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ORIGINAL COMMUNICATION

High-sensitivity cardiac troponin T and severity of cerebral white matter lesions in patients with acute ischemic stroke

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Abstract

Introduction Cardiac troponin (hs-cTnT) is a sensitive marker of myocardial injury and has been linked to incident dementia. The underlying mechanism of that observation is still unknown. Given that severity of cerebral small vessel disease is a predictor of cognitive decline, we aimed to explore whether there is an association between hs-cTnT and severity of white matter lesions (WML) as a marker of cerebral small vessel disease in patients with ischemic stroke.

Methods We analyzed consecutive acute ischemic stroke patients admitted to Charité-University Hospital, Berlin from 2011 to 2013. Severity of WML was graded on 3T-MRI using the age-related white matter severity score (ARWMS). Patients with hs-cTnT elevation suggestive of acute coronary syndrome (ACS) were excluded (hs-cTnT > 52 ng/l or dynamic change of hs-cTnT > 50%, ESC guideline). We performed unadjusted and adjusted quantile regression models to assess the association between increased hs-cTnT (dichotomized at the 99th percentile, 14 ng/l) and severity of WML.

Results A total of 860 patients was analyzed (median age 73 years, 44.8% female, median ARWMS 6). Patients with elevated hs-cTnT had more extensive WML than those without (median ARWMS 8 vs. 5, adjusted beta for 50th percentile 1.12, 95% CI 0.41–1.84). The association between WML and hs-cTnT elevation was strongest in patients with severe WML (adjusted beta 1.77, 95% CI 0.26–3.27 for 80th WML percentile).

Conclusion Elevated hs-cTnT levels were associated with extent of WML in acute stroke patients. Further studies are needed to assess whether hs-cTnT can be used to identify stroke patients at risk for cognitive decline.

Keywords Cerebral white matter lesions · Cardiac troponin · Stroke · Cognitive impairment

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Introduction

Cardiac troponins are well-established biomarkers that are highly sensitive and specific of myocardial damage [1]. With the development of high-sensitivity assays (hs-cTnT), it has now become possible to measure lower troponin levels more accurately and detect myocardial injury at an earlier stage [2]. Studies suggest that higher levels of hs-cTnT are associated with poorer performance in cognitive tests as well as increased risk of hospitalization with diagnosed dementia during long-term follow-up [3, 4]. This highlights the notion that there may be a connection between subclinical cardiac dysfunction and (subclinical) brain injury.

The degree of subclinical brain injury may be evaluated by performing brain imaging and assessing white matter lesions (WML). WML are a common finding on brain images of older adults [5] and their severity is linked to the degree of cerebral small vessel disease [6]. WML are associated with poorer performance in cognitive tests as well as cortical atrophy [7, 8]. Longitudinal studies have shown a link between WML progression and cognitive decline [9, 10]. In stroke patients, higher degree of WML at the time of the event is associated with poorer cognitive and functional outcome 1 year thereafter [11, 12]. The exact mechanism of how WML evolve is yet to be elucidated, however, their presence and severity are linked to traditional cardiovascular risk factors, such as age, hypertension and cardiac conditions like atrial fibrillation, left ventricular hypertrophy or low cardiac output [13, 14].

Stroke patients represent a high-risk population for the development of cognitive impairment or dementia [15] and cardiac comorbidity is common [16]. Thus, the aim of our study was to assess whether there is an association between hs-cTnT as a marker of subclinical myocardial injury and WML in cerebral MRI as a marker of subclinical brain injury in these patients. We hypothesized that stroke patients with evidence of subclinical myocardial injury (i.e. elevated hs-cTnT) would have more severe WML on cerebral MRI than those with normal hs-cTnT.

Methods

Study population

This cross-sectional study includes patients from the screening list for the TRELAS study cohort. The protocol of the TRELAS study was published before [17]. In short, the aim of the TRELAS study was to determine the frequency of hs-cTnT elevation in patients with acute ischemic stroke, as well as the frequency of culprit lesions in the coronary angiogram. All patients that were included in the TRELAS study underwent coronary angiography. In a matched-pair approach the frequency of coronary culprit lesions in stroke patients with hs-cTnT > 50 ng/l was compared with the frequency of coronary culprit lesions in patients with non-ST elevation acute coronary syndrome. Acute ischemic stroke was defined as acute neurological deficit with onset ≤ 72 h prior to admission and had to be confirmed by cerebral imaging (CT or MRI). To identify suitable patients, a prospective screening list was run that included all consecutive patients with acute ischemic stroke admitted to the Department of Neurology of the Charité-University Hospital, Campus Benjamin Franklin (CBF), Berlin between February 2011 and December 2013 ($n = 2046$) (NCT01263964).

Information on patients' previous medical history and medication including established risk factors for white matter lesions was acquired from medical records. Baseline characteristics included age, sex, history of hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, heart failure, diabetes, previous history of stroke and smoking status. Cognitive status of patients prior to or after the event was not systematically obtained. Figure 1 displays a detailed algorithm for inclusion and exclusion from this analysis. For this study, we evaluated data of patients who underwent cerebral MRI ($n = 1479$) as this allows a more accurate and comparable assessment of white matter lesion severity than CT imaging (see below). Patients with a diagnosis of the transient ischemic attack were excluded. In accordance with the diagnostic algorithm for suspected acute coronary syndrome provided by the European Society of Cardiology [1], patients with dynamic change of troponin values > 50% or a troponin value > 52 ng/l (rule-in cut-off to suspect myocardial infarction) in any measurement were excluded ($n = 244$). In addition, we excluded patients with a single measurement of troponin ($n = 375$). These exclusion criteria were applied because acute elevations of cardiac troponins are common in acute ischemic stroke [18] and might indicate acute myocardial injury. No patient included in this analysis had a diagnosis of acute myocardial infarction.

Neuroimaging

Participants underwent cerebral imaging using a 3T MRI (Trim Trio, Siemens AG, Erlangen, Germany). The protocol included T2*, diffusion-weighted imaging (DWI), time-of-flight MR angiography (TOF-MRA), fluid-attenuated inversion recovery (FLAIR) and perfusion imaging (PI). The assessment of imaging data was performed by trained neurologists or neuroradiologists irrespective of our particular research question. White matter lesion severity was routinely graded on FLAIR using the

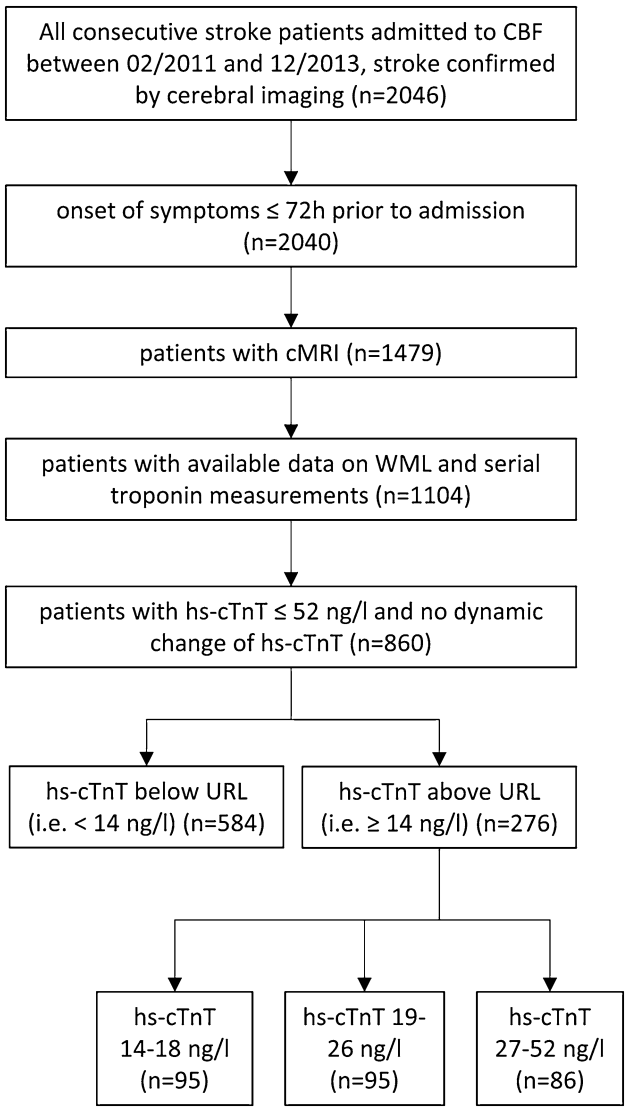

Fig. 1 algorithm for inclusion/exclusion and comparison groups. *CBF* Charité Benjamin Franklin hospital, *cMRI* cerebral magnetic resonance imaging, *WML* white matter lesions, *hs-cTnT* high-sensitivity cardiac troponin T, *URL* upper reference limit

age-related white matter severity score (ARWMS) [19]. To determine the score, five regions of the brain were examined with regard to white matter lesions: frontal, parieto-occipital, temporal, infratentorial and basal ganglia. Right and left hemisphere were assessed separately. Severity of white matter lesions was graded on a scale from 0 (no lesions) to 3 (confluent lesions) per brain region and side resulting in an individual score ranging from 0 to 30 [19]. Acute infarcts were not included in the rating. A score > 10 is considered as severe cerebral white matter damage.

Blood tests

cTnT levels were measured using a high-sensitivity Troponin T assay (Roche Elecsys Troponin Ths, Mannheim, Germany). This test has a cut-off at 14 ng/L as its upper reference limit (based on the 99th percentile of a healthy population), and a limit of detection at 3 ng/l. Actual hs-cTnT values below the upper reference limit were not provided by the laboratory until March 2013. All patients included in the analysis underwent serial hs-cTnT measurements: Initial hs-cTnT values were obtained on admission and subsequent values on the following day. Creatinine values were measured on admission and were used to estimate the glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation [20].

Statistical analysis

Univariate analyses of associations between WML and baseline characteristics were performed using Mann–Whitney *U* test for binominal and Pearson correlation analysis for continuous variables. To determine the relationship between hs-cTnT and WML, we conducted quantile regression analysis according to three different models. After running an unadjusted model, we included age (continuous) and sex (dichotomous) as covariates. In the third model, we additionally adjusted for atrial fibrillation (dichotomous), coronary artery disease (dichotomous), diabetes mellitus (dichotomous), smoking status (dichotomous), heart failure (dichotomous), hypertension (dichotomous), hyperlipidemia (dichotomous) and previous history of stroke (dichotomous).

In contrast to linear regression analysis, quantile regression can compare medians rather than means, which makes the results more robust to outliers [21]. This approach also allows to model different quantiles of the dependent variable, e.g. 80th percentile. That way, it is possible to investigate the association between hs-cTnT in relation to both the lower and upper parts of the WML distribution. For this study, we chose to perform a median quantile regression analysis, as well as quantile regression analysis for quintiles of WML (i.e. 20th, 40th, 60th and 80th percentile). Other than that, the regression coefficients indicate the effects of the covariate on the cut-offs of the respective quantiles of the dependent variable, adjusted for potential covariates, just like in any other regression model.

We used two different approaches to model hs-cTnT levels as measured on admission:

The first approach dichotomizes hs-cTnT into either "normal" (< 14 ng/l) or "elevated" (≥ 14 ng/l). In a second approach, we categorized those with elevated hs-cTnT according to tertiles, thus creating four groups (i.e. < 14 ng/l (reference group), 14–18 ng/l, 19–26 ng/l and 27–52 ng/l) to assess the presence of dose dependency. The reference group

for all analyses consisted of patients with normal hs-cTnT (< 14 ng/L).

We performed quantile regression analysis with Stata (version 14; StataCorp, College Station, TX).

SPSS Statistics 23.0 (IBM, Armonk, NY) was used for all other calculations. Statistical procedures were conducted at a 0.05 significance level. We made no adjustment for multiple comparisons.

Table 1 Univariate analysis of patient characteristics according to WML

Variable		Pearson's correlation coefficient	WML Median (IQR)	*p*
Age				
Years, median, IQR	73 (65–80)	0.397		< 0.001
Sex				
Male	55.2% (*n* = 470)		5 (4–8)	< 0.001
Female	44.8% (*n* = 390)		8 (4–12)	
hs-cTnT				
Normal	67.9% (*n* = 584)		5 (3–9)	< 0.001
Elevated	32.1% (*n* = 276)		8 (4–12)	
eGFR				
ml/min, Median (IQR)	73.26 (57.71–86.55)	− 0.193		< 0.001
Atrial fibrillation				
Yes	27.5% (*n* = 236)		7 (4–12)	0.003
No	72.5% (*n* = 624)		6 (3–10)	
CAD				
Yes	15.9% (*n* = 138)		6.5 (4–10)	0.135
No	84.1% (*n* = 722)		6 (4–10)	
Diabetes mellitus				
Yes	25.4% (*n* = 219)		7 (4–11)	0.002
No	74.6% (*n* = 641)		6 (3–10)	
Heart failure				
Yes	6.0% (*n* = 51)		8 (4–14)	0.013
No	94.0% (*n* = 809)		6 (4–10)	
History of stroke				
Yes	25.4% (*n* = 219)		8 (4–13)	< 0.001
No	74.6% (*n* = 641)		6 (3–10)	
Hyperlipidemia				
Yes	59.5% (*n* = 512)		6 (4–10)	0.042
No	40.5% (*n* = 348)		6 (3–10)	
Hypertension				
Yes	82.6% (*n* = 711)		7 (4–11)	< 0.001
No	17.4% (*n* = 149)		4 (2–6)	
Medication beta-blockers				
Yes	42.9% (*n* = 344)		8 (4–11)	< 0.001
No	57.1% (*n* = 457)		5 (3–9)	
Medication RAAS inhibitors				
Yes	47.8% (*n* = 383)		7 (4–11)	< 0.001
No	52.2% (*n* = 418)		5 (3–9)	
Smoking status				
Yes	19.5% (*n* = 168)		4 (3–8)	< 0.001
No	80.5% (*n* = 692)		6 (4–10)	

WML white matter lesions, *IQR* interquartile range, *hs-cTnT* high-sensitivity cardiac troponin T, *eGFR* estimated glomerular filtration rate, *CAD* coronary artery disease

Results

Baseline characteristics

A total of 860 patients were included in this study. Detailed information on patients' demographics are provided in Table 1. The median age of our study population was 73 years (interquartile range = IQR 65–80 years) and 44.8% of patients were female. The median ARWMS was 6 (IQR 4–10) and 32.1% of patients had hs-cTnT values above the upper reference limit (i.e. 14 ng/l).

Univariate analyses resulted in significant associations of atrial fibrillation, hypertension, diabetes mellitus, hyperlipidemia and history of stroke with WML. Women had significantly more severe WML than men in crude analysis. We observed a positive correlation between age and severity of white matter lesions. For full results of univariate analyses see Table 1.

Hs-cTnT and WML

Unadjusted median quantile regression analysis revealed that patients with hs-cTnT ≥ 14 ng/l had more extensive white matter damage than those with hs-cTnT < 14 ng/l (Fig. 2; Table 2a). This association remained significant after adjustment, although the effect was slightly attenuated. Crude analysis with hs-cTnT levels in four categories showed that all groups of patients with elevated hs-cTnT had more extensive WML compared to the reference group (Table 2b). However, the regression coefficients did not differ notably between tertiles. Again, adjustment for confounders attenuated the association. The quantile regression analysis for a range of WML percentiles (i.e. 20, 40, 60 80) revealed that the association between dichotomized hs-cTnT and WML percentile was strongest in patients with severe WML: In detail, the 20th percentile of WML was only increased by 0.38 (95% CI −0.27–1.03) for those with hs-cTnT ≥ 14 ng/L after full adjustment. This is in contrast to the coefficient of 1.41 (95% CI 0.09–2.74) for the 80th percentile of WML (also see Fig. 3; Table 3).

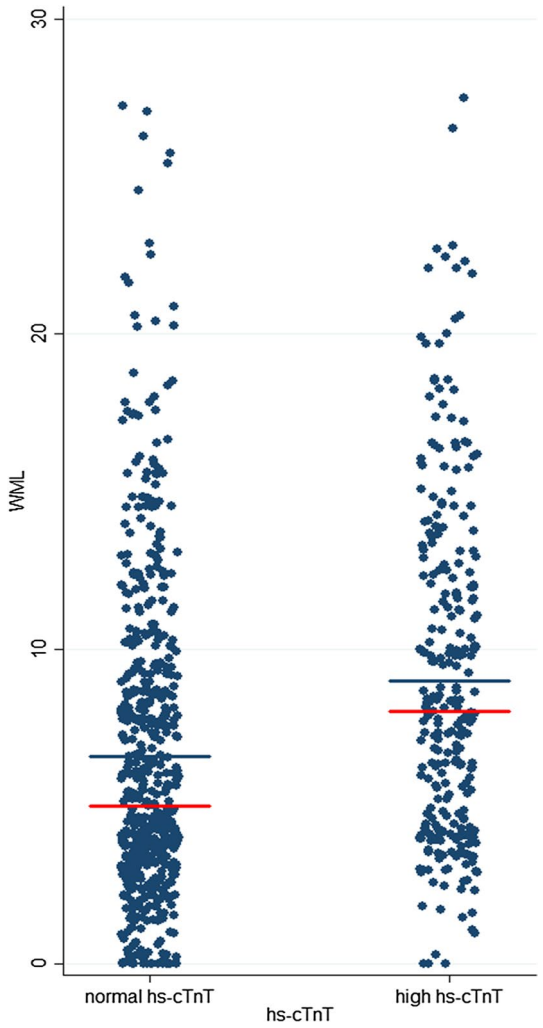

Fig. 2 Extent of white matter lesions according to hs-cTnT status. Distribution of ARWMS in patients with normal (< 14 ng/l, $n = 584$) and elevated (≥ 14 ng/l, $n = 276$) hs-cTnT. The red line indicates the median ARWMS score (5 in patients with normal hs-cTnT, 8 in patients with elevated hs-cTnT). The blue line indicates the mean ARWMS score (7 in patients with normal hs-cTnT, 9 in patients with elevated hs-cTnT). *hs-cTnT* high-sensitivity cardiac troponin T, *ARWMS* age-related white matter severity score

Discussion

In our study, we examined whether there was a link between subclinical heart and subclinical brain disease in acute stroke patients. We found that higher levels of hs-cTnT were significantly associated with more severe WML. This association remained significant after adjustment for age, sex, and manifest cardiovascular diseases. Interestingly, the association of hs-cTnT ≥ 14 ng/l was more pronounced in the upper range of WML distribution. This suggests that measurement of hs-cTnT might be useful to identify individuals with more severe WML, and vice versa, that assessment of WML severity on cMRI might help in identifying patients with (subclinical) myocardial injury.

Our findings are in line with the results of other studies that have shown an association between hs-cTnT and different markers of cerebral small vessel disease in different populations [22, 23]. Hilal et al. found a significant association between hs-cTnT and cortical cerebral microinfarcts in memory clinic patients [22]. Analyses of the ARIC (atherosclerosis risk in communities) study revealed a significant association between hs-cTnT and WML on cMRI in

Table 2 Median quantile regression analysis with hs-cTnT (a) as a dichotomous and (b) as a categorical variable

Adjustment	Model 1		Model 2		Model 3	
Stratification model	Beta (95% CI)	*p*	Beta (95% CI)	*P*	Beta (95% CI)	*p*
(a)						
hs-cTnT ≥ 14 ng/l	3.00 (2.00–4.00)	< 0.001	0.90 (0.19–1.61)	0.013	0.87 (0.13–1.60)	0.0021
(b)						
hs-cTnT group 2	3.00 (1.92–4.08)	< 0.001	1.00 (0.11–1.89)	0.028	1.14 (0.48–1.81)	0.001
hs-cTnT group 3	3.00 (0.75–5.25)	0.009	1.14 (−0.69 to 2.97)	0.221	0.96 (−0.86 to 2.77)	0.301
hs-cTnT group 4	3.00 (1.33–4.67)	< 0.001	0.57 (−0.60 to 1.75)	0.340	0.44 (−1.09 to 1.98)	0.569

Model 1: unadjusted regression analysis ($n = 860$). Model 2: adjustment for age and sex ($n = 860$). Model 3: adjustment for age, sex and other baseline characteristics as described in the methods section ($n = 860$)

hs-cTnT high-sensitivity cardiac troponin T, *CI* confidence interval

Quantile regression analysis was performed according to three adjustment models

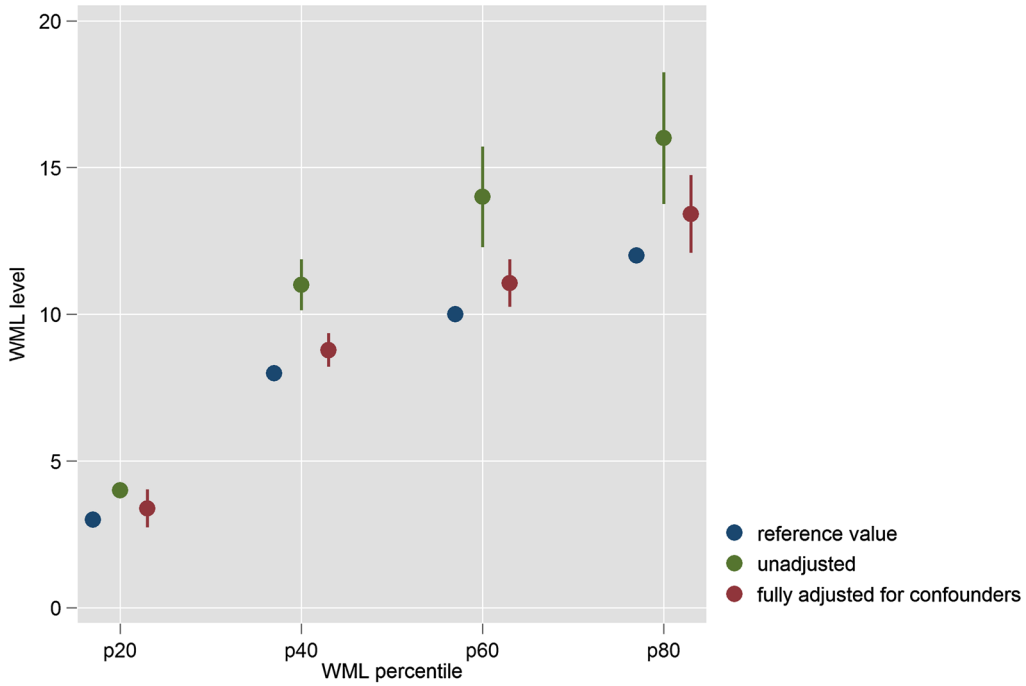

Fig. 3 Association between hs-cTnT and ARWMS in different WML percentiles. The Figure shows WML scores for each quintile of WML depending on hs-cTnT status. WML levels for patients with normal hs-cTnT are the reference group (blue). Clinically elevated hs-cTnT was significantly associated with higher ARWMS scores in all WML quintiles (green) with the effect being more pronounced in patients with higher WML levels (60th and 80th percentile). Full adjustment for confounders attenuated these effects, but remained statistically significant for the 40th, 60th and 80th WML percentile (red). *WML* white matter lesions, *ARWMS* age-related white matter severity score, *hs-cTnT* high-sensitivity cardiac troponin T

the general population [23]. However, MRI was performed approximately 3 years prior to the hs-cTnT measurements in ARIC and there was no information whether subclinical myocardial injury correlated with MRI at the same time point. Similarly, studies utilizing other markers of subclinical cardiac disease revealed an association with subclinical cerebral damage: NT-proBNP as a marker of cardiac volume overload was associated with WML volume, as well as reduced grey matter volume [24]. Russo et al. found a connection between echocardiographic determinants of subclinical cardiac damage, such as increased left atrial volume or left ventricular dysfunction, and silent brain infarcts as well as WML volume [25, 26]. All studies mentioned above were conducted either in the general population or in memory clinic patients. Our study, however, was the first to examine the association between subclinical cardiac and cerebral injury in patients with manifest cerebrovascular disease, who are at a particularly high risk of small vessel disease and cognitive decline.

Table 3 Quantile regression analysis in different WML percentiles

Percentile	Adjustment model	Variable	Beta (95% CI)	*p*
p20	Model 1	*hs-cTnT ≥ 14 ng/l*	*1.00 (1.00–1.00)*	*< 0.001*
	Model 2	hs-cTnT ≥ 14 ng/l	0.27 (− 0.19 to 0.73)	0.243
	Model 3	hs-cTnT ≥ 14 ng/l	0.38 (− 0.27 to 1.03)	0.246
p40	Model 1	*hs-cTnT ≥ 14 ng/l*	*3 (2.13–3.87)*	*< 0.001*
	Model 2	*hs-cTnT ≥ 14 ng/l*	*0.38 (0.26–1.74)*	*0.008*
	Model 3	*hs-cTnT ≥ 14 ng/l*	*0.78 (0.21–1.35)*	*0.007*
p60	Model 1	*hs-cTnT ≥ 14 ng/l*	*4 (2.28–5.71)*	*< 0.001*
	Model 2	*hs-cTnT ≥ 14 ng/l*	*1.17 (0.12–2.22)*	*0.03*
	Model 3	*hs-cTnT ≥ 14 ng/l*	*1.06 (0.24–1.87)*	*0.011*
p80	Model 1	*hs-cTnT ≥ 14 ng/l*	*4 (1.75–6.24)*	*< 0.001*
	Model 2	hs-cTnT ≥ 14 ng/l	0.93 (− 0.46 to 2.32)	0.19
	Model 3	*hs-cTnT ≥ 14 ng/l*	*1.41 (0.09–2.74)*	*0.037*

Quantile regression analysis was performed for the 20th, 40th, 60th and 80th percentile of WML. Quantile regression analysis was performed according to three adjustment models. Model 1: unadjusted regression analysis ($n = 860$). Model 2: adjustment for age and sex ($n = 860$). Model 3: adjustment for age, sex and other baseline characteristics as described in the methods section ($n = 860$)

Statistically significant results are in italic

WML white matter lesions, *CI* confidence interval, *hs-cTnT* high-sensitivity cardiac troponin T

Due to the differences in patient selection criteria, we had higher average baseline hs-cTnT levels in our cohort than in the general population. While the ARIC study grouped participants according to their hs-cTnT values below the URL, we differentiated between hs-cTnT values above the URL [23]. While only 10% of participants in the ARIC study had hs-cTnT values above the URL, more than 30% did in our cohort [23]. This might explain why we did not find significantly greater WML severity with increasing hs-cTnT when we performed the analysis after further differentiation of hs-cTnT levels. While the ARIC study performed a volume-based assessment of WML, we chose to examine WML based on a visual rating scale, which provides good sensitivity and interrater reliability [27]. By performing quantile regression analysis, we were able to quantify the association between hs-cTnT and WML depending on the extent of WML while outliers do not affect the point estimates. We found that the association between hs-cTnT and WML was strongest in patients with moderate and severe WML.

The pathogenic mechanisms that explain the link between subclinical cardiac and subclinical cerebral damage are not yet fully understood and probably multifactorial and multidirectional [28]. Currently, several hypotheses are discussed that may explain our findings: One theory states that the association between cardiac and cerebrovascular disease is mediated by common underlying systemic pathologies such as atherosclerosis and systemic small vessel disease. Even minor hs-cTnT levels were shown to indicate subclinical coronary calcification [29], which is a marker of subclinical atherosclerosis [30]. Moreover, systemic microangiopathy leads to cardiac fibrosis and myocardial hypoperfusion, which results in myocardial damage and increases the risk of heart failure and atrial fibrillation [31, 32]. This implies that cardiac and cerebrovascular disease might both be indicators of end-organ damage resulting from systemic atherosclerotic vascular damage. Furthermore, it has been proposed that cerebral hypoperfusion as a result of reduced cardiac output may lead to chronic cerebral ischemia and small vessel disease [33]. Another suggested mechanism is silent brain infarction caused by cardioembolism [34]. Lastly, the association between hs-cTnT and WML might also be caused by subclinical brain injury. Recent research has suggested that damage to certain regions of the brain, such as the insular cortex, can lead to myocardial injury and hs-cTnT elevation [35]. This implies that the interaction between heart and brain is in fact bidirectional.

Strengths of this study include the large sample size as well as standardized cMRI evaluation. Nevertheless, our study also has certain limitations. First of all, our study is cross-sectional, leaving it impossible to make any inference about the direction of the effect captured in our analyses. Second, we were not able to obtain exact hs-cTnT values below the URL in the majority of patients. Therefore, we were confined to performing our statistical analyses with hs-cTnT as a categorical variable, which may have attenuated the association with WML. Third, acute elevation of hs-cTnT is not uncommon in acute ischemic stroke, but this acute increase in hs-cTnT refers to an acute myocardial injury, suggestive of the acute coronary syndrome. To account for this, we excluded patients with a dynamic change of hs-cTnT or hs-cTnT > 52 ng/l.

Systolic function quantified by echocardiography was not available. Impaired cardiac function, i.e. heart failure has been linked to higher hs-cTnT levels [36] as well as the extent of cerebral small vessel disease and impaired cognitive function [33, 37].

Since patients' cognitive status was not systematically evaluated, we were not able to draw any conclusions regarding a possible correlation between our findings and a clinical endpoint of cognitive function.

Conclusions

Elevated levels of hs-cTnT were associated with more extensive WML in patients with acute ischemic stroke. In conjunction with previous studies, this suggests that hs-cTnT might be used to identify subjects at increased risk of cognitive impairment and dementia in the subclinical stage. Further longitudinal studies are needed to assess the effects of early detection of subclinical cardiac injury and initiation of risk-modifying therapy to prevent cognitive impairment. In addition, further research is warranted to determine the value of hs-cTnT as a marker for monitoring therapeutic effects.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Since we analysed only anonymised patient data that were obtained during clinical routine no informed consent had to be provided and consultation of the institutional review board was not required.

References

1. Twerenbold R, Boeddinghaus J, Nestelberger T et al (2018) How to best use high-sensitivity cardiac troponin in patients with suspected myocardial infarction. Clin Biochem 53:143–155
2. Lee GR, Jhanji S, Tarrant H, James S, Pearse RM, Fitzgibbon M (2014) Peri-operative troponin monitoring using a prototype high-sensitivity cardiac troponin I (hs-cTnI) assay: comparisons with hs-cTnT and contemporary cTnI assays. Ann Clin Biochem 51(2):258–268
3. Wijsman LW, de Craen AJ, Trompet S et al (2016) High-sensitivity cardiac troponin T is associated with cognitive decline in older adults at high cardiovascular risk. Eur J Prev Cardiol 23(13):1383–1392
4. Schneider AL, Rawlings AM, Sharrett AR (2014) High-sensitivity cardiac troponin T and cognitive function and dementia risk: the atherosclerosis risk in communities study. Eur Heart J 35(27):1817–1824
5. Debette S, Markus HS (2010) The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 341:c3666
6. de Groot M, Verhaaren BF, de Boer R et al (2013) Changes in normal-appearing white matter precede development of white matter lesions. Stroke 44(4):1037–1042
7. Schmidt R, Ropele S, Enzinger C et al (2005) White matter lesion progression, brain atrophy, and cognitive decline: the Austrian stroke prevention study. Ann Neurol 58(4):610–616
8. Knopman DS, Griswold ME, Lirette ST et al (2015) Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: atherosclerosis risk in communities-neurocognitive study. Stroke 46(2):433–440
9. Kloppenborg RP, Nederkoorn PJ, Geerlings MI, van den Berg E (2014) Presence and progression of white matter hyperintensities and cognition: a meta-analysis. Neurology 82(23):2127–2138
10. Schmidt R, Berghold A, Jokinen H et al (2012) White matter lesion progression in LADIS: frequency, clinical effects, and sample size calculations. Stroke 43(10):2643–2647
11. Kliper E, Ben Assayag E, Tarrasch R et al (2014) Cognitive state following stroke: the predominant role of preexisting white matter lesions. PLoS One 9(8):e105461
12. Leonards CO, Ipsen N, Malzahn U, Fiebach JB, Endres M, Ebinger M (2012) White matter lesion severity in mild acute ischemic stroke patients and functional outcome after 1 year. Stroke 43(11):3046–3051
13. van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM (2008) Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. Stroke 39(10):2712–2719
14. Rozanski M, Richter TB, Grittner U, Endres M, Fiebach JB, Jungehulsing GJ (2014) Elevated levels of hemoglobin A1c are associated with cerebral white matter disease in patients with stroke. Stroke 45(4):1007–1011
15. Savva GM, Stephan BC, Alzheimer's Society Vascular Dementia Systematic Review Group (2010) Epidemiological studies of the effect of stroke on incident dementia: a systematic review. Stroke 41(1):e41–e46
16. Kumar S, Selim MH, Caplan LR (2010) Medical complications after stroke. Lancet Neurol 9(1):105–118
17. Scheitz JF, Mochmann HC, Nolte CH et al (2011) Troponin elevation in acute ischemic stroke (TRELAS)—protocol of a prospective observational trial. BMC Neurol 11:98
18. Scheitz JF, Nolte CH, Laufs U, Endres M (2015) Application and interpretation of high-sensitivity cardiac troponin assays in patients with acute ischemic stroke. Stroke 46(4):1132–1140
19. Wahlund LO, Barkhof F, Fazekas F et al (2001) A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 32(6):1318–1322
20. Levey AS. Stevens LA. Schmid CH et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604–612
21. Beyerlein A (2014) Quantile regression—opportunities and challenges from a user's perspective. Am J Epidemiol 180(3):330–331
22. Hilal S, Chai YL, van Veluw S et al (2017) Association between subclinical cardiac biomarkers and clinically manifest cardiac diseases with cortical cerebral microinfarcts. JAMA Neurol 74(4):403–410
23. Dadu RT, Fornage M, Virani SS et al (2013) Cardiovascular biomarkers and subclinical brain disease in the atherosclerosis risk in communities study. Stroke 44(7):1803–1808
24. Zonneveld HI, Ikram MA, Hofman A et al (2017) *N*-Terminal pro-B-type natriuretic peptide and subclinical brain damage in the general population. Radiology 283(1):205–214
25. Russo C, Jin Z, Liu R et al (2013) LA volumes and reservoir function are associated with subclinical cerebrovascular disease: the CABL (Cardiovascular Abnormalities and Brain Lesions) study. JACC Cardiovasc Imag 6(3):313–323
26. Russo C, Jin Z, Homma S et al (2013) Subclinical left ventricular dysfunction and silent cerebrovascular disease: the Cardiovascular Abnormalities and Brain Lesions (CABL) study. Circulation 128(10):1105
27. Gouw AA, van der Flier WM, van Straaten EC et al (2008) Reliability and sensitivity of visual scales versus volumetry for

evaluating white matter hyperintensity progression. Cerebrovasc Dis 25(3):247–253
28. Nolte CH, Endres M (2014) The heart of the matter: a link between troponin and dementia? Eur Heart J 35(27):1779–1781
29. Saunders JT, Nambi V, de Lemos JA et al (2011) Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 123(13):1367–1376
30. Kim BJ, Lee SH, Kim CK et al (2011) Advanced coronary artery calcification and cerebral small vessel diseases in the healthy elderly. Circ J 75(2):451–456
31. Willeit K (2014) Atherosclerosis and atrial fibrillation—two closely intertwined diseases. Atherosclerosis 233:679–681
32. Adameova D (2014) Role of microangiopathy in diabetic cardiomyopathy. Heart Fail Rev 19:25–33
33. de la Torre JC (2012) Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. Cardiovasc Psychiatry Neurol 2012:367516
34. Psaty BM, Manolio TA, Kuller LH et al (1997) Incidence of and risk factors for atrial fibrillation in older adults. Circulation 96(7):2455–2461
35. Krause T, Werner K, Fiebach JB et al (2017) Stroke in right dorsal anterior insular cortex is related to myocardial injury. Ann Neurol 81(4):502–511
36. Omland T, Røsjø H, Giannitsis E, Agewall S (2015) Troponins in heart failure. Clin Chim Acta 443:78–84
37. Cannon JA, Moffitt P, Perez-Moreno AC et al (2017) Cognitive impairment and heart failure: systematic review and meta-analysis. J Card Fail 23(6):464–475