Cardiac Troponin Elevation and Outcome after Subarachnoid Hemorrhage: A Systematic Review and Meta-analysis

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Background: Cardiac abnormalities frequently occur after subarachnoid hemorrhage (SAH). Cardiac troponin (cTn) is a preferred biomarker for the diagnosis of cardiac damage, and the clinical significance of cTn elevation after SAH remains controversial. This meta-analysis was performed to assess the association between cTn elevation and patient outcomes, including delayed cerebral ischemia (DCI), poor outcome (death or dependency), and death in SAH patients. *Methods:* PubMed, Embase, and the Cochrane Library were searched for observational studies reporting an association between cTn elevation and outcome after SAH that were published before December 31, 2014. We extracted data regarding patient characteristics, cTn elevation, and outcome measurements (DCI, poor outcome, or death). Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using a random-effects model. *Results:* Twelve studies involving 2214 patients were included in data analysis. Elevation of cTn was observed in 30% of the patients. The cTn elevation was associated with an increased risk of DCI (RR, 1.48; 95% CI, 1.23-1.79), poor outcome (RR, 1.91; 95% CI, 1.51-2.40), and death (RR, 2.53; 95% CI, 2.04-3.12). At the 3- and 12-month follow-ups, cTn elevation was associated with higher rates of DCI (RR, 1.51; 95% CI, 1.11-2.07), poor outcome (RR, 1.91; 95% CI, 1.51-2.40), and death (RR, 2.78; 95% CI, 1.80-4.29). At in-hospital follow-ups, cTn elevation was also associated with the higher rate of death (RR, 2.33; 95% CI, 1.76-3.07). *Conclusions:* cTn elevation in SAH patients is associated with an increased risk of DCI, poor outcome, and death after SAH. **Key Words:** Subarachnoid hemorrhage—cardiac troponin—cardiac abnormalities—delayed cerebral ischemia—poor outcome—death.

Subarachnoid hemorrhage (SAH) is a common critical disease with approximately 50% fatality.[1] In addition to the impact caused by the initial bleeding and subsequent neurologic damage, neurocardiogenic injury has been linked with increased morbidity and mortality in patients with SAH.[2-4] Neurocardiogenic injury is believed to be a neurally mediated process as a consequence of brain damage rather than manifestation of coronary artery disease,[5,6] which could further aggravate the changes in cerebral blood flow induced by SAH.[6]

Cardiac troponins (cTn) T and I provide largely identical information and are widely used as the preferred biomarkers for the diagnosis of myocardial infarction[7] and cardiac damage after SAH.[8-10] Cardiac abnormalities including cTn elevation were associated with poor outcome in patients with SAH in a previous meta-analysis.[2] cTn is positively correlated with the severity of SAH (Hunt–Hess scale), arrhythmias like ventricular tachycardia/fibrillation, and regional wall motion abnormalities (WMAs).[3,11] One study found, after adjusting for admission Hunt–Hess grade, age, and aneurysm size, that cTnI elevation was significantly associated with vasospasm and mortality.[10] Indeed, an association between cTn elevation and poor outcome after

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SAH has been demonstrated based on previous studies.[12-18] Many studies with multiple sequential measurements have been recently published. Therefore, this meta-analysis was performed on observational studies to assess the association between cTn elevation and the occurrence of delayed cerebral ischemia (DCI), poor outcome, and death after SAH.

Materials and Methods

We conducted this study according to the methods of the Cochrane Handbook for Systematic Reviews of Interventions. The findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search Strategy

Two librarians independently searched PubMed, Embase, and the Cochrane Library for studies describing the association between the cTn elevation and outcome after SAH that were published before December 31, 2014. The following key words were used: "subarachnoid haemorrhage" OR "subarachnoid hemorrhage" OR "subarachnoid blood" OR "subarachnoid bleeding" OR "intracranial bleeding" OR "intracranial aneurysm" OR "SAB" OR "SAH." Each of these key words was combined with the key word "troponin." The bibliographies of previous reviews and the included publications were also manually checked to identify other potentially relevant studies. This procedure was repeated until no further relevant studies were found.

Study Selection

Two authors (L.M.Z. and Z.L.W.) independently assessed the eligibility of studies. Only studies published in English were included in this review. We included observational studies that examined the association between cTn and outcome after SAH. SAH was required to be documented by either computed tomography (CT) scanning or cerebrospinal fluid examination. cTnI assays are made by multiple manufacturers and different antibody pairs are used by each manufacturer, so cTn assays are different and not interchangeable in the included studies. The upper limits of normal cTn varied across the included studies and were based on the description in each article. Outcomes after SAH were defined as DCI, poor outcome, or death. Meeting abstracts, case reports, reviews, and studies with fewer than 10 patients were excluded.

Only studies that included consecutive patients were eligible to avoid selection bias. In the case of duplicate or overlapping data, only the report with the largest number of patients was used for data extraction. Disagreements with respect to the literature search and study eligibility were resolved by discussing the article in question until a consensus was reached.

Quality Assessment and Data Extraction

The 2 authors involved in selecting the studies also evaluated the quality of the included studies using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (https://www.strobe-statement.org). For every article, the 2 authors (L.M.Z. and Z.L.W.) independently assigned a score (either 0 or 1) to each of the 22 STROBE items; these scores were then added to yield the STROBE score. Several STROBE items consist of subitems which were also scored as 0 or 1 and then averaged. The 2 authors solved disagreements by direct communication.

We extracted the following data: definition of inclusion and exclusion criteria, the last name of the first author, publication year, study design (prospective cohort study or retrospective cohort study), number of included patients, sex, mean age, follow-up period, patients with poor condition on admission and patients with DCI, poor outcome, or death. In cases of disagreement, the investigators reviewed the article in question together until a consensus was reached. Neurologic condition on admission was dichotomized as either "poor" or "good" based on the following scoring system used in the particular article: Hunt–Hess,[19] World Federation of Neurosurgical Societies,[20] Glasgow Coma Scale,[21] or Botterell.[22]

Poor condition on admission was defined as a Hunt–Hess score of 3 or more, WFNS score of 3 or more, GCS score of less than 12, or a Botterell score of 3 or more. As a determinant, we extracted the incidence of cTn elevation on admission. If the studies included other determinants, we also extracted these for summary purposes, including echocardiographic WMAs, abnormal admission electrocardiograph (T-wave inversion, ST-segment abnormalities, Q waves, or QTc prolongation), elevated brain natriuretic peptide (BNP), and elevated N-terminal prohormone of B-type natriuretic peptide (NT-proBNP). The number of patients with DCI, the number of patients with poor outcome, and the number of deaths from any cause were recorded as outcome measurements. Poor outcome was defined as death or dependence on daily living activities, based on a handicap scale such as the modified Rankin Scale (dichotomized at > 3) or the Glasgow Outcome Scale (dichotomized at ≤ 3).

There were several definitions of DCI among the various studies. Considering the heterogeneity of DCI definitions, we simply extracted the number of patients with DCI reported by the studies without adjusting these numbers using a predefined DCI definition. Data regarding therapy were not assessed here, as such information was not present in several of the included studies.

Data Synthesis

Relationships between the 3 outcome measurements and cTn elevation were analyzed. The crude proportions