Serum cardiac troponins as prognostic markers in patients with traumatic and non-traumatic brain injuries: A meta-analysis

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ARTICLE INFO

Article history:
Received 13 July 2018
Received in revised form 2 October 2018
Accepted 2 October 2018

Keywords:
Traumatic brain injury
Non-traumatic brain injury mortality
Troponin

ABSTRACT

Objective: The association between brain injury and elevated serum cardiac troponin (cTn) remains poorly understood. We conducted a systematic review and meta-analysis to evaluate whether elevated cTn increases the risk of mortality in patients with traumatic (TBI) or non-traumatic brain injury (NT-BI).

Methods: Cochrane Library, MEDLINE, PubMed, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), WHO International Clinical Trials Registry Platform, and Google scholar databases, and clinicaltrials.gov were searched for a retrospective, prospective and randomized clinical trials (RCT) or quasi-RCT studies that assessed the effect of elevated cTn (conventional or high sensitive assay) on the outcomes of brain injury patients. The main outcome of interest was mortality. Two authors independently abstracted the data using a data collection form. Results from different studies were pooled for analysis, whenever appropriate. The total number of patients pooled was 2435, of which 916 had elevated cTn and 1519 were in control group.

Results: Out of 691 references identified through the search, 8 analytical studies met inclusion criteria. Among both types of brain injuries, an elevated cTn was associated with a higher mortality with an overall pooled odd ratio (OR) of 3.37 (95% CI 2.13–5.36). The pooled OR for mortality was 3.31 (95% CI 1.99–5.33) among patients with TBI and 3.36 (95% CI 1.32–8.6) among patients with NT-BI.

Conclusions: Pooled analysis indicates that elevated cTn is significantly associated with a high mortality in patients with TBI and NT-BI. Prospective clinical trials are needed to support these findings and to inform a biomarker risk stratification regardless of the mechanism of injury.

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1. Introduction

In the United States of America, traumatic brain injury (TBI) accounts for up to 30% of all injury-related deaths [1]. It also poses a significant morbidity and economic burden worldwide [2,3]. While there are significant overall advances in trauma care, the medical management options for head injury remain limited. Based on several retrospective observational studies, TBI is associated with an increased risk of mortality. Some of these studies reported higher rate of mortality in TBI patients who had elevated serum cardiac troponin (cTn) in comparison to those who had normal troponin, even in patients with isolated TBI.

Few studies have evaluated the clinical significance of the release of cTn after trauma [4–7]. Some of these studies showed that elevated troponin could reflect the degree of severity of overall body injury, regardless of direct cardiac involvement [5,6]. Furthermore, elevated troponins were reported in acute non-traumatic head injury, including acute stroke (≈27%), and subarachnoid hemorrhage (≈20%) [4,7]. However, the precise mechanism of elevated cTn is difficult to be determined due to the multitude of prevailing clinical circumstances which may influence troponin release. Moreover, the clinical significance and prognostic value of elevated troponin levels remain poorly explored in TBI patients.

Earlier studies relied mainly on the conventional troponins (TnT or Tnl) and did not examine the newer high-sensitive cTn (i.e., HsTnT) which has more sensitivity and shorter time to detect myocardial damage [7–21]. A recent meta-analysis showed that elevated troponins are commonly seen in critically-ill patients even in the absence of coronary artery disease [7,9,10,21] with a prevalence of 45% studies utilized conventional troponin assays [11], however, this figure reaches 62% with the use of HsTnT [19,21]. There is very limited data describing the association between troponin and mortality in the context of TBI, as no prospective study has yet examined this association. The use of troponin as a tool in outcome prediction for TBI patients is a relatively novel evidence based concept. In this meta-analysis, we aimed to evaluate...
whether an elevated cTn increases the risk of mortality in patients with traumatic (TBI) or non-traumatic brain injury (NT-BI).

1.1. Objective

The objective of this study is to find out the pooling effect of elevated troponin on the mortality in traumatic or non-traumatic brain injury patients.

2. Methods

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. The study was registered at the International prospective register of systematic reviews (PROSPERO n. CRD 42018096594).

2.1. Literature searches

A systematic review was carried out using Cochrane Library, MEDLINE, PubMed, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), WHO International Clinical Trials Registry Platform, clinicaltrials.gov and Google scholar electronic databases. We used the keywords “Troponin”; “traumatic brain injury”; “trauma” [in Title/Abstract]. The medical subject headings (MeSH) terms used were traumatic injury [All Fields] AND (“Troponin”[MeSH Terms]; traumatic brain injury [All Fields] AND ("Troponin"[MeSH Terms]; intracerebral hemorrhage [All Fields] AND (“Troponin”[MeSH Terms]; Subarachnoid hemorrhage [All Fields] AND ("Troponin"[MeSH Terms]. Additional searches were conducted using reference lists of studies and review articles for a selection of relevant articles.

2.2. Inclusion/exclusion criteria

The inclusion criteria were (1) original studies, (2) English language, (3) published in the period from 01 January 2000 through 30st April 2018 (4) assessed “Troponin” and “traumatic/non-traumatic brain injury” (5) patients of any age, gender, and ethnicity. Articles other than original studies such as commentaries, letters to the editor, reviews, and case reports were excluded. Literatures that did not include outcomes or comparisons were also excluded.

The consensus on inclusion/exclusion criteria was reached based on the fact that whether the study provides information regarding association between elevated troponin and mortality of patients with brain injury. Therefore, even studies with smaller sample sizes were also included in the initial evaluation.

- Participants: Brain injury patients
- Intervention: elevated troponin levels after injury (traumatic or non-traumatic).
- Control: normal troponin levels after trauma.
- Outcomes: mortality.

2.3. Data extraction

The titles of the research articles obtained from the initial database searches were screened and relevant papers were selected. Then the abstracts and full texts were reviewed according to the inclusion criteria for final selection. Studies were reviewed based on the exclusion and inclusion criteria, by two authors (senior cardiologist and bio-statistician) independently (AE and BS). Initially, titles of the studies identified from the search were assessed for inclusion. Titles approved by authors were moved to abstract screening. If both authors rejected a study at this stage, it was excluded from the review. In the third stage, full text articles were screened for eligibility. Only those studies approved by both authors were included in the review. Agreement between the authors on the quality of the articles ranged between 90 and 100%. All the disagreements were resolved by consensus among the authors. Extracted data included authors, the origin of studies, source population, study settings and duration, inclusion/exclusion criteria, data sources and measurement, sample size, and mortality.

2.4. Methodological quality

We used “Grading quality of evidence and strength of recommendations” (GRADE criteria) to assess the quality of the included studies and rate the level of evidence. The methodological quality of the selected studies was assessed based on certainty assessment [Study design, Risk of bias, Inconsistency, Indirectness, Imprecision, and Other considerations] by Cochrane Grade pro software. We have evaluated the quality of the proposed outcome i.e. mortality.

2.5. Data analysis and synthesis

Odds ratios (OR) were calculated for categorical variables. The decision to select either fixed effect or random effects model depends on results of statistical tests for heterogeneity. Data heterogeneity was assessed using the Cochrane Q homogeneity test with significance set at p < 0.10. If the studies were statistically homogeneous, fixed effect model was selected. A random effects model was used when studies were statistically heterogeneous. The Higgins’ I² test is the ratio of true heterogeneity to the total variation in observed effects. A rough guide to interpretation of I² test is 0 to 25%: might not be important; 25 to 50%: may represent moderate heterogeneity; 50 to 75%: may represent substantial heterogeneity; and >75%: considerable heterogeneity.

Publication bias was visually estimated by assessing funnel plots. Pooled estimates of mortality were calculated using a Microsoft Excel add-in, MetaXL v. 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Queensland, Australia). GRADEpro GDT was used for studies grading.

3. Results

The search produced a total of 691 articles; 640 articles were either non-relevant to the topic, duplicates or review articles which were excluded initially. The relevant titles and/or abstracts and full text of the 51 articles underwent detailed evaluation; of which 41 articles were further eliminated which were mainly based on protocol development and narrative reviews and the remaining 10 articles studies [6,7,12,14-20] were reviewed further. Among them, two studies [6,20] were excluded as per the criteria for meta-analysis and both did not have sufficient information regarding categorizing the troponin status or did not assess the outcome (mortality). Finally, eight original studies met all the review criteria and were considered for the final meta-analysis (Fig. 1, Table 1) [7,12,14-19]. Median study duration was 4.4 years with an IQR 3–6.5 years. The total number of patients pooled was 2435, of which 916 were in elevated troponin group and 1519 in control group. Overall average age was 49.6 years. Table 2 shows the details of the quality assessment based on GRADE criteria of the seven selected observational studies (all retrospective). All studies were of moderate quality. Tables 2 & 3 demonstrate the quality assessment of the included seven studies which shows the moderate level of evidence based on GRADE criteria.

3.1. Outcome measures

3.1.1. Effect of elevated troponin level on mortality in overall brain injury [TBI and NT-BI]

Eight brain injury studies compared the mortality in the elevated troponin group with a control group. Total of 826 patients died after all types of brain injury [431 in elevated troponin group and 395 in control group] with a post hoc statistical power of 100% (Fig. 2). The pooled
result manifested a statistically significant increase in mortality in the elevated troponin group compared to the control group (OR 3.37 (95% CI 2.13–5.36)). A further subgroup analysis with only conventional troponin (cTnI) showed an odds ratio (OR 3.09 (95% CI 1.90–5.03)) for mortality in the elevated troponin group compared to the control group.

3.1.2. Effect of elevated troponin level on mortality in TBI

Three traumatic brain injury studies [total sample size = 1540] compared the mortality in the elevated troponin group with a control group. Total of 586 patients died after TBI [310 in elevated troponin group and 276 in control group] with a post hoc statistical power of 100% (Fig. 3). The pooled result manifested a statistically significant increase in mortality in the elevated troponin group compared to the control group (OR 3.31 (95% CI 1.99–5.53)).

3.1.3. Effect of elevated troponin level on mortality in NT-BI

Four NT-BI studies [total sample size = 895] compared the mortality in the elevated troponin group with a control group. Total of 240 patients died after NT-BI [121 in elevated troponin group and 119 in control group] with a post hoc statistical power of 100% (Fig. 4). The pooled result manifested a statistically significant increase in mortality in the elevated troponin group compared to the control group (OR 3.36 (95% CI 1.32–8.6)).
Table 1
Summary of the eligible studies for the meta-analysis.

<table>
<thead>
<tr>
<th>Authors &amp; year</th>
<th>Injury</th>
<th>Study duration (years), design &amp; population</th>
<th>Primary outcome</th>
<th>Type of troponin</th>
<th>Key findings</th>
<th>Beta blockers used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hays &amp; Diringer, 2006 [14]</td>
<td>Nontraumatic head injury</td>
<td>4 years, retrospective study, 235 spontaneous ICH patients whose TnI level measured within 24 h</td>
<td>Whether elevated cTnI influences outcome from ICH</td>
<td>TnI</td>
<td>Mortality was higher in the 18% with a peak TnI level &gt; 0.4 ng/mL (58 vs 34%; p = 0.009); Elevated cTnI was an independent predictor of in-hospital mortality (OR, 3.68; 95% CI, 1.2–11.2).</td>
<td>No</td>
</tr>
<tr>
<td>Ramappa et al., 2008 [15]</td>
<td>Nontraumatic head injury</td>
<td>4 years, retrospective study, 83 patients with SAH and at least 1 measured TnI</td>
<td>Association of elevation of serum cTnI with mortality and neurological outcome in patients with SAH</td>
<td>TnI</td>
<td>Patients with high TnI were more likely to die (55 vs 27%); Peak TnI (p = 0.04) and admission GCS score of &lt;12 (p = 0.02) were independent predictors of death.</td>
<td>No</td>
</tr>
<tr>
<td>Salim et al., 2008 [12]</td>
<td>Severe TBI</td>
<td>8 years, retrospective study, 420 severe TBI patients who had serial TnI testing during 1st 24–48 h</td>
<td>Association and prognostic significance of cTnI elevation in severe TBI</td>
<td>TnI</td>
<td>After adjusting for injury severity, elevated TnI was an independent predictor for mortality (OR, 8.5; 95% CI, 3.46–22.15).</td>
<td>Yes</td>
</tr>
<tr>
<td>Sandhu et al., 2008 [16]</td>
<td>Nontraumatic head injury</td>
<td>Retrospective study, TnI was tested within 24 h in patients with stroke (161/175), ICH (94/107) and SAH (96/96).</td>
<td>Association between increased TnI and in-hospital mortality in patients with ischemic stroke, ICH, and SAH</td>
<td>TnI</td>
<td>Patients with ischemic stroke, ICH, and SAH with elevated TnI had increased in-hospital mortality.</td>
<td>No</td>
</tr>
<tr>
<td>Gupte et al., 2013 [17]</td>
<td>Nontraumatic head injury</td>
<td>3 years, retrospective study, 225 SAH patients, 23% had positive TnI</td>
<td>Frequency of troponin abnormalities in SAH and determine its impact on in-hospital mortality</td>
<td>TnI</td>
<td>In unadjusted analysis, increased TnI was significantly associated with in-hospital mortality; however, on multivariable logistic regression, only age and severe grade hemorrhage were the predictors of mortality. Patients with highest TnI (≥0.21 ng/mL) had significantly higher risk of in-hospital mortality (HR, 1.39; 95% CI, 1.04–1.88) compared with patients with undetectable TnI. Mortality risk increases with higher troponin levels (p &lt; 0.0001).</td>
<td>No</td>
</tr>
<tr>
<td>Cai et al., 2016 [18]</td>
<td>TBI</td>
<td>6.5 years, retrospective study, 580 TBI patients; 30.9% had detectable TnI within 24 h of admission</td>
<td>Association of cTnI elevation with all cause in-hospital mortality following isolated sTBI</td>
<td>TnI</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hasanin et al. 2016 [7]</td>
<td>Severe TBI</td>
<td>1 year prospective observational study. Cohort of 50 patients with severe TBI. In hospital mortality was (32) 64%. Elevated troponin was in 27 patients and rest was control.</td>
<td>To report the incidence of cardiac injury in patients with TBI and its impact on patient outcome.</td>
<td>TnI</td>
<td>In hospital mortality was (32) 64%. Elevated troponin was in 27 patients and rest was control. There were 22 mortalities in elevated troponin group (27) and 10 mortalities in normal (23).</td>
<td>No</td>
</tr>
<tr>
<td>El-Menyar et al. 2018 [19]</td>
<td>TBI</td>
<td>4 years, retrospective study, 826 patients sustained TBI and required intubation. Of these patients, 490 underwent serum HsTnT testing. Overall (n = 490)</td>
<td>Predictive value of serum HsTnT in intubated patients who had sustained traumatic brain injury (TBI)</td>
<td>HsTnT</td>
<td>Positive HsTnT was an independent predictor of mortality in multivariate models (adjusted OR 3.10, 95% CI 1.308–7.351) even after excluding chest injury (adjusted OR 4.18, 95% CI 1.320–13.231).</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 2
Quality assessment of the included observational studies.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Non-RCT, Retrospective study</td>
<td>Non-RCT, Retrospective study</td>
<td>Non-RCT, Retrospective study</td>
<td>Non-RCT, Retrospective study</td>
<td>Non-RCT, Retrospective study</td>
<td>Non-RCT, Retrospective study</td>
<td>Non-RCT, Retrospective study</td>
<td>Non-RCT, Retrospective study</td>
</tr>
<tr>
<td>Risk of bias Inconsistency</td>
<td>No. The study population was ICH, intervention was elevated troponin level vs normal, and outcome assessment was consistent in terms of mortality.</td>
<td>No. The study population was SAH, intervention was elevated troponin level vs normal, and outcome assessment was consistent in terms of mortality.</td>
<td>Yes. This study has wide confidence interval. The study population was ICH and SAH patients, intervention was elevated troponin level vs normal, and outcome assessment was consistent in terms of mortality.</td>
<td>No. The study population was severe TBI, intervention was elevated troponin level vs normal, and outcome assessment was consistent in terms of mortality.</td>
<td>No. The study population was severe TBI, intervention was elevated troponin level vs normal, and outcome assessment was consistent in terms of mortality.</td>
<td>No. The study population was severe TBI, intervention was elevated troponin level vs normal, and outcome assessment was consistent in terms of mortality.</td>
<td>No. The study population was intubated traumatic brain injury patients, intervention was elevated troponin level vs normal, and outcome assessment was consistent in terms of mortality.</td>
<td>No. The study population was intubated traumatic brain injury patients, intervention was elevated troponin level vs normal, and outcome assessment was consistent in terms of mortality.</td>
</tr>
<tr>
<td>Indirectness</td>
<td>There is no indirectness as all adults [mean age 52] ICH patients were included, intervention was cTnI ≥ 0.10 ng/mL, and comparator group was similar with cTnI = 0.10 ng/mL, outcome measure was appropriate to assess the effect of intervention.</td>
<td>There is no indirectness as all adult [mean age 59] SAH patients were included, intervention was cTnI ≥ 2.0 ng/mL, and comparator group was similar with cTnI = 2.0 ng/mL, outcome measure was appropriate to assess the effect of intervention.</td>
<td>There is no indirectness as all adult [mean age 43.9] ICH and SAH patients were included, intervention was cTnI ≥ 0.4 ng/mL, and comparator group was similar with cTnI ≤ 0.30 ng/mL, outcome measure was appropriate to assess the effect of intervention.</td>
<td>There is no indirectness as all adult [mean age 67] ICH and SAH patients were included, intervention was cTnI &gt; 0.5 ng/mL, and comparator group was similar with cTnI ≤ 0.14 ng/mL, outcome measure was appropriate to assess the effect of intervention.</td>
<td>There is no indirectness as all adult [mean age 56.3] severe TBI patients were included, intervention was cTnI &gt; 0.06 ng/mL, and comparator group was similar with cTnI ≤ 0.06 ng/mL, outcome measure was appropriate to assess the effect of intervention.</td>
<td>There is no indirectness as all adult [mean age 31] severe TBI patients were included, intervention was cTnI &gt; 0.056 ng/mL, and comparator group was similar with cTnI ≤ 0.056 ng/mL, outcome measure was appropriate to assess the effect of intervention.</td>
<td>There is no indirectness as all adult [mean age 30.5] intubated severe TBI patients were included, intervention was HsTnT (≥ 14 ng/L), and comparator group was similar with negative HsTnT (&lt; 14 ng/L), outcome measure was appropriate to assess the effect of intervention.</td>
<td>There is no indirectness as all adult [mean age 24.9] ICH patients were included, intervention was cTnI ≥ 0.4 ng/mL, and comparator group was similar with cTnI ≤ 0.4 ng/mL, outcome measure was appropriate to assess the effect of intervention.</td>
</tr>
<tr>
<td>Imprecision</td>
<td>There is no possibility of imprecision. It does not appear to be an issue. Mortality 1.24 (0.73, 2.11)</td>
<td>There is no possibility of imprecision. It does not appear to be an issue. Mortality 3.00 (1.29, 8.40)</td>
<td>There is no possibility of imprecision because of wide confidence interval. One point imprecision may exists. Mortality 1.94 (1.26, 3.00)</td>
<td>There is possibility of imprecision because of wide confidence interval. Intervention was positive. Mortality 9.21 (4.91, 17.27)</td>
<td>There is no possibility of imprecision. It does not appear to be an issue. Mortality 3.51 (1.75, 7.05)</td>
<td>There is no possibility of imprecision. It does not appear to be an issue. Mortality 2.85 (1.97, 4.12)</td>
<td>There is possibility of imprecision because of wide confidence interval. One point imprecision may exists. Mortality 5.72 (1.6, 20.45)</td>
<td>There is no possibility of imprecision. It does not appear to be an issue. Mortality 5.95 (3.29, 10.76)</td>
</tr>
<tr>
<td>Other considerations</td>
<td>There is no publication bias, large effect, dose response gradient. But anticipated plausible confounding factor might reduce demonstrated effect because it is a prospective non RCT.</td>
<td>There is no publication bias, large effect, dose response gradient. But anticipated plausible confounding factor might reduce demonstrated effect because it is a prospective non RCT.</td>
<td>There is no publication bias, large effect, dose response gradient. But anticipated plausible confounding factor might reduce demonstrated effect because it is a prospective non RCT.</td>
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<td>There is no publication bias, large effect, dose response gradient. But anticipated plausible confounding factor might reduce demonstrated effect because it is a prospective non RCT.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
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</tbody>
</table>

* This study has low or unclear risk of bias. Plausible bias unlikely to seriously alter the results. This study has no serious risk of bias, which does not downgrade the quality.
Table 3
GRADE summary of finding for elevated troponin compared to normal for mortality in brain injury patients.

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Summary of findings</th>
<th>Mortality among brain injury patients</th>
<th>Mortality among TBI patients</th>
<th>Mortality among NT-BI patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants (studies)</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>916 cases</td>
<td>Not serious</td>
<td>Serious</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td>1519 controls (8 observational studies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>653 cases</td>
<td>Not serious</td>
<td>Serious</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td>887 controls (4 observational studies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>263 cases</td>
<td>Not serious</td>
<td>Serious</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td>632 controls (4 observational studies)</td>
<td></td>
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</tbody>
</table>

CI: confidence interval; OR: odds ratio.

a Sandhu et al. [16] study has wide confidence interval.
b Hasanin et al. [7] study has wide confidence interval.
3.2. Heterogeneity among included studies

The results for the test of heterogeneity for the meta-analysis of effect of elevated troponin level on mortality were displayed towards the bottom of the forest plot in the line: for all brain injury studies $Q \chi^2 = 33.16$, $p = 0.001$, $I^2 = 79\%$, $\tau^2 = 0.326$ (Fig. 2), for TBI $Q \chi^2 = 10.01$, $p = 0.02$, $I^2 = 70\%$, $\tau^2 = 0.174$ (Fig. 3), for NT-BI $Q \chi^2 = 23.12$, $p = 0.001$, $I^2 = 87\%$, $\tau^2 = 0.788$ (Fig. 4). However, $I^2$ was not $\geq 75\%$, a random effect model was considered. $\tau^2$ reflected the amount of true heterogeneity among the studies, which was less in the TBI group, compared to other two groups (NT-BI and overall brain injuries).

3.3. Publication bias and funnel plots

For all of the above analyses, sensitivity analysis yielded consistent results. Based on a visual inspection of the funnel plot, there has been no evidence of publication bias for the included studies (Fig. 5).

4. Discussion

The present meta-analysis highlights the utility of serum cardiac troponins testing post-brain injury regardless of the mechanism of injury. Although, there is no published randomized clinical trial yet, at least 10 published studies have addressed the association of elevated serum cardiac troponins and risk of mortality in patients with brain injury [6,7,12,14-20]. We identified eight, moderate-quality observational studies that described this association and met the inclusion criteria for meta-analysis [7,12,14-19]. Fig. 1 summarizes each study population based on the troponin status and outcome. The mortality rates were greater in those who had positive troponin test regardless of the type of brain injury (traumatic or non-traumatic) in comparison to those who had normal troponin test. Also, the type of troponin assay did not change such relationship between the test positivity and mortality post-brain injury.

Seven studies using cTnI were conducted in the United States of America ($n = 6$) and Egypt ($n = 1$) [7,12,14-18], while one study from Qatar utilized HsTnT assay [19]. Four retrospective studies [7,15-17] were under powered and having wide confidence interval, whereas...
the other four retrospective studies were appropriately powered to measure the study outcomes.

There is one meta-analysis assessed cTn use in non-cardiac patients from 25 studies [21]. These studies included patients who were admitted to an intensive care unit (n = 10 studies), patients with pulmonary embolism (n = 7 studies), sepsis (n = 5 studies), chronic obstructive lung disease (n = 3 studies), diabetic ketoacidosis (n = 1 study), and hypertensive emergency (n = 1 study). Among these studies, the cardiac troponins used included cTnI (n = 17), cTnT (n = 8) and HsTnT (n = 2). Based on the inclusion criteria and search, the use of the conventional serum Troponin T in TBI studies has not been reported yet [22]. Elevated troponin and 30-day in-hospital mortality showed a pooled OR of 3.88 (95% CI 2.90 – 5.19). The duration of the included studies follow-up ranged from 28 days to 4 years, until discharge or up to in-hospital mortality. In addition, there was an increased risk of long-term mortality at 6 months while pooling six studies (OR 4.21, 95% CI 1.84 – 9.64). All these studies were graded a moderate quality evidence for both long- and short-term mortality but this meta-analysis did not include any brain injury studies [21].

In patients with TBI, Salim et al. [12] found that elevated cTnI is an independent predictor of in-hospital mortality (OR 1.94, 95% CI (1.26 – 3.00)). Further in 2016, Cai et al. reported that elevated cTnI level was an independent predictor of in-hospital mortality (OR 2.85, 95% CI (1.97 – 4.12)), showing a dose-response trend [18]. Hasanin et al. [7] also reported that elevated cTnI level increased the in-hospital mortality (OR 5.72, 95% CI (1.6, 20.45)). In 2018, El-Menyar et al. found that positive HsTnT was associated with in-hospital mortality among TBI patients (OR 5.95, 95% CI (3.29 – 10.76)). Our meta-analysis showed among TBI patients, the effect of elevated troponin on mortality had a pooled odds ratio of 3.31 (95% CI 1.99 – 5.53) among TBI patients and 3.36 (95% CI 1.32 – 8.6) among NT-BI patients.

There are several factors that could explain the release of troponin in patients with TBI apart from the direct cardiac contusion. These factors include stress-induced hyperadrenergic status that may cause microthrombosis, coronary spasm, cardiomyopathy or arrhythmias [19,22,23]. Similarly, NT-BI such as acute stroke has been found to increase sympathetic tone and the risk of arrhythmias and myocardial damage [22]. The sympathetic activity measured by plasma norepinephrine levels were found to be higher in the stroke patients compared with the control group [22]. In one study evaluated TnI release as a prognostic marker in patients with subarachnoid hemorrhage, found that peak TnI levels were associated with a significantly increased risk of LV dysfunction [24]. Also, patients with subarachnoid hemorrhage were found to have a threefold greater in their plasma norepinephrine levels [25].

This meta-analysis could be of great clinical interest to improve survival and functional outcomes of TBI patients, as there are no guidelines or consensus for management of TBI patients based on the cardiac marker (i.e. troponin test status) yet. We suggest the use of high sensitive troponin assay to detect myocardial injury at early stage (within the first 3 h post-brain injury); however its cost-effectiveness in comparison to the conventional assay needs further evaluation. Serum cardiac

**Fig. 4.** Forest plot representing effects of elevated troponin on the mortality of non-traumatic brain injury patients.

**Fig. 5.** Funnel plot of (a) all brain injury studies (b) TBI studies, (c) NT-BI studies.
Troponin test may rapidly identify patients at high risk of death for whom beta blockers could have a substantial clinical benefit (if no contraindication) by counteracting the effect of brain injury-induced catecholamine surge [12,19,22,23]. The present meta-analysis could raise the debate for a potential therapeutic use and benefit of early beta blockers administration in patients with brain injury regardless of the mechanism of injury and based on the initial troponin results.

A recent meta-analysis [26] included 9 studies (2005 TBI patients with beta blocker use and 6240 without beta blockers), showed that beta blockers use post-TBI was associated with a significant reduction of hospital death (pooled OR 0.39, 95% CI: 0.27–0.56). The authors conditionally recommended the hospital beta blockers use in adults with acute TBI with no contraindications (i.e., heart rate < 50 with symptoms or SBP < 90 mm Hg). Studies in the meta-analysis [26] showed a consistent effect and did not report a significant cardiovascular deterioration from the beta blockers use; however, this recommendation was based on a synthesis of low quality studies that necessitate further prospective randomized clinical trials with enough power to initiate a cascade for practical changes.

5. Limitations

The searches for this review were in most of the citation databases and reference lists from the included studies and we have accessed the paid articles as well. We also contacted the authors to fix errors in one published paper [7]. Our study included the published studies as we could not find out the gray literature that was not published and so we admit the potential publication bias. Inclusion of only eight studies in this meta-analysis could be one of the limitations, however, we have done a post hoc power calculation for mortality comparison, there were 395 mortality out of 1519 in control group (normal troponin) and 431 out of 916 in intervention group (elevated troponin) which showed a power of 100% at 5% significance level. The timing to check troponin post-brain injury is also an important cofounder. The associated direct cardiac injury was not given in most of the studies included in this meta-analysis. Moreover, outcomes in these studies were not adjusted for the thoracic injuries except for one study [19].

In conclusion, elevated troponin is associated with higher mortality in patients with traumatic and non-traumatic brain injury. Furthermore, high-quality prospective clinical trials are needed to support the implication of troponin as a prognostic marker in brain injury patients.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Author’s contribution

All authors contributed substantially in the design of the study interpretation of the data, writing the manuscript and approving the submission.

Acknowledgment

We thank all the research office team at the trauma and vascular surgery units at HMC.

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