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Peak Troponin I Levels Are Associated with Functional Outcome in Intracerebral Hemorrhage

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Abstract

Background: Troponin I is a widely used and reliable marker of myocardial damage and its levels are routinely measured in acute stroke care. So far, the influence of troponin I elevations during hospital stay on functional outcome in patients with atraumatic intracerebral hemorrhage (ICH) is unknown. ***Methods:*** Observational single-center study including conservatively treated ICH patients over a 9-year period. Patients were categorized according to peak troponin I level during hospital stay (≤0.040, 0.041–0.500, >0.500 ng/mL) and compared regarding baseline and hematoma characteristics. Multivariable analyses were performed to investigate independent associations of troponin levels during hospital stay with functional outcome – assessed using the modified Rankin Scale (mRS; favorable 0–3/unfavorable 4–6) – and mortality after 3 and 12 months. To account for possible confounding propensity score (PS)-matching (1:1; caliper 0.1) was performed accounting for imbalances in baseline characteristics to investigate the impact of troponin I values on outcome. ***Results:*** Troponin elevations (>0.040 ng/mL) during hospital stay were observed in 308 out of 745 (41.3%) patients and associated with poorer status on admission (Glasgow Coma Scale/National Institute of Health Stroke Scale). Multivariable analysis revealed troponin I levels during hospital stay to be independently associated with unfavorable outcome after 12 months (risk ratio [95% CI]: 1.030 [1.009–1.051] per increment of 1.0 ng/mL; $p = 0.005$), but not with mortality. After PS-matching, patients with troponin I elevation (≥0.040 ng/mL) versus those without had a significant higher rate of unfavorable outcome after 3 and 12 months (mRS 4–6 at 3 months: <0.04 ng/mL: 159/265 [60.0%] versus ≥0.04 ng/mL: 199/266 [74.8%]; $p < 0.001$; at 12 months: <0.04 ng/mL: 141/248 [56.9%] versus ≥0.04 ng/mL: 179/251 [71.3%]; $p = 0.001$). ***Conclusions:*** Troponin I elevations during hospital stay occur frequently in ICH patients and are independently associated with functional outcome after 3 and 12 months but not with mortality.

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Introduction

Patients with intracerebral hemorrhage (ICH) show 1-year mortality rates up to 60% [1]. Several complications such as intraventricular hemorrhage (IVH), acute hydrocephalus, early hematoma expansion, and perihemorrhagic edema may occur during hospital stay and have been previously verified to independently impact outcome [2–6]. In addition, recent studies reported a high rate of cardiac complications presumably linked to a further increase in mortality of patients with intracranial hemorrhage [7–10].

Troponin I is a widely used and reliable marker of myocardial damage and its levels are routinely measured in acute stroke care. While several studies observed frequently elevated troponin levels and electrocardiographic abnormalities and their independent associations with mortality and functional outcome in patients with subarachnoid hemorrhage [8, 11, 12], the importance of troponin in patients with ICH is relatively unestablished. In one small study, elevated troponin I levels on admission were evident in roughly 20% of ICH patients and associated with higher rates of in-hospital mortality, yet methodological shortcomings partly undermined that conclusion [10]. In another analysis of surgically evacuated ICH patients, troponin levels on admission and post-surgery were associated with in-hospital mortality [9]. Given these uncertainties, we systematically assessed the natural course of troponin levels in non-surgical ICH patients and – using appropriate statistical approaches to account for confounding – explored the influence of troponin levels during hospital stay on clinical outcomes.

Methods

Patient Selection

All consecutive patients with atraumatic ICH admitted between 2006 and 2014 to the Department of Neurology, Friedrich-Alexander University Erlangen-Nuremberg (FAU), Erlangen, Germany, were collected in a prospective longitudinal institutional database and is part of the UKER-ICH registry, which was approved by the local Ethics Committee and institutional review board (Friedrich-Alexander-University Erlangen-Nuremberg, Germany, 115_17B). Informed consent was obtained by all patients or their closest relatives/legal representatives included in this study. Patients with secondary ICH due to hemorrhagic transformation of tumor or ischemic stroke, ruptured aneurysm, or bleeding of arteriovenous malformation were excluded. This analysis focused on those patients only with available data on troponin-levels during hospital stay, without surgical hematoma evacuation and without myocardial infarction or stroke 6 weeks prior to ICH (Fig. 1).

Clinical Parameters

We assessed data on demographic parameters (age, sex), prior medical history (i.e., prior myocardial infarction and stroke), clinical and radiological status on admission (Glasgow Coma Scale [GCS], National Institute of Health Stroke Scale [NIHSS]) as well as laboratory data. According to our institution's protocol, troponin I levels were measured on admission in the emergency department and at least once within 72 h after admission to detect myocardial damage. All serial troponin levels during hospital stay were integrated into our database after reviewing the patient's medical charts and institutional laboratory databases. According to our laboratory's standards and to the manufacturer of the measuring device, troponin I levels were interpreted as normal (troponin ≤0.040 ng/mL), as cardiovascular syndrome (troponin 0.040–0.500 ng/mL), or as manifest myocardial infarction (>0.500 ng/mL) [13]. All troponin levels were assessed using a chemiluminescent immunoassay for quantitative determination of cardiac troponin I (AccuTnI from Beckmann Coulter; https://www.beckmancoulter.com).

Imaging

Diagnosis of ICH was made upon CT imaging (SIEMENS Somatom Volume Zoom, Somatom Sensation 64, Somatom Definition AS+) or magnetic resonance tomography (SIEMENS Magnetom Sonata 1.5T, Magnetom Aera 1.5). Two neuroradiologists blinded to clinical data scored ICH location, estimated the hemorrhage volume using ABC methods [14] and documented the presence and extent of IVH [15]. Hemorrhage enlargement was scored if ICH volume on follow-up imaging exceeded 33% compared to initial imaging [16].

Outcome Measures

Functional outcome was assessed using the modified Rankin Scale (mRS) after 3 and 12 months by either mailed questionnaires or semi-structured telephone interviews performed by physicians certified for stroke outcome assessments [17]. In case of patients' readmissions, we documented the mRS-score assessed by a physician at the hospital of treatment. Favorable outcome was defined as mRS = 0–3 and unfavorable outcome as mRS = 4–6 [18].

Primary outcome of this study was the proportion of patients with favorable functional outcome 12 months after ICH categorized according to the peak troponin I during hospital stay. Secondary outcomes comprised the proportion of patients with favorable functional outcome at 3 months as well as mortality rates at 3 and 12 months.

Statistical Analyses

All statistical analyses were performed using SPSS (IBM, SPSS Statistics 22) and R 3.12 (r-project.org). For analysis of baseline characteristics, patients were initially categorized according to peak troponin I values during hospital stay (≤0.040, 0.040–0.500, and >0.500 ng/mL). The significance level was set at $\alpha = 0.05$ and both-sided statistical tests were performed. Nominal data were compared using chi-square or Fisher's exact test. For comparison among those groups, analysis of variance and Kruskal-Wallis test were performed dependent on mode of data distribution. All parameters showing a statistical trend in univariate analysis were included in a multivariate regression model (log Poisson with robust estimator) to identify parameters being independently associated with primary and secondary outcomes. Further, subanalyses were performed for (i) for patients without comorbidities affecting tro-

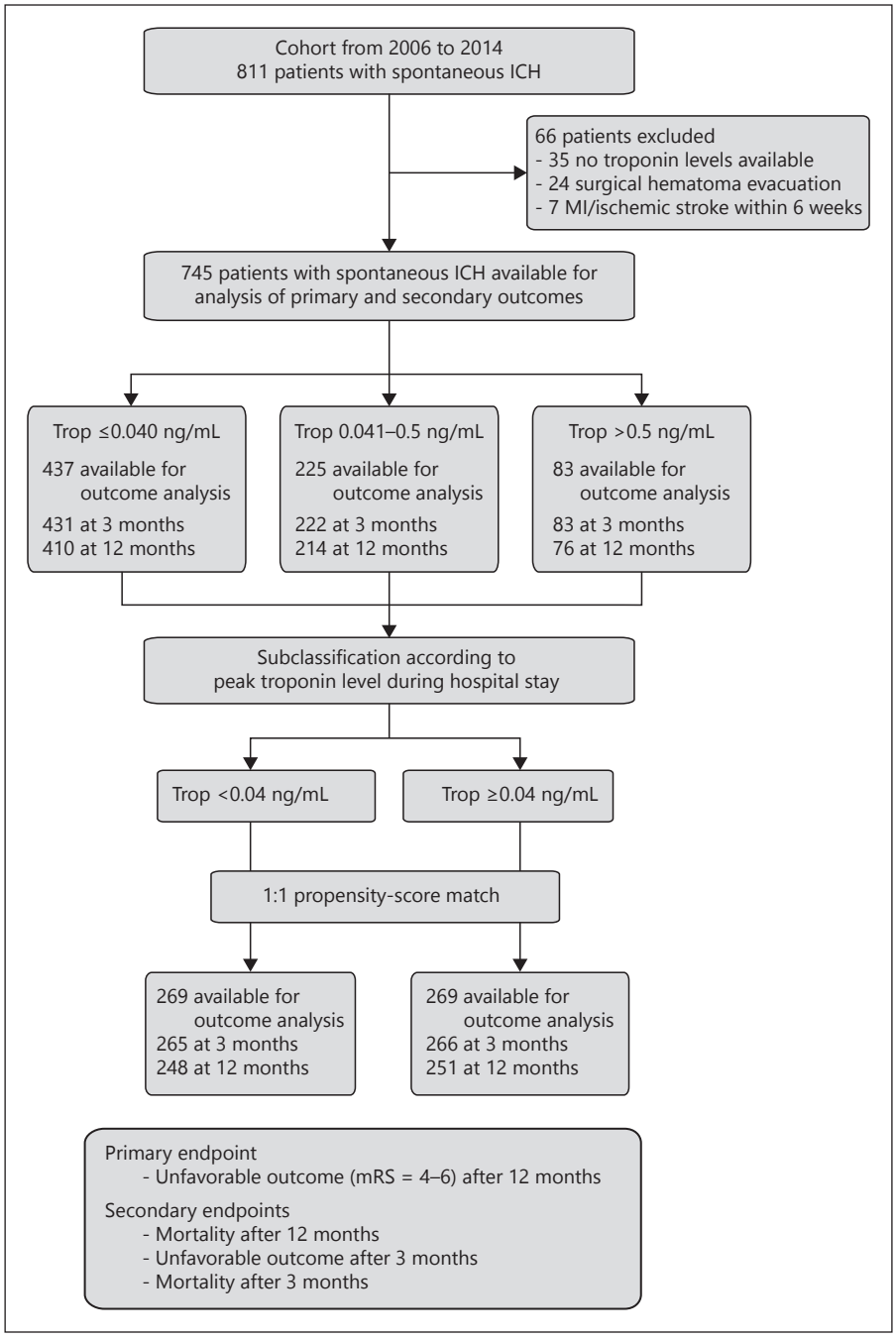


Fig. 1. Flowchart of patients. Over 9 years, 811 patients with ICH were identified. After exclusion of 38 patients because of missing troponin I values, 24 because of surgical hematoma evacuation, and 7 because of MI or ischemic stroke within 6 weeks prior index ICH, 745 patients with spontaneous conservatively ICH were available for analyses. For outcome analysis, patients were categorized according to the peak troponin I level during hospital stay. Further subclassification was undertaken according to the best discriminative cutoff value identified in ROC-analysis (see online suppl. Fig. I). ICH, intracerebral hemorrhage; MI, myocardial infarction; PS, propensity score; ROC, receiver operating characteristics.

ponin-levels (known congestive heart failure or abnormal kidney function) and (ii) for patients with normal troponin-levels on admission (troponin I ≤0.040 ng/mL) who developed a troponin elevation during hospital stay. Troponin elevations were categorized in the latter group according to the peak troponin I level measured at hospital into modest (peak troponin I between 0.040 and 0.500 ng/mL) and severe elevation (peak troponin I equal or greater than 0.500 ng/mL).

Further, receiver operating characteristics analysis was performed to investigate associations of peak troponin levels during hospital stay with the primary outcome to determine the best cutoff value for its prediction [19]. Subsequently, patients were dichotomized according to the identified cutoff value and compared using Student *t* test for normally and Mann-Whitney U test for non-normally distributed data. To minimize bias by confounding, we performed propensity score (PS) matching (1:1 match, caliper 0.1) to adjust for imbalances of clinically relevant parameters differing among the dichotomized groups [20]. Analyses of primary and secondary outcomes were based on the propensity score matched cohorts.

Results

Figure 1 shows the study design. Over a 9-year period, a total of 811 patients participated in our longitudinal database. After exclusion of 35 patients because of missing troponin I values, 24 because of surgical hematoma evacuation and 7 because of myocardial infarction or ischemic stroke 6 weeks prior to index ICH, 745 patients remained for final analysis (Fig. 1). Patients were grouped according to the peak troponin I level either (i) remaining ≤0.040 ng/mL during the entire hospital stay (n = 437/745; 58.7%), (ii) ranging between 0.040 and 0.500 ng/mL (n = 225/745; 30.2%), and (iii) exceeding >0.500 ng/mL (n = 83/745; 11.1%; see Methods and Table 1).

Patient Characteristics and Natural Course of Troponin I

Table 1 provides an overview of clinical and neuroradiological characteristics of ICH patients according to the abovementioned classification. While there were no differences in patient demographics, with increasing troponin category, we observed (i) higher rates of comorbidity (prior to congestive heart failure or abnormal kidney function), (ii) poorer clinical status on admission, (iii) more often ICH in deep location, and (iv) a higher rate of IVH (Table 1). Whereas neither ICH volume nor the proportion of patients with hematoma enlargement was significantly differing among all groups, unadjusted functional outcomes at discharge were in unfavor of increasing troponin levels (Table 1). These differences in clinical status on admission and hematoma characteristics remained significant after exclusion of patients with prior comorbidities possibly confounding troponin I levels, such as known congestive heart failure or abnormal kidney function (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000492395).

The natural course of troponin I levels during acute stay is illustrated in Figure 2. While on admission 522 out of 639 (81.7%) had no troponin elevation (≤0.04 ng/mL), on day 3, almost every second patient showed increased troponin levels (≤0.04 ng/mL: 111/201 [55.2%] versus >0.04 ng/mL 90/201 [44.8%]). In patients with troponin levels between 0.040 and 0.500 ng/mL troponin levels were highest at day 2 (median [interquartile range (IQR)] at day 2: 0.060 [0.040–0.110]). In patients with peak troponin levels greater 0.500 ng/mL, troponin levels were highest at day 4 (median [IQR] at day 4: 0.895 [0.165–1.948]; Fig. 2). In the latter group, the median peak troponin level during hospital stay was 1.60 (IQR 0.82–4.82) ng/mL (Table 1).

Association of Peak Troponin Levels with Functional Outcome

To explore associations of troponin I levels with primary and secondary outcomes, we in a first step performed multivariable regression analyses to identify parameters independently related to outcome measures. Regarding the primary outcome, next to established parameters such as age, hematoma volume, IVH and NIHSS, peak troponin I levels during hospital stay were independently associated with unfavorable outcome at 12 months (mRS 4–6 after 12 months: risk ratio [95% CI]: 1.030 [1.009–1.051]; per increment of 1.0 ng/mL; p = 0.005; Table 2) but not with mortality after 3 and 12 months (online suppl. Table 2a, c). Further analysis of patients with normal troponin-values on admission revealed troponin elevations during hospital stay to be independently associated with unfavorable outcome at 12 months (risk ratio [95% CI]: modest elevation 1.261 [1.100–1.446], p = 0.001; severe elevation 1.326 [1.063–1.654], p = 0.012; online suppl. Table 3).

In light of the independent association of peak troponin levels with functional outcome, we performed receiver operating characteristics-analysis to identify the best discriminate threshold predisposing unfavorable outcome (online suppl. Fig. 1). Graphical regression analysis revealed a true-positive significant association of both troponin levels on admission as well as peak troponin levels with unfavorable outcome after 12 months (AUC [95% CI]: troponin on admission 0.616 [0.571–0.662]; $p < 0.001$; peak troponin: 0.627 [0.581–0.673]; $p < 0.001$) with a best discriminative threshold of peak troponin levels of ≥0.04 ng/mL during hospital stay (Youden index: 0.238; sensitivity 59.0%; specificity 67.5%). Interestingly, this statistical determined cutoff point was very close to our laboratory's threshold for cardiovascular syndrome (defined as troponin I >0.04 ng/mL).

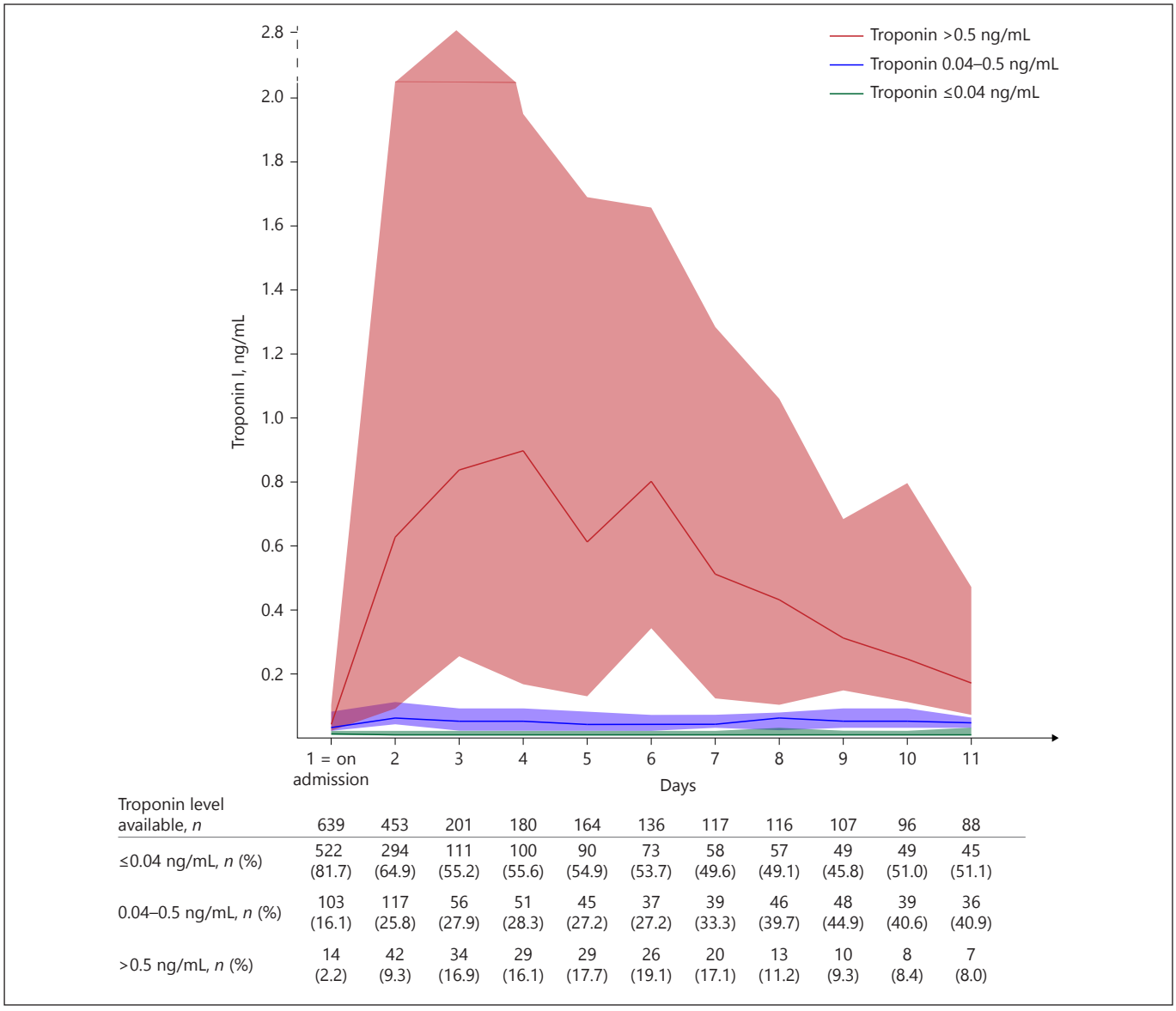
Dichotomizing our study cohort into patients with the identified cutoff threshold troponin I levels <0.04 vs. ≥0.04 ng/mL during hospitalization revealed significant and relevant imbalances (comorbidity, clinical, and radiological ICH severity) in baseline characteristics in unfavor of patients with increased troponin I levels (Table 3a). To investigate the clinical significance of elevated troponin I levels ≥0.04 ng/mL – accounting for this confounding – we performed propensity score matching to achieve 1:1 evenly balanced cohorts (each n = 269) available for analysis of primary and secondary outcomes (Table 3b).

Table 1. Characteristics of ICH patients according to peak troponin level during hospital stay

Patients with spontaneous ICH (n = 745)	Troponin ≤0.040 ng/mL (n = 437)	Troponin 0.040–0.500 ng/mL (n = 225)	Troponin >0.500 ng/mL (n = 83)	p value
Age, years, median (IQR)	74 (65–80)	72 (61–80)	70 (57–78)	0.107
Gender, female, n (%)	220 (50.3)	99 (44.0)	36 (43.4)	0.214
Prior comorbidities, n (%)				
Premorbid mRS	1 (0–2)	1 (0–2)	0 (0–2)	0.137
Hypertension	357 (81.7)	188 (83.6)	74 (89.2)	0.245
Diabetes mellitus	123 (28.2)	54 (24.0)	24 (28.9)	0.471
Coronary artery disease	50 (13.1)	31 (15.0)	17 (23.3)	0.081
Congestive heart failure	**46 (10.7)**	**32 (14.3)**	**22 (27.5)**	**<0.001**
Abnormal kidney function	**41 (9.4)**	**41 (18.2)**	**19 (22.9)**	**<0.001**
Prior ischemic stroke	79 (18.2)	51 (22.7)	14 (16.9)	0.321
Prior hemorrhagic stroke/major bleeding	43 (9.9)	18 (8.0)	6 (7.2)	0.599
Prior myocardial infarction	52 (12.0)	34 (15.1)	17 (20.5)	0.102
Antiplatelet medication	137 (31.4)	69 (30.8)	27 (32.5)	0.958
Oral anticoagulation	56 (12.8)	19 (8.4)	10 (12.0)	0.241
Admission status, median (IQR)				
GCS	**13 (8–15)**	**12 (3–14)**	**11 (3–13)**	**<0.001**
NIHSS	**11 (5–22)**	**17 (9–32)**	**19 (11–32)**	**<0.001**
ICH score	**1 (0–2)**	**2 (1–3)**	**2 (1–3)**	**<0.001**
Initial imaging				
ICH volume, cm^3, median (IQR)	13.7 (4.8–39.6)	16.1 (6.1–40.7)	14.1 (6.3–32.9)	0.672
IVH, n (%)	**182 (41.6)**	**153 (68.0)**	**51 (61.4)**	**<0.001**
GRAEB score, median (IQR)	**0 (0–4)**	**2 (0–6)**	**1 (0–6)**	**<0.001**
Location, n (%)				
Deep	**178 (40.7)**	**114 (50.7)**	**56 (67.5)**	**<0.001**
Lobar	**219 (50.1)**	**77 (34.2)**	**15 (18.1)**	**<0.001**
Cerebellar	25 (5.7)	23 (10.2)	7 (8.4)	0.103
Brainstem	14 (3.2)	11 (4.9)	5 (6.0)	0.308
Left-hemispheric	229 (52.6)	125 (55.6)	44 (53.0)	0.772
Hematoma enlargement, n (%)	42 (/12.2)	21 (11.2)	9 (12.2)	0.936
Treatment, n (%)				
External ventricular drainage	**99 (22.7)**	**102 (45.3)**	**38 (45.8)**	**<0.001**
Mechanical ventilation	**142 (32.9)**	**135 (60.0)**	**63 (76.8)**	**<0.001**
Withdrawal of care <24 h	66 (15.1)	22 (9.8)	10 (12.0)	0.150
Initial laboratory parameters, median (IQR)				
INR	1.03 (0.98–1.13)	1.04 (0.98–1.12)	1.04 (0.99–1.14)	0.570
Hemoglobin	13.7 (12.3–14.9)	13.7 (12.5–15.1)	14.1 (12.5–15.3)	0.650
Leucocytes	**8.5 (6.8–10.8)**	**10.4 (7.9–13.4)**	**9.7 (7.7–13.0)**	**<0.001**
Creatinine	**0.85 (0.69–1.03)**	**0.92 (0.73–1.16)**	**0.99 (0.71–1.26)**	**0.002**
Estimated GFR	**83 (66–102)**	**79 (59–102)**	**74 (58–95)**	**0.021**
Troponin levels, ng/mL, median (IQR)				
Troponin on admission	**0.01 (0.01–0.02)**	**0.03 (0.02–0.08)**	**0.04 (0.02–0.10)**	**<0.001**
Peak troponin level	**0.02 (0.01–0.03)**	**0.09 (0.06–0.17)**	**1.60 (0.82–4.82)**	**<0.001**
Outcome				
At discharge, median (IQR)	**4 (3–5)**	**5 (4–6)**	**5 (5–6)**	**<0.001**
mRS 0–3, n (%)	**139 (31.8)**	**26 (11.6)**	**5 (6.0)**	**<0.001**
mRS 4–6, n (%)	**298 (68.2)**	**199 (88.4)**	**78 (94.0)**	**<0.001**
Mortality, n (%)	97 (22.2)	57 (25.3)	22 (26.5)	0.538

All available ICH patients were categorized according to peak troponin I level during hospital stay in patients with troponin ≤0.040, 0.041–0.500, and >0.500 ng/mL. Comparisons among the 3 groups were calculated using chi-square as well as Fisher test for nominal and analysis of variance as well as Kruskal-Wallis test for continuous parameters. Significant findings are expressed in bold.

ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale (range 0, no deficit, to 6, death); GCS, Glasgow coma scale; NIHSS, National Institute of Health Stroke Scale; INR, international normalized ratio; IQR, interquartile range.



Troponin level available, *n*	639	453	201	180	164	136	117	116	107	96	88
≤0.04 ng/mL, *n* (%)	522 (81.7)	294 (64.9)	111 (55.2)	100 (55.6)	90 (54.9)	73 (53.7)	58 (49.6)	57 (49.1)	49 (45.8)	49 (51.0)	45 (51.1)
0.04–0.5 ng/mL, *n* (%)	103 (16.1)	117 (25.8)	56 (27.9)	51 (28.3)	45 (27.2)	37 (27.2)	39 (33.3)	46 (39.7)	48 (44.9)	39 (40.6)	36 (40.9)
>0.5 ng/mL, *n* (%)	14 (2.2)	42 (9.3)	34 (16.9)	29 (16.1)	29 (17.7)	26 (19.1)	20 (17.1)	13 (11.2)	10 (9.3)	8 (8.4)	7 (8.0)

Color version available online

Fig. 2. Natural course of troponin levels during hospital stay. The natural course of median troponin I levels over the first 10 days after admission is illustrated for ICH patients with peak troponin values ≤0.04 , 0.041–0.500, and >0.500 ng/mL including the number of available troponin assessments and the number (percentage) of patients at each category at each time point. Interquartile ranges are provided for each day illustrated as shaded areas.

Primary and Secondary Outcomes

The primary and secondary outcomes are displayed in Figure 3. As compared to patients with peak troponin I levels <0.04 ng/mL, the proportion of patients with unfavorable functional outcome at 12 months was significantly increased in patients with peak troponin I levels ≥0.04 ng/mL (mRS 4–6 at 12 months: <0.04 ng/mL: 141/248 [56.9%] versus ≥0.04 ng/mL: 179/251 [71.3%]; $p = 0.001$). Regarding secondary outcomes, as compared to patients with peak troponin I levels <0.04 ng/mL, the proportion of patients with unfavorable functional outcome at 3 months was significantly increased in patients with peak troponin I levels ≥0.04 ng/mL (mRS 4–6 at 3 months: <0.04 ng/mL: 159/265 [60.0%] versus ≥0.04 ng/mL: 199/266 [74.8%]; $p < 0.001$), yet mortality rates did not differ among both groups neither at 3 months nor at 12 months (Fig. 3).

Table 2. Multivariable analysis of parameters associated with functional outcome

Parameter	Risk ratio (95% CI)	*p* value
Age (per increment 1 year)	**1.021 (1.017–1.026)**	**<0.001**
Initial NIHSS (per increment 1 point)	**1.028 (1.023–1.034)**	**<0.001**
Initial ICH volume (per increment 1 cm^3)	**1.002 (1.001–1.003)**	**<0.001**
Initial Graeb score (per increment 1 point)	**1.027 (1.013–1.041)**	**<0.001**
Peak troponin level during hospital course (per increment 1.0 ng/mL)	**1.030 (1.009–1.051)**	**0.005**

Multivariable regression analysis (log Poisson) was calculated for the association with unfavorable outcome after 12 months, defined as a score between 4 and 6 on the mRS. Only parameters have been included in multivariable model which were significant ($p < 0.05$) in prior univariate testing, that is, age, initial NIHSS, initial ICH volume, extent of IVH (Graeb Score) and peak troponin I level. Significant findings are expressed in bold.

Table 3. Characteristics of patients dichotomized to troponin threshold (0.04 ng/mL) before and after PS-matching

Patients with spontaneous ICH	Troponin <0.04 ng/mL	Troponin ≥0.04 ng/mL	*p* value
a. Pre-PS match (*n* = 745)	*n* = 376	*n* = 369	
Age, years, median (IQR)	74 (65–80)	71 (61–80)	0.059
Gender, female, *n* (%)	192 (51.1)	163 (44.2)	0.060
Prior comorbidities, *n* (%)			
Premorbid mRS	0 (0–2)	1 (0–2)	0.046
Congestive heart disease	40 (10.8)	60 (16.5)	0.025
Abnormal kidney function	30 (8.0)	71 (19.2)	<0.001
Admission status, median (IQR)			
GCS	14 (9–15)	12 (3–14)	<0.001
NIHSS	10 (4–20)	18 (9–32)	<0.001
Initial imaging			
ICH volume, cm^3, median (IQR)	16.6 (6.5–40.7)	12.4 (4.3–38.4)	0.031
GRAEB score, median (IQR)	0 (0–3)	2 (0–6)	<0.001
Deep location, *n* (%)	153 (40.7)	195 (52.8)	0.001
b. Post-PS match (*n* = 538)	*n* = 269	*n* = 269	
Age, years, median (IQR)	74 (63–80)	73 (62–80)	0.774
Gender, female, *n* (%)	125 (46.5)	131 (48.7)	0.604
Prior comorbidities, *n* (%)			
Premorbid mRS	1 (0–2)	1 (0–2)	0.579
Congestive heart disease	35 (13.0)	37 (13.8)	0.800
Abnormal kidney function	29 (10.8)	38 (14.1)	0.240
Admission status, median (IQR)			
GCS	13 (6–15)	13 (8–14)	0.693
NIHSS	13 (6–25)	14 (8–23)	0.472
Initial imaging			
ICH volume, cm^3, median (IQR)	14.3 (4.4–43.4)	15.6 (5.5–40.1)	0.597
GRAEB score, median (IQR)	0 (0–5)	1 (0–5)	0.208
Deep location, *n* (%)	126 (46.8)	132 (49.1)	0.605

PS matching (caliper 0.1, ratio 1:1, nearest neighbor approach) was performed according to the following parameters: age, premorbid mRS, gender female, congestive heart disease, abnormal kidney function, GCS and NIHSS on admission, ICH volume on initial imaging, extent of IVH measured by Graeb score and deep location of ICH). After PS-matching 269 ICH patients with Troponin <0.04 ng/mL and 269 with troponin ≥0.04 ng/mL during hospital stay remained for outcome analysis.

GCS, Glasgow coma scale; NIHSS, National Institute of Health Stroke Scale; PS, propensity score; mRS, modified Rankin Scale score; ICH, intracerebral hemorrhage.

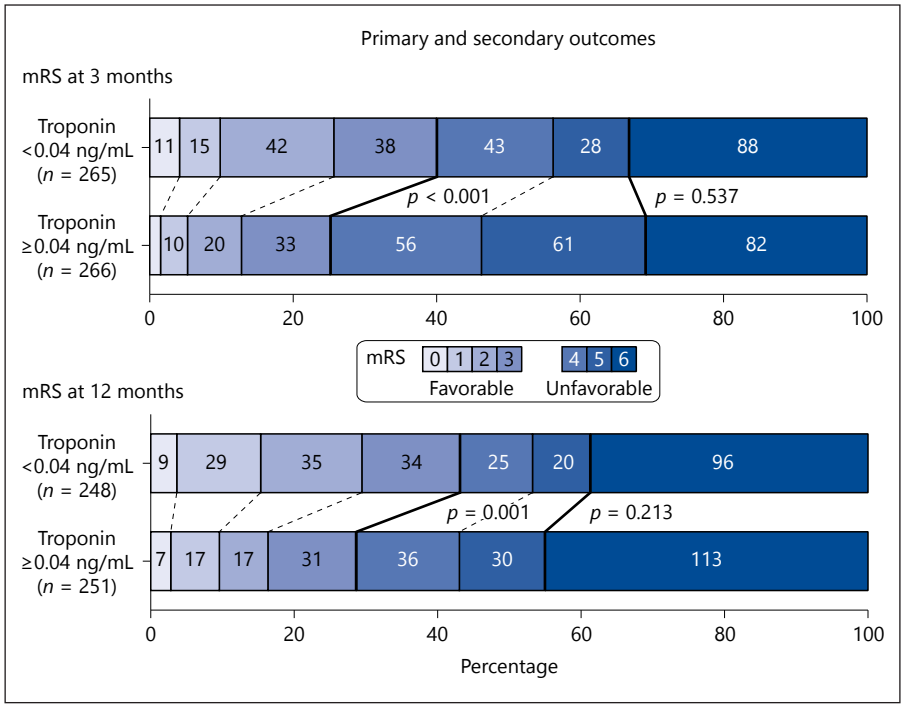


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Fig. 3. Distribution of modified Rankin Scale (mRS) in patients with troponin <0.04 vs. ≥0.04 ng/mL after PS-matching. Functional outcome at discharge, 3 and 12 months is shown as mRS-plot for patients with troponin I values <0.04 vs. ≥0.04 ng/mL after PS-matching (for detailed procedure see Table 3). Dashed lines separate each score on the mRS. The thick lines illustrate the proportion of patients with favorable (defined as mRS = 0–3) and unfavorable outcome (mRS = 4–6). *p* values were calculated for the comparison of unfavorable outcome among patients with troponin <0.04 vs. ≥0.04 ng/mL at each time-point.

Discussion

In this observational cohort of patients with spontaneous ICH, the elevation of troponin I levels during hospital stay occurred in almost every second patient and was associated with increased rates of unfavorable functional outcome both at 3 and 12 months, yet without affecting mortality at these time-points. Several aspects deserve attention.

In line with results of prior studies, elevated troponin levels on admission were frequently observed and evident in about 1 of 5 ICH patients [10]. Assessment of serial troponin I levels during hospital stay revealed a further increase in the rate of elevated troponin levels, a finding predominantly driven by increased ventricular involvement. As reported previously for patients with subarachnoid hemorrhage [21], elevation of troponin I levels may, on the one hand, result from intraventricular blood and, therefore, meningeal irritation, leading to strong systemic stress-responses [22, 23]. As a result, an enhanced release of catecholamines and consequently higher myocardial stress may reflect a neurocardiac dysbalance, evident also after ICH, notably in those patients with intraventricular involvement [21, 22, 24]. In addition, up to now, the longitudinal occurrence of troponin elevations in ICH patients was only insufficiently established and pathophysiological considerations further include an increase of intracranial pressure additionally triggering sympathetic storms [10, 21, 24–26]. To protect patients with cerebrovascular diseases from this excessive stress, the use of beta-blockers is currently discussed [27, 28]; however, this treatment is currently not considered in current guidelines for ICH-patients [29].

Questions remain as to why patients with elevated troponin levels show worse functional outcome. Considering associations of elevated troponin levels with left-ventricular dysfunction and systemic hypotonia in SAH-patients [8], observed differences in functional outcome may be based on an impaired blood and oxygen supply of the perihemorrhagic penumbra, that is, brain tissue surrounding the ICH at high risk for secondary ischemic damage [30, 31]. Such secondary neurological deterioration may be driven by tolerating hypotensive blood pressure values in ICH patients in order to primarily prevent hematoma enlargement [32]. Contrary to recent investigations reporting higher rates of mortality in patients with elevated troponin levels on admission [10], we did not observe similar associations after applying sophisticated statistical approaches to adjust for confounding [33–35]. It remains to be established whether the increased rates of troponin I levels influenced functional outcomes by means of possible secondary cardiac complications or if elevated troponin levels reflect an epiphenomenon of increased comorbidity which – despite strict

statistical adjustments – exerted subliminally impact on outcome measures [36]. In ICH patients with pathologically increased troponin values, it seems reasonable to perform prompt cardiac work-up – including ECG, echocardiography, and cardiac catheter examination, if applicable – to differentiate between underlying structural cardiac diseases and stress-induced cardiomyopathy and to consider feasible treatment approaches in those patients. Possibly, the prompt cardiac evaluation and consequent treatment of ICH patients with troponin elevations may improve the functional outcome of this patient cohort. In light of the findings presented here, it seems valuable to seek for a prospective analysis including longitudinal cardiac assessments in order to verify the significance of elevated troponin I levels in patients with ICH. Ongoing studies will clarify the value of biomarkers, such as troponin, for the prediction of functional outcome in ICH patients and which patients may benefit from additional medical therapy ([37] and ClinicalTrials.gov Identifier: NCT02935985).

This study has several limitations, notably its retrospective and monocentric design. Further, serial troponin assessments during hospital stay – joined by electro- and echocardiographic findings – did not follow a priori defined time-points, but were rather obtained based on individual physicians' discretions. As a result of this retrospective design, serial troponin measurements were not available in all patients, which may lead to the overestimation of troponin elevations during hospital stay in the presented cohort. Further, we did not specifically note the timing and amount of administered catecholamines and the occurrence and duration of cardiac arrhythmias. In addition, despite adjustments residual confounding, notably response bias as a result of our outcome assessment, cannot be fully excluded and complications reported to be potentially associated with troponin elevations, such as cerebral herniation [38], were not specifically documented. Due to the exclusion of secondary causes of ICH, such as hemorrhagic transformation or ruptured arteriovenous malformation, our findings cannot be applied to all subtypes of ICH-patients.

Summary

In conclusion, elevated troponin I levels occur frequently during hospital stay and are associated with functional outcome after ICH. Further studies are needed to clarify pathophysiological mechanisms behind these observations and its clinical relevance in acute ICH.

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