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REVIEW

Impact of echocardiographic wall motion abnormality and cardiac biomarker elevation on outcome after subarachnoid hemorrhage: a meta-analysis

Limin Zhang[1] · Bing Zhang[1] · Sihua Qi[1]

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Abstract

Cardiac abnormalities (echocardiographic wall motion abnormality (WMA), biomarker elevation of cardiac troponin (cTn), B-type natriuretic peptide (BNP), or N-terminal prohormone of B-type natriuretic peptide (NT-proBNP)) frequently occur after subarachnoid hemorrhage (SAH). The clinical significance of cardiac abnormalities after SAH remains controversial. This meta-analysis was performed to assess the association between cardiac abnormalities and patient outcomes, including delayed cerebral ischemia (DCI), poor outcome, and death in SAH patients. PubMed and Embase were searched for observational studies reporting an association between cardiac abnormalities and outcome after SAH that were published before 31 December 2017. We extracted data regarding patient characteristics, cardiac abnormalities, and outcome measurements (DCI, poor outcome, or death). Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using a random-effects model. Twenty-six studies involving 3917 patients were included in our data analysis. WMA showed significant associations with higher rates of DCI (RR, 2.03; 95% CI, 0.99–4.15), poor outcome (RR, 1.45; 95% CI, 1.08–1.93), and death (RR, 2.54; 95% CI, 1.59–4.05). cTn elevation was associated with an increased risk of DCI (RR, 1.48; 95% CI, 1.23–1.79), poor outcome (RR, 1.85; 95% CI, 1.49–2.30), and death (RR, 2.68; 95% CI, 2.19–3.27). Elevation of BNP or NT-proBNT was significantly associated with higher rates of DCI (RR, 1.87; 95% CI, 1.16–3.02). WMA and elevation of cTn, BNP, and NT-proBNP in SAH patients are associated with an increased risk of DCI, poor outcome, and death after SAH.

Keywords Subarachnoid hemorrhage · Cardiac abnormalities · Echocardiographic wall motion abnormality · Cardiac biomarker elevation · Delayed cerebral ischemia · Poor outcome · Death

Introduction

Subarachnoid hemorrhage (SAH) is a devastating cerebrovascular disease that occurs at a relatively young age and threatens brain perfusion and function. SAH is a serious and significant health problem, especially given its poor prognosis, high rates of mortality and disability, and poor clinical outcomes [1]. Cardiac abnormalities after SAH have been described in many reports, and cardiac abnormalities, including echocardiographic wall motion abnormalities (WMA) and elevated biochemical markers of myocardial damage and congestive heart failure, are associated with poor outcomes in some studies [2]. Cerebral autoregulation is disturbed following SAH [3], and cardiac abnormalities may lead to decreased focal and global cerebral perfusion and may contribute to the development of delayed cerebral ischemia (DCI) [4, 5]. DCI is the single most crucial cause of mortality and morbidity after SAH [6]. These findings highlight the clinical importance of cardiac abnormalities for the outcome of SAH.

We conducted a meta-analysis on observational studies to assess the association between cardiac abnormalities (WMA and elevated biochemical markers of myocardial damage and congestive heart failure) and the occurrence of DCI, poor outcome, and death after SAH. Electrocardiographic changes in the articles were heterogeneous [2, 7]; therefore, we did not assess ECG abnormalities in this study.

✉ Bing Zhang
zhang20170616@163.com

✉ Sihua Qi
sihuaqi2014@163.com

[1] Department of Anaesthesiology, The Fourth Affiliated Hospital, Harbin Medical University, Yiyuan Street 37, Harbin 150001, China

Materials and methods

We managed this study according to the methods of the *Cochrane Handbook for Systematic Review and Meta-Analysis*. We reported the findings according to the *Preferred Reporting Items for Systematic Review and Meta-Analysis* statement.

Search strategy

Two authors (LZ and BZ) independently searched PubMed and Embase for studies reporting associations between cardiac abnormalities and SAH outcome that were published before 31 December 2017. The following keywords were used: "subarachnoid hemorrhage" OR "subarachnoid hemorrhage" OR "subarachnoid blood" OR "subarachnoid bleeding" OR "intracranial bleeding" OR "intracranial aneurysm." Each of these keywords was combined with the keyword "echocardiography," "echocardiographic," "stunning," "left ventricular dysfunction," "LV dysfunction," "apical ballooning," "takotsubo," "myocardial damage," "myocardial necrosis," "troponin," "B-type natriuretic peptide," "BNP," "N-terminal prohormone of B-type natriuretic peptide," and "NT-proBNP" in different combinations. We also manually checked the bibliographies of the included studies and previous reviews to identify other potentially eligible studies. We followed this procedure until no additional studies were found.

Study selection

Two authors (LZ and BZ) independently assessed the eligibility of studies. Only articles published in English were included in this study. We included observational studies that examined the association between cardiac abnormalities and outcome after SAH. SAH had to be diagnosed by either computed tomography (CT) scanning or cerebrospinal fluid examination. Cardiac abnormalities were defined as WMA, elevated cardiac troponin (cTn) levels for myocardial damage, and elevated B-type natriuretic peptide (BNP) or N-terminal prohormone BNP (NT-proBNP) levels for congestive heart failure. Outcomes after SAH are defined as DCI, poor outcome, or death. Studies with fewer than ten patients, conference abstracts, reviews, and case reports were excluded.

Studies that included non-consecutive patients were excluded to avoid selection bias. When there were duplicate or overlapping data, only the report with the largest number of patients was eligible for data extraction. When we had disagreements regarding the literature search and eligibility, we resolved the disagreements by reviewing the article in question until a consensus was reached.

Data extraction and quality assessment

We recorded the definition of inclusion or exclusion criteria of each searched article. We extracted the following data from each included article: the first author's last name, publication year, study design (prospective cohort study or retrospective cohort study), number of included patients, sex, mean age, patients with poor condition on admission, follow-up period, patients with cardiac abnormalities, and patients with DCI, poor outcome, or death. We reviewed the article in question together until a consensus was reached in the case of a disagreement.

The neurological condition on admission in the included articles was defined as poor according to one of the following scoring systems: Hunt-Hess ≥ 3 [8], World Federation of Neurosurgical Societies ≥ 3 [9], and Glasgow Coma Scale < 12 [10]. As determinants, we extracted the incidence of WMA, cTn elevation, and BNP or NT-proBNP elevation. The number of patients with DCI, the number of patients with poor outcome, and the number of deaths from any cause were extracted as outcome measurements. Poor outcome was defined by a handicap scale such as the modified Rankin scale (dichotomized at > 3) or the Glasgow Outcome Scale (dichotomized at ≤ 3).

Among the included studies, there were several varying definitions of DCI. Considering the heterogeneity of DCI definitions, we simply extracted the number of patients with DCI reported by the studies. We did not extract therapy data in the meta-analysis because this information was not present in some of the included studies.

The two authors (LZ and BZ) involved in selecting the studies also evaluated the quality of included studies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (https://www.strobe-statement.org). For every included article, the two authors (LZ and BZ) independently assigned a score (either 0 or 1) to each of the 22 STROBE items. Several STROBE items consist of subitems; the subitems of each item were also scored as 0 or 1 and averaged. These scores were then added to generate the STROBE score. The two authors solved disagreements by direct communication.

Data synthesis

Relationships between cardiac abnormalities (WMA, cTn elevation, and BNP or NT-proBNT elevation) and the three outcome measurements were analyzed. The crude proportions of the extracted variables were calculated. Cross-tables were structured to calculate risk ratios (RRs) for each determinant and outcome in each study. We calculated the pooled RRs with their corresponding 95% confidence intervals (CIs) using a random-effects model with Cochrane's Review Manager version 5.3 (The Cochrane Collaboration, London, UK). We

also tested the statistical heterogeneity (I^2) of the effects using the same program; a value greater than 50% was considered to indicate significant heterogeneity [11].

Results

Study characteristics

The initial database search identified 2590 studies that reported cardiac abnormalities after SAH, and a search of other sources found no additional studies (Fig. 1). Ninety-seven studies were selected after title screening and detailed abstract evaluation. Twenty-six studies [4, 12–36] were selected after detailed evaluation of the full article. No overlap was found among these 26 studies. No study was excluded due to non-English language alone.

Baseline characteristics

Table 1 shows the baseline characteristics of patients included in the meta-analysis. Twenty-six studies with a total of 3917

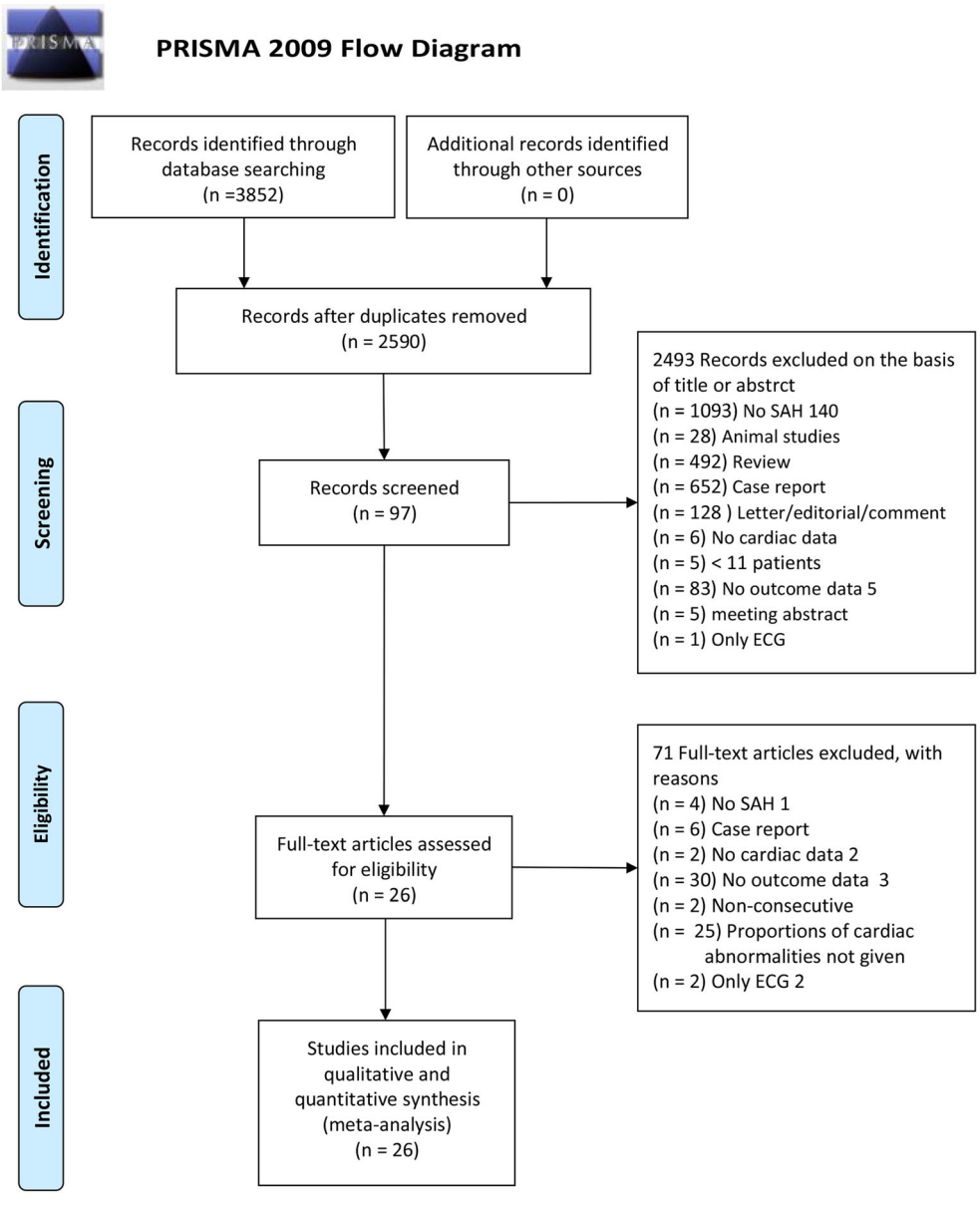

Fig. 1 Flow diagram of the employed search strategy and study selection. Abbreviations: SAH, subarachnoid hemorrhage; ECG, electrocardiograph

Table 1 Baseline characteristics of the included studies

Reference	First author	Year	No. of patients	Men (%)	Mean age (year)	Study design	Strobe score	Patients with poor condition on admission (%)	Follow-up period
[12]	Pollick	1988	13	39	52	P	14	3 (23)	In hospital
[4]	Mayer	1999	72	35	51	R	20	26 (36)	In hospital
[13]	Parekh	2000	39	39	54	P	18	14 (36)	In hospital
[14]	Deibert	2003	43	33	55	P	14	25 (58)	In hospital
[15]	Sviri	2003	38	45	49	P	17	14 (39)	6 months
[16]	Kopelnik	2005	223	37	54	P	17	98 (44)	In hospital
[17]	Naidech	2005	253	28	55	R	17	171 (68)	3 months
[18]	Schuiling	2005	68	22	–	P	17	32 (47)	3 months
[19]	Banki	2006	173	32	54	P	18	–	8 days
[20]	Kothavale	2006	300	32	55	P	18	145 (48)	–
[21]	Yarlagadda	2006	235	40	55	P	18	–	In hospital
[22]	Ramappa	2008	83	40	59	R	18	–	In hospital
[23]	Sandhu	2008	91	34	51	P	17	–	In hospital
[24]	Sugimoto	2008	47	11	62	P	17	35 (74)	2 months
[25]	Hravnak	2009	204	29	55	P	18	121 (59)	3 months
[26]	Miketic	2010	239	28	54	P	17	139 (58)	3 months
[27]	Jyotsna	2010	56	40	46	P	15	26 (46)	10 days
[28]	Ichinomiya	2010	71	20	70	P	17	40 (56)	In hospital
[29]	Temes	2010	119	38	–	P	18	80 (67)	In hospital
[30]	Taub	2011	119	29	58	P	18	61 (51)	In hospital
[31]	Degos	2012	368	37	50	P	19	–	12 months
[32]	Gupte	2013	225	33	57	P	18	122 (56)	In hospital
[33]	Kilbourn	2013	299	106	55	R	17	112 (37)	In hospital
[34]	Bilt	2014	301	91	57	P	20	145 (48)	3 months
[35]	Kilbourn	2015	63	22	57	P	17	26 (41)	3 months
[36]	Duello	2015	175	77	57	R	18	–	30 days
Total			3917	34	55	21/26	Median 18	1435/2790 (51)	

P, prospective; R, retrospective

patients were included. In the 26 studies in which sex distributions were reported, the mean percentage of men was 34%. The mean age varied from 46 to 70 years, with a weighted mean of 55 years (24 studies). The follow-up duration (for outcome assessment) varied from follow-up during the hospital stay (13 studies) to 12 months of follow-up (1 study). The percentage of patients with poor condition on admission varied from 23 to 74% (mean, 51%; 20 studies).

Table 2 presents the proportions of patients with cardiac abnormalities and the proportions of patient outcomes. WMA was reported in 9 to 71% of patients (mean, 22%; 17 studies), cTn elevation in 11 to 52% (mean, 29%; 15 studies), and BNP or NT-proBNT elevation in 9 to 71% (mean, 36%; 5 studies). The cTn, BNP, and NT-proBNT values were measured during the acute stage of SAH. The percentage of patients with DCI varied from 6 to 54% (mean, 27%; 10 studies). The definitions of DCI were slightly different and included the following: scores of temporary focal neurologic signs [13], neurological deterioration and imaging evidence of spasms or CT evidence of infarction [4, 14, 15, 17, 18, 30, 33], neurological deterioration excluding other causes (using CT) [21], development of a new CT lucency with confirmation of vasospasm by serial transcranial Doppler or angiography [29], or probable and definite DCI as one event [34].

A wide interval of the baseline characteristics is one of the major limitations of this study; however, we may not be able to overcome this limitation.

Relationship between determinants and outcome

The chosen end points are not represented in each included study; thus, only a fraction of the studies could be included in the specific analysis (DCI, poor outcome or death).

Figure 2 shows the pooled RRs and corresponding 95% CIs of WMA for DCI, poor outcome, and death. WMA showed significant associations with higher rates of DCI (RR = 2.03; 95% CI, 0.99–4.15; $P = 0.05$; $I^2 = 88\%$), poor outcome (RR = 1.45; 95% CI, 1.08–1.93; $P = 0.01$; $I^2 = 34\%$), and death (RR = 2.54; 95% CI, 1.59–4.05; $P < 0.0001$; $I^2 = 68\%$).

Figure 3 shows the pooled RRs and corresponding 95% CIs of cTn elevation for DCI, poor outcome, and death. cTn elevation showed significant associations with higher rates of DCI (RR = 1.48; 95% CI, 1.23–1.79; $P < 0.0001$; $I^2 = 0\%$), poor outcome (RR = 1.85; 95% CI, 1.49–2.30; $P < 0.00001$; $I^2 = 0\%$), and death (RR = 2.68; 95% CI, 2.19–3.27; $P < 0.00001$; $I^2 = 0\%$).

Table 2 Prevalence of cardiac abnormalities and outcome

Reference	WMA	↑cTn	↑BNP/NT-proBNP	No. of patients with DCI (%)	Patients with poor outcome (%)	No. of deaths (%)
[12]	4 (31)	–	–	–	12 (52)	3 (23)
[4]	9 (13)	–	–	26 (36)	–	–
[13]	5 (13)	8 (21)	–	16 (41)	–	5 (13)
[14]	7 (16)	12 (28)	–	19 (44)	27 (63)	7 (16)
[15]	–	–	17 (45)	14 (37)	–	–
[16]	146 (71)	–	–	–	–	30 (13)
[17]	55 (22)	126 (50)	–	33 (13)	117 (46)	70 (28)
[18]	–	35 (52)	–	–	40 (59)	–
[19]	48 (28)	41 (24)	–	–	–	31 (18)
[20]	79 (26)	–	–	–	–	39 (13)
[21]	45 (19)	52 (22)	14 (9)	18 (6)	–	38 (13)
[22]	–	31 (37)	–	–	–	31 (37)
[23]	–	20 (21)	–	–	–	16 (17)
[24]	13 (28)	–	–	–	–	17 (36)
[25]	19 (15)	64 (31)	–	–	36 (24)	–
[26]	–	80 (33)	–	–	59 (29)	–
[27]	15 (27)	–	–	–	–	5 (9)
[28]	–	8 (11)	–	–	31 (44)	–
[29]	13 (11)	–	–	19 (16)	84 (71)	–
[30]	–	–	59 (50)	46 (39)	–	9 (8)
[31]	–	80 (22)	–	–	–	64 (17)
[32]	15 (9)	47 (23)	–	–	–	51 (23)
[33]	49 (16)	–	–	48 (12)	–	51 (17)
[34]	59 (20)	97 (37)*	159 (71)†	164 (54)	66 (22)	58 (19)
[35]	11 (17)	–	–	–	25 (38)	9 (14)
[36]	–	36 (22)	21 (19)	–	–	32 (18)
Total	592/2665 (22)	737/2576 (29)	270/741 (36)	403/1518 (27)	497/1338 (37)	566/3106 (18)

Data are presented as number (percentage)

cTn, cardiac troponin; WMA, echocardiographic wall motion abnormalities; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; DCI, delayed cerebral ischemia

*Elevated cTn T; others are elevated cTn I

† Elevated NT-proBNP; others are elevated BNP

Figure 4 shows the pooled RRs and corresponding 95% CIs of BNP and NT-proBNT elevation for DCI, poor outcome, and death. Elevation of BNP and NT-proBNT exhibited a significant association with higher rates of DCI (RR = 1.87; 95% CI, 1.16–3.02; $P = 0.01$; $I^2 = 53\%$).

Discussion

The main finding of this meta-analysis patently indicates that cardiac abnormalities (WMA, cTn elevation, and BNP or NT-proBNT elevation) in a high proportion of SAH patients are predictors for adverse clinical outcome in SAH. Because these cardiac abnormalities are also risk factors for the occurrence of DCI, the relationship between cardiac abnormalities and outcome may therefore, at least in part, be explained by the contribution of cardiac abnormalities to the development of DCI.

The cause of cardiac abnormalities after SAH cannot be answered by the present study. Myocardial ischemia is an unlikely cause of the dysfunction because normal myocardial perfusion was reported [37]. The generally accepted cause is that a catecholamine burst due to massive sympathetic activation causes myocardial dysfunction by microvascular dysfunction, epicardial coronary vasospasm, or hyperdynamic contractility with midventricular or outflow tract obstruction;

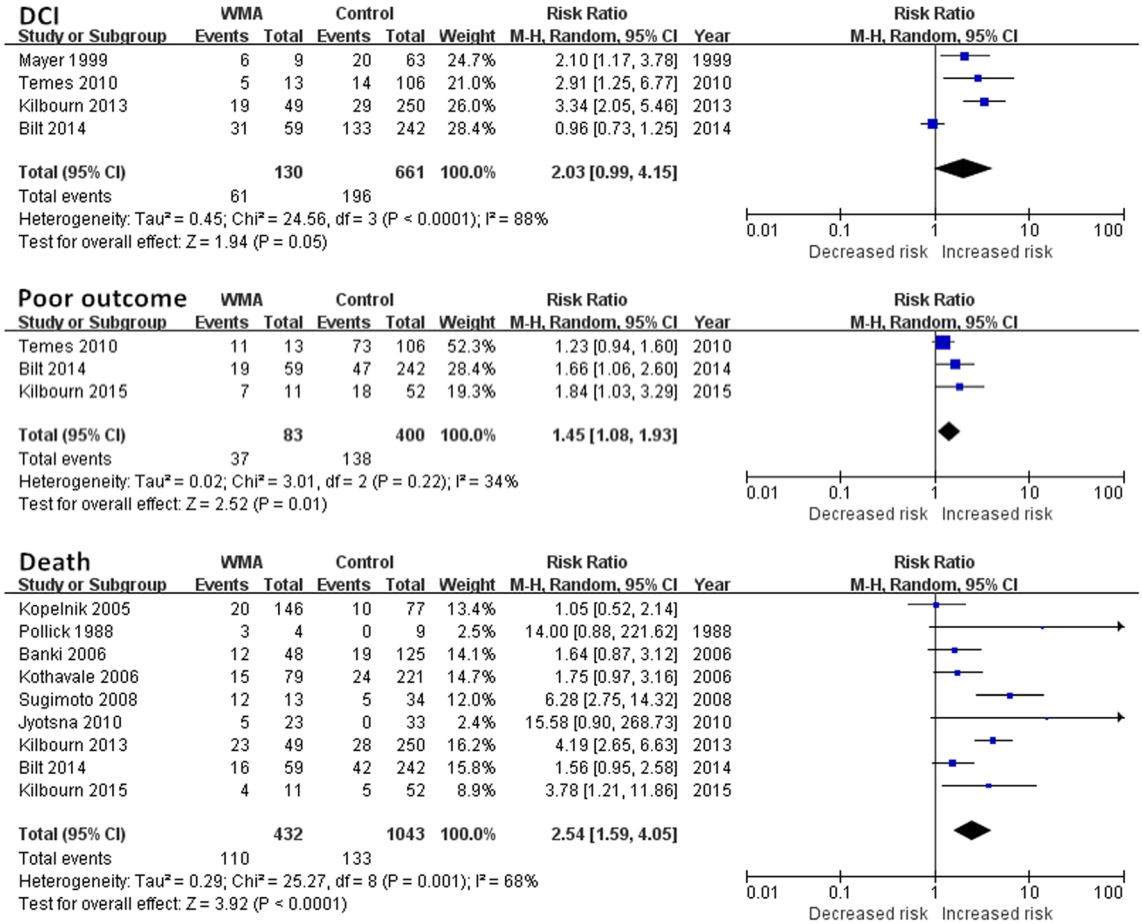

Fig. 2 The pooled RRs of WMA for the outcome measurements. Abbreviations: RRs, risk ratios; CI, confidence interval; WMA, echocardiographic wall motion abnormalities; DCI, delayed cerebral ischemia

another explanation is that these abnormalities are caused by the direct effects of catecholamines on cardiomyocytes [38].

On echocardiography, basal and midventricular segments of the anteroseptal and anterior walls are the most frequently affected in neurogenic stunned myocardium [19, 24, 25, 39]. The transient regional WMA of SAH patients typically extends beyond the territory of a single coronary artery [13, 34, 40–42]. Thus, the apical-sparing pattern of left ventricular dysfunction is believed to favor a neurally mediated mechanism of injury and argues against obstruction or vasospasm of the coronary arteries [43]. Cardiogenic shock can occasionally accompany neurogenic-stunned myocardium with coexisting left ventricular outflow tract obstruction, systolic anterior motion, or mitral regurgitation [44]. On two-dimensional echocardiography using the velocity-vector technique, left ventricular systolic and diastolic dysfunction occurs not only in the radial direction but also in the longitudinal direction in patients with stress cardiomyopathy [45]. Newer techniques such as two-dimensional speckle tracking echocardiography have also been used to distinguish stress cardiomyopathy from other conditions, such as systolic dysfunction complicated by occlusion of the left anterior descending coronary artery [46].

cTn is the most sensitive and specific marker of myocardial injury after SAH among the various biomarkers [13, 14, 47]. cTn elevation is positively correlated with regional WMA [25, 39, 48]. Three protein subunits (troponins I, T, and C) constitute the troponin complex. Troponins I and T have been shown to be unique cardiac isoforms, whereas troponin C isoforms exist in cardiac and skeletal muscle, rendering troponin C unsuitable for diagnostic use. cTns are complexed with actin in cardiac myofibrils, with a smaller fraction (3–6%) soluble in the cytoplasm [49]. cTnI and cTnT are the most widely used biomarkers for myocardial necrosis in clinical patients with suspected acute coronary syndrome [50]. cTnI and cTnT provide identical information and are widely used as the preferred biomarkers to diagnose myocardial infarction [47] and cardiac damage after SAH [13, 14, 17]. Elevated cTnI level is associated with the severity of SAH (Hunt-

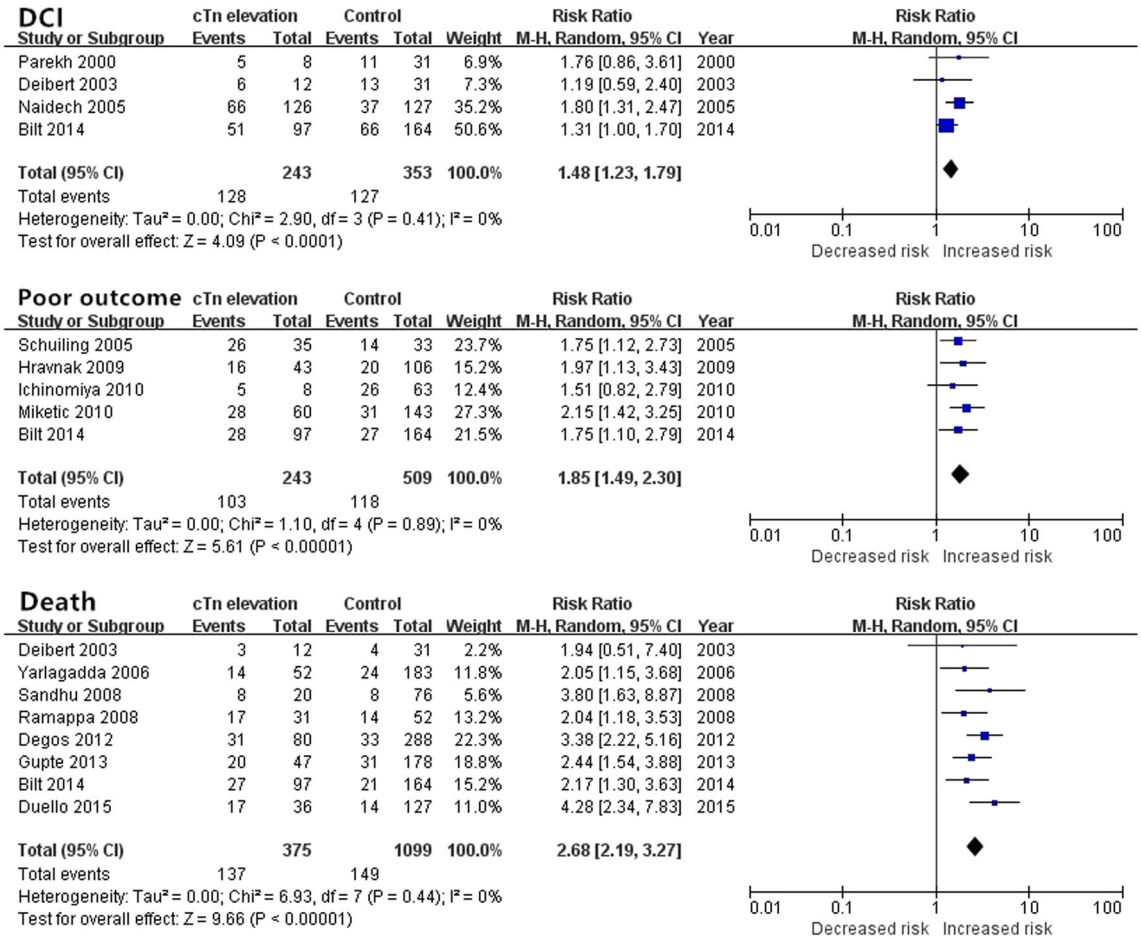

Fig. 3 The pooled RRs of cTn elevation for the outcome measurements. Abbreviations: RRs, risk ratios; CI, confidence interval; cTn, cardiac troponin; DCI, delayed cerebral ischemia

Hess scale) [13, 17, 22, 39, 48], which typically peaks within 2 days after ictus and shows a subsequent decay in levels [17, 48]. cTn elevation (categorized into quintiles: undetectable, > 0–0.5, > 0.5–2.0, > 2.0–10.0, and > 10.0 μg/L) was reported to be significantly associated with an increased likelihood of poor outcome (as measured by a modified Rankin scale score of 4–6) at discharge and at 3 months [17]. In this respect, the presence and the degree of the cardiac abnormality may influence the outcome; therefore, the degree of cTn elevation has been associated with poor outcome. However, after adjusting for age, clinical grade, and aneurysm size, this positive association remained significant at discharge but not at 3 months [17].

B-type natriuretic peptide, a vasoactive hormone with natriuretic, diuretic, and vasodilator activity, is predominantly expressed in the ventricles in response to cardiac overload [51]. BNP is mainly synthesized in cardiac tissue as a result of myocyte stretch [52]. The secretion of BNP and NT-proBNP by the cardiac ventricles occurs in response to increased myocardium wall stress when WMA occurs after SAH [20, 29, 33, 35]. This finding is supported by studies showing that levels of BNP/NT-proBNT in stress cardiomyopathy or takotsubo cardiomyopathy following SAH are elevated and correlate with catecholamine increase and the severity of left ventricular dysfunction [37, 53]. NT-proBNP values increased over the first several days after admission [53–56]. The best subset of variables predicting high NT-proBNP load were female sex, advanced age, high plasma troponin I and T levels at admission, and worse clinical condition at admission [53, 56]. BNP and NT-proBNP appear to have very similar utility in the diagnosis and prognosis of congestive heart failure after SAH and could be used for a screening tool for stress cardiomyopathy after SAH [20, 29, 35, 53–56].

DCI occurs unpredictably at 4–12 days after the initial hemorrhage in approximately 30% of patients [57] and is an important contributor to poor outcome. Many patients with SAH have hypovolemia and narrowed arteries, and cerebral

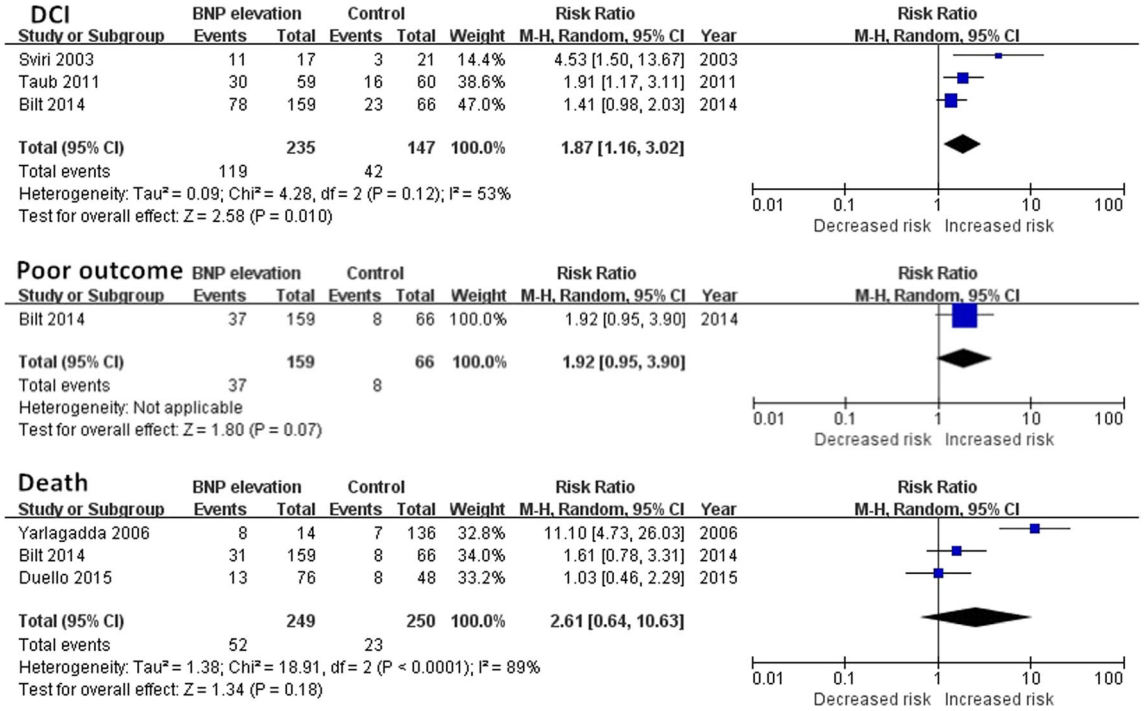

Fig. 4 The pooled RRs of BNP and NT-proBNT elevation for the outcome measurements. Abbreviations: RRs, risk ratios; CI, confidence interval; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; DCI, delayed cerebral ischemia

perfusion autoregulation is disturbed after SAH [58, 59]. The total amount of extravasated blood, the duration of loss of consciousness at the time of ictus [60] and the occurrence of hypovolemia and hypotension [61] are powerful and independent predictors of DCI. The pathogenesis of DCI is usually attributed to vasospasm of the intracranial arteries. However, vasospasm cannot be the only cause of DCI because vasospasm does not exist in one third of patients with DCI, and DCI is not observed in one third of patients with severe vasospasm [62]. Novel pathological mechanisms, including microthrombosis, cortical spreading depression, and damage to cerebral tissue during the first 72 h after aneurysm rupture ("early brain injury"), have been suggested to contribute to DCI [63]. In the current study, we established an association between cardiac abnormalities and DCI after SAH.

These results should be interpreted with caution, as this study has several shortcomings. First, the inclusion of five retrospective studies introduces a high risk of bias in the data collection of retrospective observational studies. Second, the included studies were published over a period of 27 years. During this period, case fatality rates have decreased because the diagnosis and treatment of SAH have improved [1], possibly affecting the prevalence and consequence of cardiac complications on outcomes. Third, the baseline characteristics of the included studies and the prevalence of cardiac abnormalities and outcomes showed large variations, indicating differences in study populations that influence the results. Finally, the heterogeneity of the timing of assessment, the different clinical severity scores and the thresholds used to dichotomize cTn and BNP/NTproBNP may be complicating factors.

Conclusions

WMA and elevation of cTn, BNP, and NT-proBNP are associated with an increased risk of DCI, poor outcome, and death after SAH. Future research should be directed toward elucidating the pathophysiologic mechanisms and potential treatment options for improving outcomes for this vulnerable patient population.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent For this type of study, informed consent is not required.

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