[23] Eight studies did not report their findings on the relationship between sex and mortality.[22 24 27 33 34 36 39 42] Finally, several of the included studies also examined and reported the mixed relationships between race,[23 29 31 35 41] marital status,[29 43] employment status,[29 43] rurality[23 40 41] as well as insurance status[23 35 41 44] and mortality. Effect sizes varied greatly; details are shown in table 1.

Select injury characteristics and outcome

Out of the 12 studies that examined and reported on injury severity in adjusted multivariate analyses, all found a significant association between increasing injury severity and increase in both short-term[30 33 37 41 46–48] and long-term[26 28 35 44] mortality.[31] We refer the reader to table 1 for effect sizes reported in individual studies. TBI resulting from falls,[26 29] violence[29] and all other causes[26] were found to be significantly associated with increased

risk of long-term mortality when compared with TBI from motor vehicle collisions. On the contrary, one study did not report any significant findings.[31]

Relationship of comorbidity and outcome

Measures used and outcome

Adjusting for confounders, four of the five studies identified a varying effect size, but all significant association, between CCI and mortality after TBI[23 28 32 44] (table 1). Among the three studies that used the ECI,[35 36 41] two found significant association between all groups of comorbidities and increased short-term and long-term mortality rates,[35 41] with exception of the 'other' category, which was not significantly associated with short-term post-TBI mortality.[41] The final study that used the ECI found low sensitivity and specificity for prediction of short-term mortality.[36]

Comorbid condition load and outcome

Two studies evaluated the relationship between the number of comorbid conditions and mortality after TBI.[26 39] The first study found no significant associations between the number of comorbid conditions and short-term mortality.[39] Another study that investigated 1-year mortality found a significant relationship between having one or more comorbidities and long-term mortality.[26] One study examining the association of the presence of any comorbidity and short-term mortality did not report any significant findings.[48]

Comorbidity type and outcome

Among comorbidity groups, mental health disorders were the most commonly examined comorbid conditions, with seven studies examining its relationship with post-TBI mortality across varying severities.[22 23 26 29 40 43 45] Effect sizes varied greatly (table 1). While one study found significant association between mental health conditions and post-TBI mortality,[43] three others did not.[26 40 45] Similarly, findings on individual mental health disorders were also mixed.

Five studies examined the role of epilepsy and stroke in predicting mortality post-TBI with varying results.[27 40 43 45 47] Epilepsy was found to be a significant predictor of long-term mortality post severe-TBI mortality[45] but not short-term in-hospital morality.[40] Stroke was found to be significantly associated with an increase in both short-term in-hospital and long-term mortality post-TBI across severities.[27 40 43] with the exception of one study.[47] We refer the reader to table 1 for specifics.

With respect to cardiovascular diseases, the two studies which examined this comorbidity found no significant association with short-term post-TBI mortality[39 40] while four studies found significant associations between specific heart conditions and increases in both short-term and long-term mortality.[22 33 36 47] Studies also reported conflicting findings for the role of hypertension in predicting short-term mortality among patients.[33 40 46] All of the three studies that examined low blood pressure (i.e., hypotension) found significant associations with short-term mortality.[34 47 48] Of the two studies that examined the association between cancer and short-term mortality, one reported significant findings[33] while the other did not.[47] When examining liver-renal disorders, studies found significant associations between liver cirrhosis, renal dialysis and increased long-term and short-term post-TBI mortalities, respectively.[25 40 47] In addition, one study found significantly higher long-term mortality rates among individuals with liver cirrhosis and heart failure, hypertension and/or renal failure compared with those without.[25] Finally, two studies examining diabetes found significant associations with increased short-term post-TBI mortality.[40 46] while one did not.[47] Among studies that examined stress-induced high levels of sugar, or glucose, in the blood (i.e., hyperglycaemia), two studies found significant associations with short-term mortality[24 38] while a single study did not[46] (table 1).

In addition to comorbidity groups, several studies examined the association between specific comorbid conditions and clinical signs and mortality. Among the comorbid conditions and co-occurring conditions, hypoglycaemia,[38] disorders of the blood,[47] coagulation (i.e., blood clotting) disorders[33] and sepsis (i.e., systemic inflammatory response to infection)[41] were significantly associated with increased short-term mortality, and spinal cord injury[29] was significantly associated with decreased long-term mortality. On the other hand, smoking,[46] hyperlipidaemia (i.e., harmful cholesterol levels),[40] alcohol consumption[46] and cerebral infarction[30] were not found to be associated with short-term mortality. Similarly, having a previous head injury also did not predict long-term mortality.[43] Finally, two studies examined the association between alcohol and tetrahydrocannabinol (THC) exposure during injury and mortality postinjury among individuals with unknown TBI severities. While not indicative of any comorbid conditions, these studies found reduced odds of mortality post-TBI for patients who are exposed to THC or alcohol at the time of injury.[31 42]

DISCUSSION

Given the large degree of heterogeneity in the characteristics of each study population, the methods used to measure different types of comorbidity, as well as how the outcomes were defined and presented among the 27 included studies, a meta-analysis could not be conducted.

Relationship of baseline clinical characteristics and outcomes

Confounding effect

When examining the relationship between comorbidities and mortality, all studies adjusted their findings by baseline sociodemographic and clinical characteristics of the patients with TBI. Specifically, all studies included age as a variable within their final adjusted models. All but four studies also adjusted their findings by sex and/or gender. Among the studies that did not include sex and/or gender as a confounder in the analyses, two excluded the variable as it was not significant in univariate analyses,[26 32] one excluded the variable as it was neither clinically nor statistically

significant in bivariate analyses[30] and one did not provide reason for exclusion.[37] With respect to other confounders, 17 studies included injury severity[24 26 28 30 31 34–39 41 42 44 46–48] and seven studies included mechanism of injury[23 26 29 39 40 42 48] as one of the confounding variables, respectively. Two studies adjusted their findings by the time since injury.[29 38] A complete list of all the confounders included by each study can be found in table 1.

Select sociodemographic characteristics and outcome

In summary, several potential clinical characteristics that predict mortality among patients with TBI had been investigated. Concurrent with previous literature,[51 52] most included studies found age to be significant predictor of mortality. However, given the higher expected death rate among the general older population, one study found the rate ratio to be generally lower for the older age groups (≥50 years of age) than that of the younger age groups (<50 years of age) in the TBI population.[26] As such, it is important to consider the death rates among the general population when examining the influence of TBI and other conditions on mortality. While sex and gender had been known to show an influence on post-TBI recovery, such as functional and cognitive outcomes,[53 54] findings within the included studies were mixed, which is in line with the current lack of consensus on this topic. Additional demographic variables, such as race, marital status, employment status, rurality and insurance status, were also examined. However, given the limited number of studies and mixed findings in this review, it was not possible to determine the effects of these sociodemographic variables on mortality.

All studies that examined injury severity found increasing severity to be associated with increased short-term and long-term mortality postinjury, which was expected. The relationship between injury mechanism and mortality was also examined. However, studies used varying classifications when determining the risk of mortality from each form of injury mechanism. As such, future work should consider adopting a standardised classification of injury mechanism to enhance consistency and aid comparisons across studies.

Comorbidity measures and outcomes

As a validated comorbidity, the CCI was the most commonly used comorbidity scale among the included studies.[49] Patients with TBI across all severities with higher scores on the CCI were found to be at higher risk of both short-term and long-term mortality. However, a study on older adults with TBI and short-term mortality reported contradictory findings.[37] While the CCI had previously been validated in acutely hospitalised older adult population,[55] a literature search failed to reveal any validation studies on the TBI population. Hence, these conflicting findings could be attributed to the CCI's limitations in describing the relationship between comorbidity and mortality within this specific population.

The ECI was another commonly used comorbidity scale across studies. However, the findings on the TBI population across all severities were mixed. Unlike the CCI, the ECI explicitly excludes causes of substantial comorbidity in elderly patients, including myocardial infarction and stroke.[56] Hence, it may not capture the comorbidities experienced by older adults with TBI, which would account for the lack of association reported in the study. Therefore, modifications may need to be made to the ECI to enhance its ability to capture the full comorbidity profile of the TBI population, especially among older adults.

Comorbidity load and outcomes

The absolute number and/or presence of comorbidities had been found to be significantly associated with long-term[26] but not short-term mortality.[39 48] This suggested that comorbidities may have varying impact on mortality across the life span of an individual post-TBI. However, given the lack of specification on the types of comorbid conditions included in the comorbidity count, caution should be taken when making inferences on the influence of specific comorbidities on mortality,

Comorbidity type and outcomes

Mental health disorders

Among studies examining mental health disorders, findings remained mixed. A single study found a significant relationship between anxiety, bipolar disorder, psychosis, depression and substance abuse and reduced short-term mortality.[23] These findings highlighted an important methodology concern when establishing psychiatric diagnoses among the TBI population. Specifically, psychiatric disorders may go unrecognised in patients with TBI who are unconscious at the time of hospitalisation.[23] Given that these individuals who are conscious postinjury are more likely to survive, there is a potential for the rate of psychiatric diagnoses in those who survive to be bolstered, leading to the observed protective effect of psychiatric disorders on post-TBI mortality. As such, efforts should be taken to reduce the information bias by establishing preinjury psychiatric disorders among the TBI.

In addition, two studies found a significant association between exposures to alcohol and THC and reduced mortality. As these prior exposures are determined at time of injury, they were not indicative of any comorbid substance abuse. Nonetheless, they provide insight on the potential neuroprotective effects of alcohol and THC on the brain at time of injury, which is in line with previous preclinical work.[57 58]

Neurological/nervous system disorders

In line with previous literature, epilepsy had been found to have a significant relationship with increased long-term mortality. However, the same relationship was not observed with respect to short-term mortality, which could be attributed to the chronic nature of the disorder.[59] As such, it is important for postinjury services to take into consideration the complications that individuals with TBI and epilepsy may encounter throughout their healthcare trajectory. Stroke was found to be significantly associated with increases in both short-term and long-term mortality

post-TBI across all severities.[27 40 43] with the exception of one study.[47] Given that majority of the studies found significant associations, assessment for the presence of stroke aetiology at time of TBI is critical to enhance the management and mitigation of adverse outcomes associated with stroke comorbidity.

Cardiovascular disorders

Among studies that examined cardiac diseases, four studies[22 33 36 47] observed a significant association with increased mortality. While studies that did not find any associations examined groups of cardiac-related conditions, the four studies that found significant associations examined specific heart diseases and markers such as congestive heart failure, myocardial infarction and coronary artery calcium levels. This suggests that specific cardiac conditions and biomarkers may play a role in influencing adverse outcome post-TBI and future work should focus on identifying these conditions.

Liver–renal disorders

Three studies examined the association between liver and renal disorders and mortality[25 40 47] with one having explicitly considered the effect of multimorbidity and liver cirrhosis on short-long-term mortality. This is of importance as the cumulative effect of these diseases may lead to the complication of care for individuals with multiple comorbid conditions.[60] Nonetheless, while all studies found significant associations between these disorders including liver cirrhosis and renal failure with the need for dialysis and increased long-term and short-term mortalities, respectively, the study setting was limited to patients in Asia (Japan and Taiwan). Given the different aetiologies of these disorders between societies in the East and West,[25] there is a need to build on this preliminary evidence through further examinations of these conditions in other study populations and settings.

Hypertension and Hypotension

While most studies examining hypertension did not find significant associations with mortality, one study found hypertension to be protective of short-term mortality among older adults with severe TBI.[33] Previous research has found improved survival outcomes post-TBI among patients consuming beta-blockers, a commonly prescribed antihypertensive medication.[61] Given the chronic nature and increasing prevalence of hypertension with age,[62] older adults are more likely to be using these medications compared with younger adults. As such, the consumption of beta-blockers may account for the decreased odds of short-term mortality among the hypertensive older adult TBI population found by the studies in our review.

A number of studies had established the relationship between low blood pressure and short-term mortality,[34 47 48] which highlights the importance of assessing the presence of hypotension at time of hospital admission in order to mitigate the potential risk of mortality among the TBI population.

Diabetes mellitus and stress-induced hyperglycaemia

While the association between diabetes mellitus and short-term mortality had been inconsistent,[40 46 47] most studies examining the effects of stress-induced hyperglycaemia, a marker of oxidative stress and catabolic illnesses, identified a significant association with increased short-term mortality in patients with severe TBI except for a single study, which distinguished between patients with stress-induced hyperglycaemia and diabetes.[46] While one study has differentiated between stress-induced and diabetic hyperglycaemia, they are not mutually exclusive categories as diabetic hyperglycaemic patients may have some degree of stress response invoking their hyperglycaemia.[24] As a result, further work to distinguish the various causes of stress-induced hyperglycaemia and their relationship with mortality is warranted.

Other disorders, injury, and symptoms and signs

In addition to the comorbidities examined by the multiple studies above, single studies also found comorbidities including hypoglycaemia,[38] hematologic disorders,[47] coagulation disorders[33] and sepsis[41] to be significantly associated with increased short-term post-TBI mortality and spinal cord injury[29] significantly associated with decreased long-term mortality. On the other hand, smoking,[46] hyperlipidaemia,[40] alcohol consumption[46] and cerebral infarction[30] were not found to be associated with short-term mortality. Similarly, having a previous head injury also did not predict long-term mortality.[43] However, given the moderate quality of the studies and paucity of supporting evidence, these associations ought to be interpreted with caution.

Risk of bias and study methodology

The study results depend on the quality of included studies, of which none were high quality based on the risk of bias assessment. Included studies were frequently penalised for being retrospective cohort studies, incomplete reporting when dealing with missing data and statistical analysis. Although most studies performed some form of adjustment for confounders, this was often not described in detail. Most studies did not account for severity of the comorbidity under study, or whether or not the studied comorbidity was adequately controlled by medication, remained untreated or was treatment resistant. In addition, many studies did not control for TBI severity. The lack of consistency in variables included in the modelling process (table 1) and details about independency between included variables (ie, risk factors studied), restricts comparison between the studies.

Closer examination of discrepancies between studies' results revealed a methodological difference between studies that observed a significant and non-significant association. To elaborate, most studies that employed administrative databases did not establish a significant association between psychiatric disorders and mortality[27 40] while most studies that used medical records did.[22 43] While administrative data had previously been

found to agree with medical records for recording of comorbidities, there is a tendency for under-reporting of comorbid conditions in administrative data.[63] As such, the association between comorbidities and mortality can be potentially masked by the reporting discrepancy. Together, these methodological inconsistencies among studies examined preclude conclusive inferences on the role of comorbidities on post-TBI mortality. Future efforts in this field can focus on performing in-depth examinations of these relationships in order to substantiate evidence, which can inform decision-making and planning of healthcare strategies tailored for patients with TBI with these comorbid conditions.

Limitations

We acknowledge heterogeneity in the included studies, which demonstrate a great deal of variations in the populations studied, forms and types of comorbidities examined and the mortality outcome. Moreover, various methodologies were employed among studies focusing on similar comorbidities and there were a lack of consideration of the onset of these conditions with respect to TBI. As such, the estimates provided by each study could not be pooled together.

In addition, despite mortality being the most robust and reliable outcome,[64] the unequal sex and age distribution among the primary studies may have affected the generalisability of the estimates to the TBI population. TBI has been historically considered an injury of younger men and older women.[65] As such, primary studies focusing on older adults have an over-representation of women and vice versa. While most studies attempted to account for sex and age distributions within their regression modelling, there remains a possibility that comorbid conditions that mainly affect under-represented TBI individuals may not have been captured by the studies.

Most studies focused on multiple types or groups of comorbid conditions. However, the time frame of comorbidity determination was unclear. As such, it was not possible to determine if the conditions were pre-existing or had developed in conjunction with the TBI. Moreover, our assumption was that in the case where statistical significance or the magnitude of an association was not reported, despite the inclusion of a variable in a statistical model, the association was not statistically significant. Thus, the roles of some comorbid conditions that were examined but their relationships were not reported could be underestimated in this review. Furthermore, patients who were treated and who were adherent to treatment for their comorbid conditions may also have exhibited other health behaviours, which could lead to residual confounding.

CONCLUSION

To the best of our knowledge, we conducted the first systematic review to investigate the relationship between comorbidity, and all-cause mortality in populations with TBI, taking into account sociodemographic and clinical characteristics of persons with TBI. Overall, the evidence supported hypotension as a predictor for short-term mortality, and the evidence about other comorbidities and comorbidity load was mixed. Given the high number of comorbid conditions that were examined by single studies, research is required to further substantiate the evidence and address conflicting findings. In addition, an enhanced set of comorbidity scales that are suited for the TBI population will allow for better risk stratification to guide TBI management and treatment. Finally, given the trend towards big data analysis, future large population-based studies with long follow-up periods, a sufficient number of outcome events, a broad range of population demographic and clinical characteristics, and standardised measures used to define comorbidity (preinjury vs postinjury and severity) are needed to explore further the potential prognostic role of comorbidity in TBI mortality and enable comparisons across TBI populations.

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REFERENCES

1 Menon DK, Schwab K, Wright DW, *et al*. Position statement: definition of traumatic brain injury. *Arch Phys Med Rehabil* 2010;91:1637–40.
2 Maas AI, Menon DK, Adelson PD, *et al*. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol* 2017;16:987–1048.
3 The Lancet N. The changing landscape of traumatic brain injury research. *Lancet Neurol* 2012;11.
4 Schwarzbold ML, Rial D, De Bem T, *et al*. Effects of traumatic brain injury of different severities on emotional, cognitive, and oxidative stress-related parameters in mice. *J Neurotrauma* 2010;27:1883–93.

5 Colantonio A, Saverino C, Zagorski B, *et al*. Hospitalizations and emergency department visits for TBI in Ontario. *Can J Neurol Sci* 2010;37:783–90.
6 Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol* 2008;7:728–41.
7 Soo M, Robertson LM, Ali T, *et al*. Approaches to ascertaining comorbidity information: validation of routine Hospital episode data with clinician-based case note review. *BMC Res Notes* 2014;7:253.
8 Young JS, Hobbs JG, Bailes JE. The impact of traumatic brain injury on the aging brain. *Curr Psychiatry Rep* 2016;18:81.
9 Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. *J Chronic Dis* 1970;23:455–68.
10 Chan V, Mollayeva T, Ottenbacher KJ, *et al*. Clinical profile and comorbidity of traumatic brain injury among younger and older men and women: a brief research notes. *BMC Res Notes* 2017;10:371.
11 Brooks JC, Shavelle RM, Strauss DJ, *et al*. Long-Term survival after traumatic brain injury Part II: life expectancy. *Arch Phys Med Rehabil* 2015;96:1000–5.
12. Fu TS, Jing R, McFaull SR, *et al*. Recent trends in hospitalization and in-hospital mortality associated with traumatic brain injury in Canada: a nationwide, population-based study. *J Trauma Acute Care Surg* 2015;79:449–55.
13 Masel BE, DeWitt DS. Traumatic brain injury: a disease process, not an event. *J Neurotrauma* 2010;27:1529–40.
14 Cheng P, Yin P, Ning P, *et al*. Trends in traumatic brain injury mortality in China, 2006-2013: a population-based longitudinal study. *PLoS Med* 2017;14:e1002332.
15 Klauber MR, Marshall LF, Barrett-Connor E, *et al*. Prospective study of patients hospitalized with head injury in San Diego County, 1978. *Neurosurgery* 1981;9:236–41.
16 Mollayeva T, Xiong C, Hanafy S, *et al*. Comorbidity and outcomes in traumatic brain injury: protocol for a systematic review on functional status and risk of death. *BMJ Open* 2017;7:e018626.
17 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
18 Hartling L, Featherstone R, Nuspl M, *et al*. Grey literature in systematic reviews: a cross-sectional study of the contribution of non-English reports, unpublished studies and dissertations to the results of meta-analyses in child-relevant reviews. *BMC Med Res Methodol* 2017;17:64.
19 Mollayeva T, Kendzerska T, Mollayeva S, *et al*. A systematic review of fatigue in patients with traumatic brain injury: the course, predictors and consequences. *Neurosci Biobehav Rev* 2014;47:684–716.
20 Hayden JA, van der Windt DA, Cartwright JL, *et al*. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280–6.
21 Slavin RE. Best evidence synthesis: an intelligent alternative to meta-analysis. *J Clin Epidemiol* 1995;48:9–18.10.1016/0895-4356(94)00097-A
22 Ahmadi N, Hajsadeghi F, Yehuda R, *et al*. Traumatic brain injury, coronary atherosclerosis and cardiovascular mortality. *Brain Injury* 2015;29:1635–41.
23 Brandel MG, Hirshman BR, McCutcheon BA, *et al*. The association between psychiatric comorbidities and outcomes for inpatients with traumatic brain injury. *J Neurotrauma* 2017;34:1005–16.
24 Bosarge PL, Shoultz TH, Griffin RL, *et al*. Stress-Induced hyperglycemia is associated with higher mortality in severe traumatic brain injury. *J Trauma Acute Care Surg* 2015;79:289–94.
25 Cheng C-Y, Ho C-H, Wang C-C, *et al*. One-Year mortality after traumatic brain injury in liver cirrhosis Patients—A ten-year population-based study. *Medicine* 2015;94:e1468.
26 Colantonio A, Escobar MD, Chipman M, *et al*. Predictors of postacute mortality following traumatic brain injury in a seriously injured population. *J Trauma* 2008;64:876–82.
27 Dams-O'Connor K, Gibbons LE, Landau A, *et al*. Health problems precede traumatic brain injury in older adults. *J Am Geriatr Soc* 2016;64:844–8.
28 Donohue JT, Clark DE, DeLorenzo MA. Long-Term survival of Medicare patients with head injury. *J Trauma* 2007;62:419–23.
29 Harrison-Felix C, Kreider SED, Arango-Lasprilla JC, *et al*. Life expectancy following rehabilitation: a NIDRR traumatic brain injury model systems study. *J Head Trauma Rehabil* 2012;27:E69–80.
30 Marino R, Gasparotti R, Pinelli L, *et al*. Posttraumatic cerebral infarction in patients with moderate or severe head trauma. *Neurology* 2006;67:1165–71.
31 Nguyen BM, Kim D, Bricker S, *et al*. Effect of marijuana use on outcomes in traumatic brain injury. *Am Surg* 2014;80:979–83.
32 Peck KA, Calvo RY, Sise CB, *et al*. Death after discharge: predictors of mortality in older brain-injured patients. *J Trauma Acute Care Surg* 2014;77:978–83.
33 Scheetz LJ. Injury patterns, severity and outcomes among older adults who sustained brain injury following a same level fall: a retrospective analysis. *Int Emerg Nurs* 2015;23:162–7.
34 Shafi S, Gentilello L. Hypotension does not increase mortality in brain-injured patients more than it does in Non-Brain-Injured patients. *J Trauma* 2005;59:830–5.
35 Selassie AW, Cao Y, Church EC, *et al*. Accelerated death rate in population-based cohort of persons with traumatic brain injury. *J Head Trauma Rehabil* 2014;29:E8–19.
36 Thompson HJ, Dikmen S, Temkin N. Prevalence of comorbidity and its association with traumatic brain injury and outcomes in older adults. *Res Gerontol Nurs* 2012;5:17–24.
37 Utomo WK, Gabbe BJ, Simpson PM, *et al*. Predictors of in-hospital mortality and 6-month functional outcomes in older adults after moderate to severe traumatic brain injury. *Injury* 2009;40:973–7.
38 Griesdale DEG, Tremblay M-H, McEwen J, *et al*. Glucose control and mortality in patients with severe traumatic brain injury. *Neurocrit Care* 2009;11:311–6.
39 Jovanovic B, Milan Z, Djuric O, *et al*. Twenty-Eight-Day mortality of blunt traumatic brain injury and Co-Injuries requiring mechanical ventilation. *Med Princ Pract* 2016;25:435–41.
40 Liao CC, Chiu WT, Yeh CC, *et al*. Risk and outcomes for traumatic brain injury in patients with mental disorders. *J Neurol Neurosurg Psychiatry* 2012;83:1186–92.
41 Selassie AW, Fakhry SM, Ford DW. Population-Based study of the risk of in-hospital death after traumatic brain injury: the role of sepsis. *J Trauma* 2011;71:1226–34.
42 Shandro JR, Rivara FP, Wang J, *et al*. Alcohol and risk of mortality in patients with traumatic brain injury. *J Trauma* 2009;66:1584–90.
43 Spitz G, Downing MG, McKenzie D, *et al*. Mortality following traumatic brain injury inpatient rehabilitation. *J Neurotrauma* 2015;32:1272–80.
44 Schiraldi M, Patil CG, Mukherjee D, *et al*. Effect of insurance and racial disparities on outcomes in traumatic brain injury. *J Neurol Surg A Cent Eur Neurosurg* 2015;76:224–32.
45 Baguley IJ, Nott MT, Howle AA, *et al*. Late mortality after severe traumatic brain injury in New South Wales: a multicentre study. *Med J Aust* 2011;196:40–5.
46 Han M-H, Ryu JI, Kim CH, *et al*. Radiologic findings and patient factors associated with 30-day mortality after surgical evacuation of subdural hematoma in patients less than 65 years old. *J Korean Neurosurg Soc* 2017;60:239–49.
47 Shibahashi K, Sugiyama K, Okura Y, *et al*. Multicenter Retrospective Cohort Study of "Talk and Die" After Traumatic Brain Injury. *World Neurosurg* 2017;107:82–6.
48 Aiolfi A, Benjamin E, Khor D, *et al*. Brain trauma Foundation guidelines for intracranial pressure monitoring: compliance and effect on outcome. *World J Surg* 2017;41:1543–9.
49 Charlson M, Szatrowski TP, Peterson J, *et al*. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245–51.
50 Elixhauser A, Steiner C, Harris DR, *et al*. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8–27.
51 Dhandapani SS, Manju D, Sharma BS, *et al*. Prognostic significance of age in traumatic brain injury. *J Neurosci Rural Pract* 2012;3:131–5.
52 Mosenthal AC, Lavery RF, Addis M, *et al*. Isolated traumatic brain injury: age is an independent predictor of mortality and early outcome. *J Trauma* 2002;52:907–11.
53 Lavoie S, Sechrist S, Quach N, *et al*. Depression in men and women one year following traumatic brain injury (TBI): a TBI model systems study. *Front Psychol* 2017;8:634.
54 Kirkness CJ, Burr RL, Mitchell PH, *et al*. Is there a sex difference in the course following traumatic brain injury? *Biol Res Nurs* 2004;5:299–310.
55 Frenkel WJ, Jongerius EJ, Mandjes-van Uitert MJ, *et al*. Validation of the Charlson comorbidity index in acutely hospitalized elderly adults: a prospective cohort study. *J Am Geriatr Soc* 2014;62:342–6.
56 Gagne JJ, Glynn RJ, Avorn J, *et al*. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol* 2011;64:749–59.
57 Brennan JH, Bernard S, Cameron PA, *et al*. Ethanol and isolated traumatic brain injury. *Journal of Clinical Neuroscience* 2015;22:1375–81.
58 Fernández-Ruiz J, Moro MA, Martínez-Orgado J. Cannabinoids in neurodegenerative disorders and Stroke/Brain trauma: from preclinical models to clinical applications. *Neurotherapeutics* 2015;12:793–806.
59 Jacoby A, Snape D, Baker G. Epilepsy and social identity: the stigma of a chronic neurological disorder. *The Lancet Neurology* 2005;4:171–8.

60 St John PD, Tyas SL, Menec V, *et al*. Multimorbidity, disability, and mortality in community-dwelling older adults. *Can Fam Physician* 2014;60:e272–80.
61 Inaba K, Teixeira PGR, David J-S, *et al*. Beta-Blockers in isolated blunt head injury. *J Am Coll Surg* 2008;206:432–8.
62 Ong KL, Cheung BMY, Man YB, *et al*. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. *Hypertension* 2007;49:69–75.
63 Quan H, Parsons GA, Ghali WA. Validity of information on comorbidity derived from ICD-9-CCM administrative data. *Med Care* 2002;40:675–85.
64 Glaab T, Vogelmeier C, Buhl R. Outcome measures in chronic obstructive pulmonary disease (COPD): strengths and limitations. *Respir Res* 2010;11:79.
65 Thompson HJ, McCormick WC, Kagan SH. Traumatic brain injury in older adults: epidemiology, outcomes, and future implications. *J Am Geriatr Soc* 2006;54:1590–5.