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NT-pro-BNP correlates with disease severity and predicts outcome in cerebral haemorrhage patients: Cohort study

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ABSTRACT

Background: Intracerebral haemorrhage (ICH) is a devastating condition, with more than half of patients dying or becoming dependent after such an event. Natriuretic peptides, frequently used in the management of heart failure, have been shown to correlate with disease severity and prognosis in brain disorders. The aim of this study was to test the hypothesis that NT-pro-BNP correlates with disease severity and is an independent prognostic marker for non-traumatic ICH patients.

Methods: A consecutive sample of 201 non-traumatic ICH patients, who were non-comatose on admission and medically treated in a stroke unit, were evaluated for in-hospital mortality and three-month functional dependency (modified Rankin Scale > 2). NT-pro-BNP measurement was performed after admission. Independent predictors of the outcomes in study were assessed using logistic regression and the incremental value of NT-pro-BNP on three previously validated severity scores was evaluated using the variation in C-statistic (Δc). Values of $p < .05$ were considered significant.

Results: In-hospital mortality rate was 8.0%, and 40.3% of patients achieved good functional outcome. NT-pro-BNP correlated with hematoma volume (r = 0.186) and amount of intraventricular blood (r = 0.240). Higher levels of NT-pro-BNP were independently associated with death (Expß = 1.650) and functional dependency (Expß = 1.449). NT-pro-BNP increased the discrimination of the ICH-GS for mortality prediction (Δc = 0.043) and of FUNC and ICH scores for functional outcome prediction (Δc = 0.060 and 0.055 respectively). Admission NT-pro-BNP levels were independently associated with hematoma size.

Conclusions: NT-pro-BNP is an independent prognostic factor for low-risk non-traumatic ICH patients and a valid marker of disease severity in this patient population.

1. Introduction

Intracerebral haemorrhage (ICH) is a devastating disorder, with an estimated incidence of 24.6 per 100.000 patients per year. The fatality rate after such an event is 40%, with only 12–39% of affected patients regaining independence [1]. N-terminal-pro-BNP (NT-pro-BNP) is a prohormone with a 76 amino acid N-terminal inactive protein that is cleaved from the molecule to release brain natriuretic peptide (BNP) [2]. BNP and NT-pro-BNP, which are synthesized in response to ventricular stretch and ischemic injury [3] have been extensively studied in heart disease, particularly congestive heart failure [4]. Studies have documented that these peptides are also elevated in several brain

Abbreviations: ICH, Intracerebral Haemorrhage; BNP, Brain Natriuretic Peptide; NT-pro-BNP, N-Terminal-pro-Brain Natriuretic Peptide; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; GCS, Glasgow Coma Scale; MDRD, Modification of Diet in Renal Disease; mRS, Modified Rankin Scale; ROC, Receiver Operating Characteristics; NIHSS, National Institute of Health Stroke Scale; CHF, Congestive Heart Failure; CAD, Coronary Artery Disease

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disorders regardless of the presence of heart disease [5–7], with their values correlating with different markers of disease severity. In stroke patients, they have been found to correlate with stroke severity, as assessed by the NIHSS score, and to independently predict mortality [8].

The primary objective of this study was to test the hypothesis that NT-pro-BNP correlates with two markers of disease severity in non-traumatic ICH patients (hematoma volume and intraventricular blood) and that this peptide is an independent predictor of mortality and functional dependency. The secondary objective was to determine the predictors of plasma NT-pro-BNP levels in the same patient population.

2. Material and methods

2.1. Study design

The Vila Nova de Gaia Hospital Centre directly serves a population of 334,000 and serves as a reference tertiary centre for 700,000 people. As a standard of care, stroke patients not requiring mechanical ventilation or invasive neurological monitoring are cared for in a 14-bed stroke unit, which is part of a comprehensive stroke centre with around the clock neurology, neurosurgery and interventional neuroradiology support (comatose patients are primarily cared for in an intensive care unit). After discharge, patients are re-evaluated at three months to optimise secondary prevention and post discharge care, and to assess functional status.

The study population consisted of previously independent (modified Rankin Scale ≤ 2) adult, non-comatose, medically treated, non-traumatic ICH patients admitted to the Vila Nova de Gaia Hospital Centre Stroke Unit between May 1st, 2012 and December 31st, 2017. Exclusion criteria were history of previous cerebral haemorrhage, cerebral haemorrhage secondary to trauma, thrombolysis or cerebral angiographic procedures, cerebral haemorrhage secondary to haemorrhagic transformation of arterial or venous brain infarcts, brain tumour associated ICH, ICH occurring after hospital admission for another diagnosis and patients transferred to/from another institution. The variable of interest was NT-pro-BNP determined in a sample of peripheral blood collected after admission to the stroke unit. NT-pro-BNP was dosed using an electrochemiluminescence immunoassay (Elecsys proBNP II ®). Additional covariates recorded on admission were age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, temperature, level of consciousness as assessed by the Glasgow Coma Scale (GCS), hematoma volume (using the ABC/2 method [9]), hematoma location, amount of intraventricular blood using the Graeb Scale [10], serum glucose and creatinine clearance estimated using the MDRD equation [11]. Patient's medical records were also reviewed to establish the presence of hypertension, diabetes, chronic heart disease (defined as an history of angina, myocardial infarction, previous coronary revascularization or congestive heart failure) and use of anticoagulants or antiplatelet therapy. The outcomes of interest were discharge mortality and three-month functional dependency. Functional outcome was assessed by an investigator who reviewed outpatient notes blinded to NT-pro-BNP, with a modified Rankin scale (mRS) > 2 considered an unfavourable outcome. The study protocol was reviewed and approved by the local ethics committee. The results are reported in accordance with the STROBE guidelines [12].

2.2. Statistical analysis

Descriptive analysis consists of mean and standard deviation for continuous variables with normal distribution, median and interquartile range for ordinal and continuous variables with non-normal distribution and frequencies with percentages for categorical variables. NT-pro-BNP and hematoma size were log transformed to assume a normal distribution. Correlations between NT-pro-BNP and hematoma volume, Graeb Scale, SBP and DBP were performed using Pearson's r test. The predictive value of NT-pro-BNP for in-hospital mortality and three-month functional status after ICH was assessed using logistic regression. Variables with a p value of $< .1$ on univariate analysis were included in multiple logistic regression models to adjust for covariates. Chronic heart disease was kept in the final models regardless of p value, given the association between this condition and NT-pro-BNP levels. The prognostic value of NT-pro-BNP was also studied by testing the incremental value of this biomarker when added to three extensively validated grading scales; the ICH score [13], the FUNC score [14] and the ICH Grading Scale (ICH-GS) [15]. Incremental analysis was performed by comparing Receiver Operating Characteristic (ROC) curves. After calculating the C-statistic for each score, this procedure was repeated for a prediction model that included the same score with individual values of Ln (NT-pro-BNP) and both curves were compared using DeLong's test [16]. All scores were calibrated for the study sample to avoid inflation of the added value of NT-pro-BNP [17]. Independent predictors of NT-pro-BNP values on admission were studied using linear regression. Factors with a p value $< .1$ on univariate analysis were included in the final multiple linear regression model. Statistical analysis was performed using IBM SPSS Statistics v24 except for ROC curve analysis, which was performed using MedCalc v18 for Windows. Values of $p < .05$ were considered significant.

3. Results

Fig. S1 of the supplementary material describes the patient selection procedure. Overall, 258 consecutive patients fitted the inclusion and exclusion criteria, however NT-pro-BNP was not measured in 52 and CT scan images were not available for five patients. Consequently, the final sample size totalled 201. Functional status at three months was not available for eight patients, meaning that only 193 patients were included for functional outcome analysis. Table 1 summarises the study

Table 1
Study sample description.

Study sample		n = 201
Age	(years)	69.9 (± 11.9)
Gender	Male	127 (63.2%)
	Female	74 (36.8%)
SBP	(mmHg)	163.3 (± 27.8)
DBP	(mmHg)	87.1 (± 18.4)
Heart rate	Bpm	76.2 (± 15.3)
Temperature	°C	36.4 (± 0.7)
GCS	Overall	15 [13.5;15]
	13–15	161 (80.1%)
	< 12	40 (19.9%)
Hypertension		140 (69.7%)
Diabetes		61 (30.3%)
Chronic heart disease		23 (11.4%)
Anticoagulant		28 (13.9%)
Antiplatelet		56 (27.9%)
Serum Glucose	(mg/dL)	140 (± 53)
Creatinine clearance	(mL/min/1.73m^2)	89 (± 30)
Hematoma size	Cc	6.3 [1.9;15.2]
	< 30 cc	180 (89.6%)
	≥ 30 cc	21 (10.4%)
Hematoma location	Supratentorial	181 (90.0%)
	Infratentorial	20 (10.0%)
Intraventricular blood		68 (33.8%)
Graeb score		0 [0;2]
NT-pro-BNP	pg/mL	321.0 [118.0;859.5]
In-hospital mortality		16 (8.0%)
3-month mRS < 2	2–0	81 (40.3%)

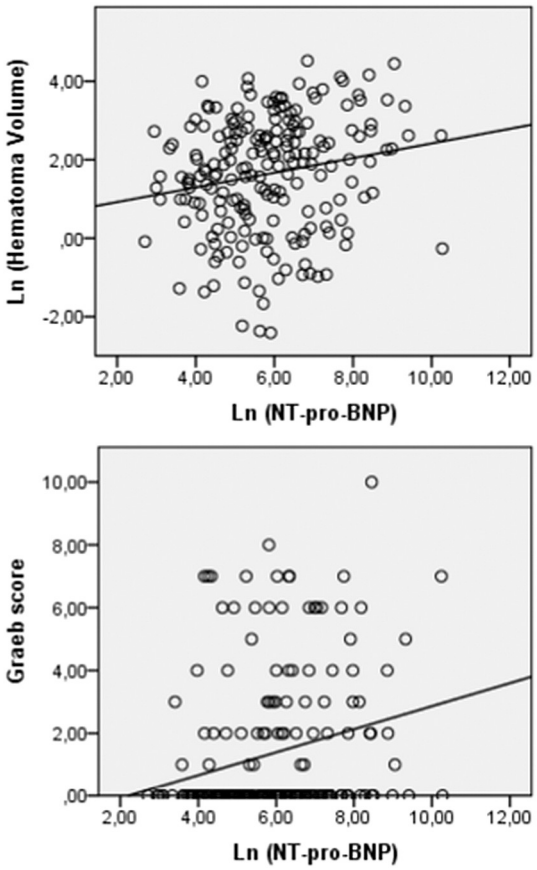

Fig. 1. Correlations between Ln (NT-pro-BNP) and A) Ln (Hematoma Volume) and B) Graeb score.

sample characteristics. The mean age of the sample was 70 years, with a higher prevalence of males (63%). Only 10% of the hematomas were infratentorial (n = 20) and, among supratentorial bleeds (n = 181), 27% were lobar (n = 49) and 73% were deep (n = 132). Approximately 70% of the patients were hypertensive and 14% were anticoagulated. Glasgow Coma Score was ≥13 on presentation for 80% of the patients and only 10% had a hematoma volume > 30 cc. Chronic heart disease was present in 23 patients. In-hospital case fatality rate was 8.0% and good functional outcome was observed in 40.3% of patients at three months.

3.1. NT-pro-BNP and ICH severity markers

Fig. 1 shows the scatterplots of Ln (NT-pro-BNP) with hematoma size and amount of intraventricular blood according to Graeb Score. Ln (NT-pro-BNP) correlated positively with both markers of disease severity, with r values of 0.186 for hematoma size (p = .008) and 0.240 for Graeb Score (p = .001).

3.2. NT-pro-BNP as an independent predictor of mortality and functional recovery

Table 2 summarises the logistic regression analysis for predictors of in-hospital mortality whilst Table 3 illustrates the same analysis for predictors of functional dependency at three months. Increased values of NT-pro-BNP were associated with in-hospital mortality and 3-month functional dependency, with these associations remaining significant even after adjustment for covariates (Exp(ß) = 1.650, p = .032 for mortality and Exp(ß) = 1.449, p = .009 for functional dependency). Other independent predictors included hematoma size for both outcomes and age for functional recovery.

3.3. Incremental value of NT-pro-BNP on the ICH score, FUNC score and ICH-GS

Table 4 summarises the incremental value of NT-pro-BNP on the three scores tested. All models improved their discriminations for the studied outcomes when NT-pro-BNP was added, but this increment was statistically significant only for mortality prediction by the ICH-GS (Δc = 0.043, p = .036) and functional outcome prediction by the ICH score and FUNC score (Δc = 0.055 and 0.060, p = .039 and .031 respectively).

3.4. Predictors of NT-pro-BNP on admission

Table 5 shows the predictors of NT-pro-BNP on admission. On univariate analysis, NT-pro-BNP was associated with age, gender,

Table 2
Predictors of in-hospital mortality.

		Univariate		Adjusted	
		Expß [95%CI]	p	Expß [95%CI]	p
Age	(years)	1.057 [1.001;1.115]	0.044	1.010 [0.941;1.084]	0.778
Gender	Male	1.826 [0.567;5.883]	0.313	–	–
	Female	–	–	–	–
SBP	(mmHg)	1.001 [0.983;1.019]	0.926	–	–
DBP	(mmHg)	0.981 [0.950;1.013]	0.235	–	–
Heart rate	(Beats/min)	1.002 [0.969;1.036]	0.897	–	–
Temperature	(° Celsius)	0.632 [0.275;1.451]	0.279	–	–
GCS		0.668 [0.542;0.823]	< 0.001	0.945 [0.723;1.236]	0.681
Hypertension		0.705 [0.244;2.035]	0.518	–	–
Diabetes		1.039 [0.345;3.130]	0.946	–	–
Chronic heart disease		0.494 [0.062;3.925]	0.505	0.180 [0.013;2.512]	0.202
Anticoagulant		1.477 [0.393;5.552]	0.564	–	–
Antiplatelet		2.159 [0.763;6.109]	0.147	–	–
Serum glucose	(mg/dL)	1.006 [0.998;1.013]	0.152	–	–
Creatinine clearance	(mL/min/1.73m^2)	0.989 [0.971;1.007]	0.220	–	–
Hematoma size	Ln (cc)	4.297 [2.120;8.711]	< 0.001	2.876 [1.293;6.397]	0.010
Hematoma location	Supratentorial	–	–	–	–
	Infratentorial	0.582 [0.073;4.658]	0.610	–	–
Graeb score		1.401 [1.169;1.679]	< 0.001	1.263 [0.985;1.619]	0.065
NT-pro-BNP	Ln (pg/mL)	1.948 [1.360;2.789]	< 0.001	1.650 [1.043;2.612]	0.032

Hosmer-Lemeshow p = .946, AUC = 0.905.

Table 3
Predictors of 3-month dependency (mRS > 2) at 3 months.

		Univariate		Adjusted	
		Expß [95%CI]	p	Expß [95%CI]	P
Age	(years)	1.067 [1.038;1.097]	< 0.001	1.056 [1.024;1.089]	0.001
Gender	Male	0.548 [0.298;1.011]	0.054	0.782 [0.355;1.725]	0.542
	Female	–	–	–	–
SBP	(mmHg)	1.003 [0.993;1.013]	0.595	–	–
DBP	(mmHg)	0.992 [0.977;1.009]	0.358	–	–
Heart rate	(Beats/min)	0.997 [0.978;1.016]	0.761	–	–
Temperature	(° Celsius)	0.724 [0.462;1.134]	0.158	–	–
GCS		0.658 [0.530;0.818]	< 0.001	0.850 [0.655;1.101]	0.218
Hypertension		1.182 [0.635;2.199]	0.598	–	–
Diabetes		1.270 [0.677;2.385]	0.457	–	–
Chronic heart disease		0.773 [0.312;1.918]	0.579	0.670 [0.205;2.191]	0.507
Anticoagulant		1.532 [0.650;3.609]	0.329	–	–
Antiplatelet		1.658 [0.859;3.198]	0.132	–	–
Serum glucose	(mg/dL)	1.006 [0.999;1.012]	0.073	1.004 [0.996;1.012]	0.329
Creatinine clearance	(mL/min/1.73m^2)	0.992 [0.982;1.001]	0.096	0.998 [0.986;1.010]	0.735
Hematoma size	Ln (cc)	1.877 [1.471;2.396]	< 0.001	1.779 [1.322;2.393]	< 0.001
Hematoma location	Supratentorial	–	–	–	–
	Infratentorial	0.546 [0.206;1.451]	0.225	–	–
Graeb score		1.203 [1.038;1.395]	0.014	1.055 [0.885;1.258]	0.551
NT-pro-BNP	Ln (pg/mL)	1.781 [1.399;2.268]	< 0.001	1.449 [1.106;2.034]	0.009

Hosmer-Lemeshow p = .563, AUC = 0.830.

Table 4
Incremental analysis of the added value of Ln (NT-pro-BNP) on the ICH score, FUNC score and ICH-GS for the prediction of in-hospital mortality and 3-month functional outcome.

	C-statistic for mortality				C-statistic for functional dependency			
	Model 1[a]	Model 2[b]	Δc	P	Model 1[a]	Model 2[b]	Δc	p
ICH score	0.849 [0.792;0.896]	0.890 [0.838;0.929]	0.040 [−0.023;0.109]	0.254	0.690 [0.620;0.754]	0.745 [0.677;0.805]	0.055 [0.003;0.107]	0.039
FUNC score	0.765 [0.700;0.822]	0.838 [0.780;0.886]	0.073 [−0.013;0.159]	0.096	0.692 [0.622;0.756]	0.752 [0.685;0.811]	0.060 [0.005;0.115]	0.031
ICH-GS	0.856 [0.800;0.902]	0.899 [0.849;0.937]	0.043 [0.003;0.084]	0.036	0.696 [0.626;0.760]	0.743 [0.675;0.803]	0.047–[0.004;0.097]	0.069

[a] Score.
[b] Score + Ln (NT-pro-BNP).

systolic blood pressure, temperature, Glasgow coma score, hypertension, chronic heart disease, anticoagulant therapy, serum glucose, creatinine clearance, haematoma size and amount of intraventricular blood. On multivariate analysis, NT-pro-BNP remained independently associated with haematoma volume along with age, gender, systolic blood pressure, Glasgow coma score, chronic heart disease, anticoagulant therapy, creatinine clearance and haematoma location.

Table 5
Predictors of Ln (NT-pro-BNP) on admission.

		Univariate		Adjusted	
		ß [95%CI]	P	ß [95%CI]	P
Age	(years)	0.039 [0.023;0.056]	< 0.001	0.025 [0.010;0.040]	0.001
Gender	Male	−0.872 [−1.282;-0.462]	< 0.001	−0.580 [−0.043;-0.218]	0.002
	Female	–	–	–	–
SBP	(mmHg)	0.011 [0.004;0.018]	0.003	0.007 [0.001;0.014]	0.022
DBP	(mmHg)	0.007 [−0.004;0.018]	0.236	–	–
Heart rate	(beats/min)	−0.003 [−0.017;0.010]	0.645	–	–
Temperature	(° Celsius)	−0.368 [−0.682;-0.053]	0.022	−0.157 [−0.428;0.114]	0.255
GCS		−0.238 [−0.338;-0.137]	< 0.001	−0.100 [−0.199;0.000]	0.050
Hypertension		0.604 [0.163;1.045]	0.008	0.014 [−0.382;0.409]	0.946
Diabetes		0.205 [−0.244;0.654]	0.369	–	–
Chronic Heart Disease		1.008 [0.375;1.641]	0.002	0.679 [0.076;1.282]	0.027
Anticoagulant		1.331 [0.765;1.897]	< 0.001	0.805 [0.270;1.340]	0.003
Antiplatelet		0.425 [−0.032;0.881]	0.068	0.027 [−0.383;0.437]	0.897
Serum Glucose	(mg/dL)	0.006 [0.002;0.010]	0.001	0.002 [−0.001;0.005]	0.183
Creatinine clearance	(mL/min/1.73m^2)	−0.015 [−0.022;-0.009]	< 0.001	−0.008 [−0.014;-0.002]	0.011
Hematoma size	Ln(cc)	0.186 [0.049;0.323]	0.008	0.147 [0.013;0.281]	0.032
Hematoma location	Supratentorial	–	–	–	–
	Infratentorial	0.589 [−0.096;1.273]	0.092	0.662 [0.060;1.265]	0.031
Graeb Score		0.157 [0.068;0.246]	0.001	0.070 [−0.011;0.150]	0.089

Model r^2 = 0.426.

4. Discussion

This study consistently demonstrated that NT-pro-BNP is an independent prognostic marker for intracerebral haemorrhage. Not only did NT-pro-BNP correlate with hematoma size and the amount of intraventricular blood (Fig. 1), but it also predicted in-hospital mortality and three-month functional outcome, either after adjustment for covariates in a newly derived model from the current study sample (Tables 2 and 3) or when added to previously established and well validated models such as the ICH score [18–20], the FUNC score [21,22] or the ICH Grading Scale [18,21,23] (Table 4). Reasons for the association between increased NT-pro-BNP and poor ICH prognosis remain to be determined but a direct causative role is not supported by animal studies [24]. An effect of existing chronic heart disease that shares common risk factors with ICH (age, hypertension) is also not consistent with the current analysis. Although chronic heart disease was an independent predictor of admission NT-pro-BNP levels, it was not associated with either death or dependency in the current study. More importantly, NT-pro-BNP levels were associated with unfavourable outcomes even after adjustment for this comorbidity. A more plausible explanation is that NT-pro-BNP acts as a marker of disease severity by reflecting a hemodynamic stress response, which can be found after acute injury to the central nervous system. Hypertension is common after cerebral haemorrhage even in patients with no known history of hypertension [25], and studies have shown other hemodynamic changes in the acute phase of ICH, such as increased systemic vascular resistance, left ventricular hypokinesia with apex sparing and decreased cardiac output [26,27]. Previous studies also demonstrated that BNP, another member of the natriuretic peptides, is elevated in acute neurological diseases such as intracerebral haemorrhage [6], ischemic stroke [7] and head trauma [5], and correlates with markers of disease severity like haematoma volume, infarct volume, NIHSS score, intraventricular haemorrhage, mass effect, ICH score and survival [6,28,29]. It can then be hypothesised that higher disease severity would reflect itself in a hemodynamic stress [30] which, in turn, would translate into higher levels of circulating natriuretic peptides and possibly cardiac dysfunction. In a study with traumatic brain injury patients, Krishnamoorthy and collaborators were able to demonstrate a relationship between higher systolic blood pressure in the first 12 h after admission and development of systolic dysfunction, proposing a catecholaminergic surge as the causative mechanism [31]. In accordance with this hypothesis, the levels of NT-pro-BNP in this study also correlated with systolic (but not diastolic) blood pressure (Fig. S2 of the supplementary material). Interestingly, this hypothesis considers the occurrence of acute cardiac dysfunction or stress in the context of the neurological event. In fact, NT-pro-BNP was an independent prognostic factor for ICH patients even after adjustment for traditional prognostic factors such as age, haematoma size, Glasgow Coma Scale, intraventricular blood and serum glucose. These findings are in accordance with the possibility that hemodynamic stress might constitute, in ICH patients, a maladaptive response that aggravates the prognosis beyond the damage induced by the initial haematoma. Other authors have also proposed this neurocardiogenic injury hypothesis in other populations such as subarachnoid haemorrhage patients [32]. Such hypothesis certainly deserves to be further explored in future studies, as it would open a new window of intervention for cerebral haemorrhage patients. Whether the effect of brain lesions on the cardiovascular system is nonspecific or related to a particular site in the brain remains to be determined. Wijdicks proposed that higher levels of natriuretic peptides could be found in subarachnoid haemorrhage patients when aneurisms were closer to the hypothalamus [33]. Although the current study was not designed for this purpose, an independent association between infratentorial bleeds and higher levels of NT-pro-BNP on admission was found (Table 5).

This study has important clinical implications. Firstly, NT-pro-BNP demonstrated incremental value to the ICH score, FUNC score and ICH Grading Scale, three extensively validated prognostic scores for ICH patients. Guidelines propose the use of such scores to help streamline assessment and communication between providers [34]. Adding this biomarker to each of the scores improved their discrimination for both outcomes, albeit significantly only for mortality by the ICH-GS and three-month functional status by the FUNC and ICH scores. It should be noted that the increase in discrimination as assessed by the variation in C-statistics was modest, from 0.043 for mortality prediction by the ICH-GS to 0.060 for functional outcome prediction by the FUNC score. However, one should take into account the fact that these models already perform well without the biomarker, as can be seen in Table 4 (Model 1) and in the results of other studies [35]. In these circumstances, the variation in C-statistic has been pointed as a less sensitive form of evaluating the incremental value of adding a biomarker [36]. Since NT-pro-BNP can be easily and quickly quantified at the point-of-care in emergency departments, future studies should confirm this incremental value for ICH grading scales and determine the appropriate cut-off values. Of interest would be to determine if, in early presenting patients, NT-pro-BNP would identify patients at risk of neurological deterioration. Secondly, natriuretic peptides have been mostly studied in the diagnosis and management of congestive heart failure and other forms of heart disease [4]. However, the current study demonstrated that NT-pro-BNP levels in ICH patients on admission are also affected by neurological factors such as haematoma size or haematoma location. This relationship between natriuretic peptides and neurological disease factors found in the current study as well as other studies, means that natriuretic peptide testing interpretation for the purposes of heart disease is probably altered in patients with acute brain lesion. Supporting this view, Koenig et al demonstrated that elevated NT-pro-BNP levels were not independently associated with heart failure in ischaemic and haemorrhagic stroke patients [37].

This study has limitations that must be pointed. Firstly, the study sample consisted of non-comatose patients, with only 10% of patients presenting with a hematoma volume of ≥ 30 cc. This means our patients were at lower risk of death and functional dependence and as such, these findings need to be confirmed in higher risk patients. For the same reason, mortality rates were low in the study, therefore the results for mortality prediction should be interpreted with caution. Secondly, echocardiography was not routinely performed on the study population and chronic heart disease was determined from anamnesis. Thirdly, NT-pro-BNP was dosed after admission to the stroke unit, a timeline that varied from patient to patient. Timing of measurement can be an important issue in natriuretic peptide research [6]. By measuring NT-pro-BNP on admission, natriuretic peptide measurement was performed at different time points after disease onset for different patients. However, hospital admission is an easily reproducible clinical time point, increasing the external validity of our study and facilitating the replication of our results in clinical practice. Since NT-pro-BNP has a longer half-life than BNP (60 min versus 20 min), it might be preferable to use this peptide [4]. Finally, a significant number of patients (n = 52) failed to undergo NT-pro-BNP measurement on admission. Compared to patients who underwent measurement, these patients were younger, had a slightly lower Glasgow Coma Score (14 vs 15), more often had infratentorial bleeds (29% vs 10%), less often had intraventricular haemorrhage (48% vs 66%), had a higher in-hospital mortality rate (23% vs 8%), but did not differ in terms of good functional outcomes among survivors (37% vs 40%) (Table S1 of the supplementary material).

5. Conclusions

NT-pro-BNP correlates with disease severity and constitutes an independent prognostic factor for low-risk ICH patients. The association between ICH related factors and NT-pro-BNP levels might impact on the interpretation of this test for the purposes of heart disease management in this population. NT-pro-BNP levels also improve the discrimination

of previously well-established prognostic scores such as the ICH score, FUNC score and ICH Grading Scale. Future studies should confirm these findings in high-risk patients and potentially optimise ICH severity scores, by means of incorporating this biomarker into such instruments.

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Declaration of interests

The authors declare they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.02.014.

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