

Cardiovascular Abnormalities and in-Hospital All-Cause Mortality in Patients with Spontaneous Sub-Arachnoid Hemorrhage: An Observational Study

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Received: October 11, 2016 / Published online: December 15, 2016
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ABSTRACT

Introduction: Patients with spontaneous sub-arachnoid hemorrhage (SAH) might develop various cardiac abnormalities, however; the prognostic implications of these cardiac abnormalities are not well known. This study aimed to detect the cardiac abnormality that correlates best with in-hospital all-cause mortality in patients with SAH.

Methods: In this retrospective study, all patients admitted to our institution with a primary diagnosis of SAH, and underwent a transthoracic echocardiogram (TTE) from July 2011 until May 2014, were enrolled. Data gathered included patients' demographics, Hunt and Hess clinical grading, computed tomography SAH Fisher grading, troponin T

level, electrocardiographic (ECG) changes, TTE, and in-hospital all-cause mortality. Multivariate logistic regression of the cardiac abnormalities and in-hospital all-cause mortality was performed.

Results: A total of 247 patients were included in our analysis. In-hospital all-cause mortality was 15.6% (38 patients). The presence of elevated troponin T levels, resting segmental wall motion abnormalities, reduced ejection fraction (<35%), and prolonged corrected QT interval (QTc) on ECG were associated with increased in-hospital all-cause mortality on univariate analysis. On multivariable regression, QTc prolongation was the only independent predictor for in-hospital all-cause mortality ($p = 0.04$).

Conclusions: Prolonged QTc interval on ECG was independently associated with in-hospital all-cause mortality in patients presenting with spontaneous SAH. Whether this is a causative association or a marker of underlying severe clinical presentation of SAH remains unknown.

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Keywords: Cardiac; Echocardiography;
Mortality; Sub-arachnoid hemorrhage

INTRODUCTION

Sub-arachnoid hemorrhage (SAH) is associated with a high mortality, particularly within the first 48 h of presentation [1, 2]. Although cardiac injury in SAH has been previously described [3–5], the prognostic implications of cardiac injury and its relationship with short-term mortality remain controversial. In a meta-analysis of 25 studies, there was a positive association between various cardiovascular abnormalities and mortality in SAH [6]. A few studies illustrated an association and prognostic significance of prolonged QTc in relation to SAH morbidity and mortality [7, 8], while other studies demonstrated that elevated troponin level was associated with increased mortality [9, 10]. A recent study suggested that resting segmental wall motion abnormality (RSWMA) was the only prognostic indicator of short-term mortality, while other cardiovascular abnormalities including QTc prolongation, elevated troponins, or pro-brain natriuretic peptide (BNP), were not significant on multivariable regression analysis [11]. The aim of our study was to further determine which cardiovascular abnormalities in patients with spontaneous SAH correlate with in-hospital all-cause mortality.

METHODS

Study Population

All patients with SAH admitted to the University of Florida, a tertiary academic hospital, from July 2011 until May 2014, using International Statistical Classifications of Diseases (ICD)-9 code 430, for identification of SAH patients, were enrolled. As transthoracic echocardiogram (TTE) findings were pertinent to our study, only patients who had a TTE

performed during the admission were included. TTE was identified by the Current Procedural Terminology (CPT) code 93303. Patients <18 years old, patients mislabeled as SAH, or those with traumatic SAH were excluded from the study. The diagnosis of spontaneous SAH was confirmed by reviewing the computerized tomography (CT) scan reports and the admission documentation notes.

The following data were obtained: patients' age, sex, history of hypertension, diabetes, coronary artery disease, prior stroke, smoking status, chronic kidney disease, baseline Hunt-Hess score (from I to V) [12] and CT scan Fisher grading for SAH (from 1 to 4) [13]. Based on the heart rate measured on the first ECG report, we categorized the patients' rhythm into: tachycardia (>100 bpm), normal (60–100 bpm), and bradycardia (<60 bpm). A prolonged QTc was defined as QTc interval >450 ms in males and >470 ms in females [14]. Bazett's formula was used to calculate the QTc value from the report of first ECG performed after admission [15]. ST elevation was defined as elevation of >1 mm above the J-point in limb leads and 2 mm in chest leads. Ejection fraction was divided into: >55%, 35–55%, and <35%. The presence and location of RSWMA, apical ballooning, and global hypokinesis was also recorded. A cardiologist, expert in cardiac ultrasound, who was not directly involved in the study, reported the TTE results. Highly sensitive troponin T is the cardiac biomarker of choice in our institution, with a reference range of <0.03 ng/ml, thus 0.03 ng/ml and above was considered as elevated troponin T level. In-hospital mortality was confirmed by a death note recorded by the physician at the time of death. All study data were collected and managed using REDCap electronic data capture tools hosted at the University of Florida [16]. All procedures followed were in accordance with

the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. The study protocol was approved by the University of Florida Institutional Review Board, which has waived the informed consent given the retrospective nature of the study.

Statistical Analysis

Descriptive statistics was performed for the baseline demographics, ECG, TTE, troponin levels, and in-hospital mortality. Data were reported as frequencies for categorical variables, as well as mean and standard deviation for continuous variables. Logistic regression with robust standard errors [17] for the estimation of the odds ratio was performed to identify the significant predictors of in-hospital mortality. A final multivariate model included the significant predictors of in-hospital mortality. Results were reported as odds ratio (OR), and corresponding 95% confidence intervals (CI) for the cardiovascular abnormalities. Data analysis was conducted using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline Characteristics

The study initially enrolled 2058 patients with SAH, 295 of them had a TTE performed during the hospitalization. Forty-nine patients had either traumatic SAH or were mislabeled as SAH and thus were excluded from the study. A total of 244 patients were included in the final analysis. The mean age was 59 years, with two-thirds of the patients being females. The

majority of the patients had a clinical (Hunt–Hess) grading of II–IV and a CT Fisher grading of 2. In-hospital all-cause mortality was 15.6% of the patient population (Table 1). Compared to the SAH survivors, the deceased patients were older ($p = 0.009$), with a history of coronary artery disease ($p = 0.02$), higher Hunt-Hess grade ($p < 0.001$), and higher incidence of hydrocephalus ($p = 0.021$) (Table 2).

Cardiac Biomarkers, ECG, and TTE Findings

One hundred thirty-five patients had a troponin level drawn, 37% of those patients had an elevated troponin level during their admission (50 patients), with a mean peak troponin value of 0.15. Meanwhile, 193 patients had an ECG performed during their stay; 78% of those had an abnormal ECG finding (152 patients). The commonest ECG abnormality was prolonged QTc occurring in 57% (95 patients); 13% (26 patients) were found to have tachycardia. Sixteen percent of the total patient population (39 patients) had a RSWMA on TTE, and five patients were found to have findings compatible with takotsubo syndrome (Table 1).

Cardiovascular Predictors of in-Hospital All-Cause Mortality

On univariate analysis, prolonged QTc ($p < 0.005$), elevated troponin level ($p = 0.03$), EF $< 35\%$ ($p = 0.03$), and RSWMA ($p = 0.03$) were associated with an increased risk of in-hospital all-cause mortality. However, T-wave inversion ($p = 0.12$), ST elevation ($p = 0.22$), and tachycardia ($p = 0.24$) were not significantly associated with increased mortality (Table 3). On multivariable regression analysis, prolonged QTc was the only cardiac

Table 1 Patients' characteristics, electrocardiographic, echocardiographic, and cardiac biomarker abnormalities

Patient's demographics	Percentage*
Age, mean (SD)	59 (14)
Male	34
Diabetes	20
Hypertension	71
Chronic kidney disease	3
Prior stroke	7
Prior coronary artery disease	17
Clinical grade (Hunt and Hess)	
I	12
II	26
III	35
IV	21
V	6
CT Fisher grading	
0	1
1	7
2	62
3	30
Hydrocephalus	60
ICU admission	94
ECG changes**	
ST elevation	6
ST depression	10
T wave inversion	26
Prolonged QTc	57
Echo	
EF 35–55%	70
EF < 35%	5
RSWMA	16
Global hypokinesis	3
Apical ballooning	2

Table 1 continued

Patient's demographics	Percentage*
Cardiac biomarkers**	
Elevated troponin	37

SD standard deviation, ICU intensive care unit, EF ejection fraction, RSWMA resting segmental wall motion abnormality

* Percentages are approximated to the nearest whole number

** Percentages represent the number of patients who had the procedure performed, not the total patient population

abnormality that was associated with increased in-hospital mortality (OR 5.1, 95% CI 1.04–25.28, $p = 0.04$) (Table 4).

DISCUSSION

This retrospective analysis illustrates the prognostic significance of prolonged QTc, in relation to in-hospital all-cause mortality in patients with spontaneous SAH. The presence of prolonged QTc interval was associated with a five-times-increased risk of death in SAH patients, compared to those with normal QTc interval. This concurs with the previous studies that evaluated prolonged QTc interval prognostic significance [7, 8]. Ichinomiya et al. reached a conclusion similar to ours; however, they used the Glasgow Outcome Scale at hospital discharge, as a primary outcome, rather than in-hospital mortality. They found that a QTc of 448 ms at day 7 of admission was 73% sensitive (95% CI 68–78%) and 93% specific (95% CI 90–96%) prognostic tool to detect such outcome [7]. Marafioti et al. reported that prolonged QTc was an independent prognostic tool for detection of index mortality in SAH patients when it was

Table 2 Demographic comparison of both dead and alive sub-arachnoid hemorrhage patients

Clinical presentation	Dead patients (%)	Alive patients (%)	<i>p</i> value
Age, mean (SD)	64 (13)	58 (14)	0.009
Male	32	34	0.79
Diabetes	16	21	0.02
Hypertension	79	70	0.001
Chronic kidney disease	0	4	0.085
Smoking*			
Non-smoker	45	33	
Ex-smoker	11	26	
Current smoker	21	31	
History of prior stroke	0	8.5	0.013
History of coronary artery disease	24	16	0.02
Clinical grade (Hunt and Hess)*			<0.001
I	3	14	
II	0	32	
III	24	37	
IV	52	14	
V	21	2	
CT Fisher grading*			0.072
0	0	1	
1	0	5.5	
2	37	44	
3	37	18	
Hydrocephalus	78	56	0.021

All values are approximated to the nearest integer

SD standard deviation, *CT* computerized topography

* Values do not add to 100% due to missing data

compared to other prognostic risk factors such as clinical and CT grading of SAH. Most of the other cardiovascular abnormalities found in SAH such as T-wave inversion, ST changes, and RSWMA, were not reported in that analysis [8].

This study was not designed to address the pathophysiology behind prolonged QTc

association with increased short-term all-cause mortality. However, the association might be explained by either a causal relationship, where prolonged QTc increases the chances of developing ventricular arrhythmias and thus sudden cardiac death [18], or the prolonged QTc could be just a reflection of severe SAH grade, which is associated with poor prognosis [7, 8]. A

Table 3 Univariate analysis of the various cardiac abnormalities and in-hospital mortality

Cardiovascular abnormality	Odds ratio	95% confidence interval	<i>p</i> value*
Hypertension	2.3	0.89–5.68	0.09
Heart rate >100	2.6	0.72–9.19	0.24
ST segment elevation	2.5	0.58–10.73	0.22
T-wave inversion	2.0	0.82–4.95	0.12
Prolonged QTc	5.4	1.77–16.29	<0.005
Elevated troponin	3.0	1.17–7.55	0.03
EF < 35%	3.6	1.24–10.52	0.03
RSWMA	2.7	1.19–6.01	0.03
Global hypokinesis	2.9	0.50–16.28	0.23

QTc corrected QT interval, EF ejection fraction, RSWMA resting segmental wall motion abnormality

* *p* value of less than 0.05 was considered to be statistically significant

Table 4 Multivariable analysis of in-hospital mortality

Cardiac abnormality	Odds ratio	95% confidence interval	<i>p</i> value*
RSWMA	0.8	0.19–3.55	0.79
Elevated troponin	2.8	0.75–10.10	0.13
EF < 35%	1.5	0.49–4.54	0.48
Prolonged QTc	5.1	1.04–25.28	0.04

RSWMA resting segmental wall motion abnormality, EF ejection fraction, QTc corrected QT interval

* *p* value of less than 0.05 was considered to be statistically significant

prospective study by Frontera et al. illustrated the prognostic significance of arrhythmia (including atrial fibrillation, atrial flutter, and sustained ventricular tachycardia) in SAH patients, showing an increased risk of mortality compared to those with normal heart rhythm (OR 8.0, 95% CI 1.9–34.0, *p* = 0.005) [19].

In a multicenter prospective study by van der Bilt, et al. [11], RSWMA was found to be the

only prognostic indicator of short-term mortality, while other cardiovascular abnormalities including QTc prolongation, elevated troponins, or proBNP, lost their significance on multivariable regression analysis. Although our study reached a different conclusion, multiple considerations should be pointed out. First, that study primarily enrolled patients with mild clinical grading, and thus patients who might have the highest risk of in-hospital mortality were excluded. Also, it was not clear, from their method, how the QTc interval was analyzed and if it was incorporated in the multivariable regression analysis or not. Finally, their primary outcome was delayed cerebral ischemia while mortality at 3 months was reported as a secondary outcome, rather than index hospitalization mortality.

Elevated troponin level increased the risk of in-hospital death in our study by univariate analysis; however, this risk lost its significance after the multivariable regression analysis. This observation concurs with some of the previous studies [1, 11]. Meanwhile, studies reporting elevated troponin as a prognostic risk factor for mortality were not adjusted for other cardiovascular abnormalities [10, 20]. In addition, echocardiographic features of takotsubo cardiomyopathy have been linked to worse outcomes [21]; however, owing to the small number of patients who had findings of takotsubo syndrome (i.e., five patients), thus our study could not confirm this association.

Limitations of our study include: first, as a tertiary center we were more likely to have more complex patients, compared to non-tertiary hospital SAH population, however, no patients were excluded because of severity of SAH. Second, there were missing data regarding some of the cardiovascular abnormalities collected, including troponin levels and ECG

reports; however, we do not believe that those were not large enough to affect our final analysis. Third, QTc interval was calculated by computer, which used Bazett's formula. Bazett's formula at best may be imprecise; however, it remains the simplest and most applicable formula for calculation of QTc [22]. Finally, the confidence interval for prolonged QTc association with in-hospital mortality is wide, which might be due to our sample size, and thus any conclusion drawn from our study needs to be confirmed in a larger patient population.

CONCLUSIONS

Among the variable cardiac abnormalities seen in patients with spontaneous SAH, prolonged QTc interval on ECG was the only independent cardiac predictor of in-hospital mortality. These data add to the current literature regarding the cardiac abnormalities to predict short-term all-cause mortality in SAH patient population. Whether this abnormality is a cause of SAH mortality or simply a marker of severe underlying disease remains an unanswered question.

ACKNOWLEDGEMENTS

No funding or sponsorship was received for this study or publication of this article. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Disclosures. Ahmed N. Mahmoud, Akram Y. Elgendy, Hend Mansoor, and Islam Y. Elgendy have nothing to disclose.

Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. The study protocol was approved by the University of Florida Institutional Review Board, which has waived the informed consent given the retrospective nature of the study.

Data availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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