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Prediction and prognostication of neurological deterioration in patients with acute ICH – a hospital-based cohort study

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ABSTRACT:

Objective: Patients with intracerebral haemorrhage (ICH) are at high risk of neurological deterioration (ND). We aimed at establishing predictors of early as well as late neurological deterioration and at exploring the impact of neurological stability during the first week on long-term prognosis.

Design: We conducted this study as a retrospective cohort study. ND was evaluated based on consciousness and severity of neurological symptoms. ND during the first 24 hours after admission was defined as early ND (END) and from 24 hours to 7 days as late ND (LND). Patients were followed up until February 2015.

Participants: We included 300 acute ICH-patients (≤4.5 hours from symptom-onset) admitted to our institution from March 2009 to January 2015.

Setting: Section of Acute Neurology, Department of Neurology, Bispebjerg Hospital is a specialized referral centre receiving acute stroke patients from the entire capitol region of Denmark.

Results: We found that spot sign on CT-angiography (OR 10.7 CI: 4.79-24.3) and extensive degree of interventricular haemorrhage (IVH) (OR 8.73 CI: 2.87-26.5) were independent predictors of END, whereas degree of comorbidity (Charlton Index), admission stroke severity, and degree of IVH predicted LND. On follow-up imaging, haematoma expansion was independently associated with END (OR 6.1 CI: 2.2-17.3), and expansion of IVH was independently associated with both END (OR 1.7 CI: 1.2-2.3 per point increase) and LND (OR 2.3 CI: 1.3-4.2 per point increase). ND during first week was associated with a one-year mortality of 60.5%, compared to 9.2% among the patients, who remained stable.

Conclusion: These results suggest that stability during the first week entails an optimistic prognosis. Relatively easy and effective risk-stratification of END and LND is possible on admission based on spot sign, IVH, and clinical parameters.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- The main strengths of this study are its fairly large sample size of acute ICH patients included consequently without selection; the large proportion of the patients worked up with CT-angiography in the acute setting allowing us to include the spot sign as a prognostic marker; and the detailed follow-up regarding outcome allowing very few people to be lost to follow-up.
- The major limitation of this study is the incomplete use of follow-up imaging 24 hours after stroke onset. We believe this to be owed to the wish of the authors to keep the study population unselected. Both patients with mild ICH and those with devastating strokes might be less likely to receive follow-up imaging.

INTRODUCTION:

Neurological deterioration in patients with ICH is common, as approximately 25% of patients deteriorate within the first two days following admission (1-5). However, even though the incidence of early neurological deterioration (END) is well-described, easy-to-use predictors allowing a better ultra-early risk-stratification in terms of identifying unstable patients are not well established. New imaging concepts as the CTA-based spot sign, which have proved to predict haematoma expansion, are likely a powerful tool in the acute risk-stratification of ICH-patients. Further, little is known about late neurological deterioration (LND), even through the existence of LND is well established among clinicians (4,6). Evidence indicates that the structural damage as well as secondary space-

occupying lesions in the brain occur predominantly during the very first days of illness (7-12) (provoking END and LND). Assuming minimisation of complications by means of adequate stroke unit care (including aspiration pneumonia, venous embolisms, urinary tract infections etc.) (13,14) - we propose that clinical neurological stability during the initial week after stroke onset will translate into an overall stability of the patient and hence a lower risk of long-term morbidity and mortality. Therefore, the aim of the present study was to establish predictors of END and LND present upon admission as well as the significance of the acute phase of illness on the long-term prognosis.

METHOD:

Department of Neurology, Bispebjerg Hospital maintains a database with on-going registration of consecutive patients with primary ICH admitted to the acute stroke unit within 4.5 hours after symptom onset. The present study was conducted as a retrospectively planned analysis based on this cohort including patients admitted to our acute stroke unit from March 2009 to January 2015. The number of arriving patients determined the sample-size. Patients were excluded, if deeply comatose on admission (Glasgow coma scale <5) - or if later diagnostic work-up revealed an underlying cause of the haemorrhage (final diagnosis not primary ICH). On arrival, patients underwent a standardized work-up including non-contrast computed tomography (NCCT), and a National Institute of Health Stroke Scale score (NIHSS) was obtained. Patients further underwent acute computed tomography angiography (CTA), if no contraindication to the procedure (allergy or significant kidney failure) was present. ICH patients were treated in accordance with guidelines from the European Stroke Organisation (15,16). Patients were continuously monitored, and vital values as well as Glasgow Coma Scale (GCS) and neurological symptoms (Stroke in Progression Score – SIP-score) were recorded at least every hour within the first 24 hours by the nursing staff. The SIP-score is a shortened version of the Scandinavian Stroke Scale and is used for monitoring

purposes of acute stroke patients(17) (Please see supplementary methods section). Follow-up imaging was scheduled to be performed approximately 24 hours after admission or earlier in case of neurological deterioration. When patients were assumed stable, they were transferred to rehabilitation in local hospital stroke units based on the abode of the patient. Local stroke units are monitored on quality, and all comply with the national standards regarding stroke unit care. A more detailed description of treatment procedures is presented in online supplement (Please see supplementary methods section).

Neurological Deterioration:

Neurological deterioration was defined as a decrease of ≥2 GCS(18) points or ≥4 SIP-score points, either lasting longer than 8 hours, requiring surgical intervention, or resulting in death. The cut point of 4 SIP-points was made based on the widely accepted 4 point NIHSS cut point (3,19) when defining neurological deterioration and the conversion formula between the Scandinavian Stroke Scale and NIHSS (20). Early neurological deterioration (END) was defined as occurring within the first 24 hours after admission (3,18,19,21) with the admission value of GCS and SIP-score as baseline reference. The presence of END was confirmed based on the documented GCS and SIP-score values along with medical chart descriptions. Late neurological deterioration (LND) was defined as occurring later than 24 hours after hospital admission, but within the first 7 days (6). LND was confirmed based on review of all medical chart data from day 1-7. Documented progression in the patient's condition equal to ≥2 GCS points or ≥4 SIP-score points with the GCS and SIP-score values at 24 hours after admission as reference and with no other obvious non-neurological cause such as infection or pulmonary embolism was defined as LND. Only patients, who were stable during the first 24 hours and non-surgically treated, were assessed for LND. If patients were discharged within the first week after symptom onset, patients were presumed

continuously stable. A consultant neurologist (HC) with extensive experience in stroke neurology assessed the medical charts to confirm LND.

Definitions of Patient Characteristics and Comorbidity:

Detailed descriptions on definition of patient characteristics are presented in online supplement (Please see supplementary methods section). Disability prior to stroke onset was graded using the modified Rankin Scale (mRS), and degree of comorbidity was graded using the Charlson Comorbidity Index (22).

CT and CT-angiographic Imaging and Analysis:

A senior consultant neuroradiologist (AFC) and two board-certified radiologists (IH and EK) reviewed all imaging in a systematic manner blinded to clinical data. We defined the presence of the spot sign as one or more 1 to 2 mm foci of enhancement within the haematoma on CTA source images (23) (imaging protocol details are presented in supplementary methods section). Haematoma volumes were calculated using the ABC/2-method (24). Significant haematoma expansion was defined as an increase in haematoma volume of ≥12.5mL between admission and follow-up NCCT. The volume and extent of the interventricular haemorrhage (IVH) were graded using the semi quantitative GRAEB-score (25). Subarachnoid extension of the haemorrhage (SAH) was defined as clearly visible blood in the subarachnoid space. Delayed IVH or SAH were defined as IVH or SAH on follow-up imaging, not present on admission imaging. Midline shift was measured as the distance from the septum pellucidum between the frontal horns of the lateral ventricles to a line connecting the anterior and posterior insertions of the falx cerebri on a CT slice containing the third ventricle (8). Hydrocephalus was defined as marked dilation of one or more of the ventricles.

Follow-up:

Patients were followed through the national electronic chart system. Outcome at 90 days was assessed based on records from the outpatient clinic or occupational therapy. Good outcome was defined as the ability to walk independently (mRS ≤3). Mortality of the patients was collected during the first year after the admission date or until February 20th 2014. Patients, who were not Danish citizens, were censored the day they left the country.

Ethical Statement:

As our ICH-database constitutes an observational cohort study based on medical records, it has been approved by the Danish Data Protection agency (file no. 2010-41-5205) in accordance with Danish law.

Statistics:

We compared normally distributed data using students-t-test, non-normally distributed data and ordinal scale data using Mann-Whitney-U test and categorical data using Chi-square test. We designed prediction models for END and LND using logistic regression. Baseline data that were significantly different between the two groups ($p < 0.05$) were added into the models and excluded in a backward stepwise manner. In the models, we included NIHSS as the estimator of admission neurological status due to its widespread international use. GCS or SIP-score was not additionally included due to collinearity concerns. Based on data from the follow-up imaging, we constructed two additional logistic models for END and LND. Radiological variables significantly different between the groups were included in the models. If measures of enlargement of radiological variables (e.g. absolute haematoma expansion) were used in the models, we also adjusted for

baseline variables (e.g. admission haematoma volume). Non-adjusted survival analysis during the first year after admission was undertaken using Kaplan-Meier curves stratified for neurological deterioration (ND) during the first 7 days. ND was used as a collective term of both END and LND. The independent effect of neurological deterioration on 90-days functional outcome and long-term mortality was assessed using logistic regression (good 90 days outcome) and Cox Proportional Hazard Model (long term mortality). We included age and gender, degree of comorbidity (Charlson score), factors known to be associated with ICH-outcome (26) , and surgical procedures in the models. ND was entered as a time dependent variable to avoid the immortal time bias. $P<0.05$ was considered to be significant. Statistical analyses were performed in SPSS 20 statistical software (IBM Corp, Armonk, NY, USA).

RESULTS:

We included 300 patients with acute primary ICH in the cohort (figure 1). All patients received admission non-contrast CT (224 [74.7%] underwent acute CTA) with a median (IQR) delay from symptom onset of 103.0 (76.3-143.0) minutes. At least one follow-up non-contrast CT was performed in 163 (54.3%) patients with a median (IQR) delay from admission CT of 19 (10-25) hours. One patient underwent external ventricular drain installation immediately after admission without indication of END. This patient was excluded from further analysis. Five patients underwent surgical evacuation of the haematoma, and 3 underwent placement of external ventricular drainage without previous neurological deterioration. These patients were excluded from analysis at the time they underwent surgery.

Early Neurological Deterioration:

Of the 299 patients, 89 (29.7%) fulfilled the criteria of early neurological deterioration (figure 1). Among admission characteristics (supplemental table 1) END was most notably associated with higher NIHSS (17 [11-22] vs. 10 [5-16], p<0.0001), lower GCS (12 [10-14] vs. 15 [13-15], p<0.0001), higher admission haematoma volume (45.1 [18.0-88.9] mL vs. 10.1 [3.5-24.0] mL, p<0.0001), larger degree of midline shift (2.0 [0.0-7.0] mm vs. 0.0 [0.0-0.0] mm, p<0.0001), in addition to a higher frequency of IVH (51.7% vs. 24.8%, p<0.0001), SAH (37.1% vs. 16.7%, p<0.0001) and spot sign (73.4% vs. 18.1%, p<0.0001). END was significantly associated with pre-stroke oral anticoagulation treatment (22.7% vs. 9.5%, p=0.005) but not treatment with platelet inhibitors. Of the patients with END, 20 (22.5%) required intubation with a median (IQR) time from symptom-onset of 3.00 (2.0-4.00) hours. Eleven (12.4%) patients with END underwent placement of external ventricular drain with a median (IQR) time to drain placement of 6.0 (4.0-17.0) hours. Seventeen (19.1%) of the patients with END underwent surgical removal of the ICH - all with the indication of pending herniation. In multivariate analysis among the 224 patients with CTA on admission (table 1), the most notably predictors of END were the spot sign, anticoagulation treatment, and extensive IVH. This model provided excellent discriminative capability towards END (C-statistics = 0.87, CI: 0.82-0.92). If CTA-data were not considered (n=299), the significant predictors of END were oral anticoagulation treatment, extensive IVH, and more severe stroke symptoms (NIHSS) on admission. Patients with haematoma volumes below 10 mL were in low risk. This model also provided a good discriminative capability towards END (C-statistics = 0.82, CI: 0.77-0.88). On follow-up scan, significant haematoma expansion and expansion of IVH were independently associated with END (Table 2). Of the 36 patients with END, who were alive and non-surgically treated after the initial 24 hours, 19 (52.8%) deteriorated further within the following 6 days.

Late Neurological Deterioration:

After the first 24 hours, 204 patients remained stable and non-surgically treated. During the next 6 days, 20 (9.6%) patients, who were stable during the initial 24 hours, suffered LND (figure 1). Patients with LND (supplemental table 1) most notably had significantly higher degree of comorbidity (median Charlson Score 1 [0.5-2] vs. 0 [0-1], p=0.003), higher admission NIHSS (15 [13-20] vs. 9 [5-15], p<0.0001), lower admission GCS (13 [11-14] vs. 15 [13-15], p=0.002), higher admission volume (28.5 [12.5-44.1] mL vs. 9.2 [3.0-21.1] mL, p=0.002), and higher frequency of IVH (60.0% vs. 19.6%, p<0.0001) compared to patients, who remained stable. In multivariate analysis, the significant predictors present on admission of LND were higher degree of comorbidity (Charlson Score), more extensive IVH, and higher admission NIHSS. This model provided excellent discriminative capability towards LND (C-statistics = 0.86, CI: 0.76-0.95). On follow-up scan, final extension of the IVH was associated with LND, and expansion of the IVH was an independent predictor when adjusted for extension of baseline IVH (Table 2).

Outcome:

After 90 days, 122 (72.2%) of the surviving patients, who remained stable during the first 7 days, were able to walk independently compared to 9 (20.5%) of the patients, who suffered ND (p<0.0001). Adjusted for significant prognostic factors (age, admission NIHSS, IVH, admission haemorrhage volume, and haematoma location), comorbidity (Charlson Score), surgical procedures (surgical evacuation and instalment of external ventricular drainage) - ND was an important inverse predictor of good outcome (OR 0.11 CI: 0.04-0.32) (supplemental table 2).

One year after admission, 60.5% (CI: 51.2-69.8%) of the patients, who suffered ND during the first 7 days after admission, had died (Figure 2A). In comparison, only 9.2% (CI: 4.9-13.5%) of the

patients, who remained stable during the first 7 days, had died (p<0.0001). The median survival of the patients, who suffered ND, was 20.0 days. Patient with END and LND suffered comparable mortality during first year (figure 2B). When the same significant prognostic factors as above were controlled for, neurological deterioration was established as a massive predictor of long-term mortality (HR 6.99 CI: 3.54-13.8) (supplemental table 2). Other independent predictors of mortality during the first year were age, Charlson Score, admission NIHSS, posterior fossa location, and admission haematoma volume. We only included surgical treatment of patients with pending herniation, and it appeared to affect survival, however, it was not a predictor of good functional outcome.

DISCUSSION:

Patients, who remained stable during the first week after stroke onset, were highly likely to survive the first year. Haematoma expansion is a key driving force behind END, and factors that mark the patients as unstable within the first day were essentially risk factors of haematoma expansion – spot sign, larger haematomas, and anticoagulation treatment. Patients with smaller haematomas seemed to be protected from END. In addition, extensive haemorrhage into the ventricles of the brain marked the patients as unstable during the entire first week.

This study has several strengths. We believe that the generalizability of the data is high, as this study is based on consecutive patients with as little selection as possible as they were admitted based on catchment area. Patients are admitted fast track with early symptoms of stroke, independent of e.g. age or stroke severity. The electronic follow-up of patients allowed this to be almost complete, and only very few (all foreign citizens) were lost to follow-up. The large majority

of patients in this study underwent acute CTA enabling us to investigate the spot sign as a risk factor of ND.

A weakness is the incomplete use of follow-up imaging, which could impose concerns of selection bias in the analysis of the follow-up images, however, the frequency of follow-up imaging was distributed equally among stable patients and patients suffering END or LND. It remains likely that the moribund patients, who might have concealed a large portion of haematoma expansion or IVH, as well as patients with mild symptoms were the groups most likely to be excluded from follow-up scan. Another weakness is the way in which LND was assessed. We did not possess consecutive GCS and SIP-score data further than the first day in most patients, and we thus needed to rely on medical chart data with documentation of GCS and the physicians' description of LND. However, physicians in Denmark are obligated to keep rigorous medical records, and because of this, we believe that even though it could provide information bias, it was an acceptable way to assess LND.

Our data are in consistence with other studies documenting a substantial risk of neurological deterioration during the first 24 to 48 hours. The relatively high fraction of patients undergoing END in our study is likely due to the exclusion of comatose and surgically treated patients (2-4) from other studies on END. LND is relatively poorly described in the literature. Mayer et al. (4) documented an incidence of LND relatively similar to ours. Sun et al. (6) found a higher incidence of LND, but did not exclude patients suffering END. We demonstrated that patients, who already have suffered END, will be in high risk of continuing their trajectory of deterioration during the following days and consequently give rise to a higher risk of LND, if they are not excluded.

In a newly published meta-analysis (27), it was concluded that admission haematoma volume and IVH were associated with END, however, it was not shown that haematoma expansion was significantly related to END. Our study supports the notion that haematoma expansion is one of the key driving forces behind END. This study - as well as other studies - has found that patients with early predictors of haematoma expansion such as large haematoma (28), anticoagulation treatment, and spot sign (3,19) were more likely to undergo END. In addition, a few studies have shown a direct link between haematoma expansion and END (10,11,29). In this study, we found the spot sign to be a massive predictor of END. The spot sign is a well-recognized predictor of early haematoma expansion. It is likely that much of the effect of other predictors of END (larger haematomas and anticoagulation therapy) is mediated at least in part by the spot sign. This was also observed in this study, as some of the predictors of END lost predictive effect, when the spot sign was considered in the model. This makes prediction of early neurological stability the perhaps most clinically useful utility of acute CTA, and spot sign assessment in patients with ICH should be recommended in all acute ICH patients.

That patients with IVH are in risk of END seems to be well established (27). Our data further support Sun et al. in the link between LND and IVH (6). It is highly likely that part of the process of both early and late neurological deterioration is driven by obstruction of the cerebrovascular fluid circulation and other harmful processes related to IVH (7,30,31). We encountered two phenomena not described in great detail in the literature – delayed IVH and expansion of the IVH volume. Both of these have previously been described as independent predictors of poor outcome - to the best of our knowledge never before in relation to ND (32,33), though intuitively correlated. Our study indicates that the final IVH volume is predictive of LND. This emphasises the need for follow-up imaging in all patients with ICH allowing earlier intervention.

It is clear from our results that the first week constitutes the primary critical period regarding functional outcome and long-term mortality. Even after we controlled for other well-known predictors of mortality and poor outcome (26) as well as surgical treatment strategies, ND remained a massive independent predictor of functional outcome and mortality. As the stability of the patients during the first week is very critical, when it comes to functional outcome and mortality, this study emphasizes the importance of targeting the underlying processes that drive the deterioration – haematoma expansion, obstruction of circulation in the fluid filled spaces, and comorbidities. We believe this study to possess excellent external validity. The trend today is towards a more fast track work-up of stroke patients due to the documented benefit of recanalization therapies in ischemic stroke. This means that more and more patients with ICH also will be diagnosed early. We believe that our fairly unselected population and the few patients lost to follow-up makes our study a trustworthy picture of neurological deterioration in acute ICH-patients.

CONCLUSION:

The first week constitutes a very critical period with a relative high incidence of ND. Stability during the first week entails a good prognosis. END seems directly associated with haematoma expansion. Obstruction of the fluid filed spaces seems to be associated with both END and LND. Patients with a higher degree of comorbidity are in higher risk of LND.

COMPETING INTEREST: The authors declare that they have no conflict of interest.

CONTRIBUTORS: CO and HC contributed to the study concept and design. CO, AFC, IH, CKH and EK participated in the gathering of data. CO, AFC, SR and HC participated in the analysis and

interpretation of the data. CO drafted the manuscript. All authors performed critical revision of the manuscript for important intellectual content.

ETHICS: The Danish Data Protection Agency (file no. 2010-41-5205) has approved the registry

COMPETING INTEREST: None to declare

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TABLES:

Table 1: Independent predictors of early and late neurological deterioration

	OR	95% CI	p-value
Early neurological deterioration – Patients with CTA on admission (n = 224)			
Anticoagulation treatment:	3.41	1.19-9.80	0.023
Admission GRAEB-score:			
0 points	1.00	…	…
1-5 points	2.02	0.76-5.40	0.161
6-12 points	8.73	2.87-26.5	<0.001
Admission haematoma volume:			
>60mL	1.00	…	…
10-59.9mL	0.43	0.18-1.06	0.066
<10mL	0.27	0.09-0.82	0.021
Spot Sign	10.7	4.79-24.3	<0.001
Early neurological deterioration – All patients (n = 299)			
Anticoagulation treatment:	3.87	1.65-9.11	0.002
Admission GRAEB-score:			

0 points	1.00	…	…
1-5 points	1.59	0.73-3.46	0.241
6-12 points	4.63	1.79-12.0	0.002
Admission SAH	2.24	1.03-4.87	0.042
Admission haematoma volume:			
>60mL	1.00	…	…
10-59.9mL	0.44	0.20-0.95	0.037
<10mL	0.20	0.07-0.56	0.002
Admission NIHSS (pr. point)	1.08	1.03-1.14	0.002
Late neurological deterioration – All patients at risk at day 1 (n = 204)			
Charlson Score (pr. point)	1.74	1.18-2.55	0.005
Haematoma location:			
Lobar	1.00	…	…
Basal ganglia	0.17	0.05-0.59	0.005
Posterior fossa	0.22	0.02-3.14	0.263
Admission GRAEB-score:			
0 points	1	…	…

1-5 points	4.81	1.42-16.3	0.012
6-12 points	22.2	3.66-134.8	0.001
Admission NIHSS (pr. point)	1.13	1.03-1.23	0.014

Variables offered to both END-models were Anticoagulation treatment, admission GRAEB-score, SAH on admission, serum glucose level, admission midline shift, admission haematoma volume, and admission NIHSS value (Spot sign presents only the first model). Variables offered to the LND-model were Charlson Score, admission NIHSS, admission haematoma volume, admission GRAEB-score, and admission midline shift.

Table 2: Follow-up imaging characteristics

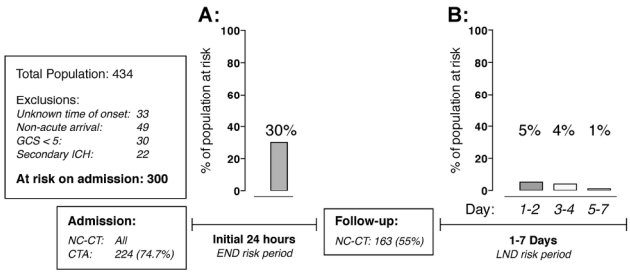
	Early neurological deterioration		Late neurological deterioration	
	Crude OR	Adjusted OR*	Crude OR	Adjusted OR †
Significant haematoma expansion, >12.5 mL	15.0 (6.3-35.5)	6.1 (2.2-17.3)	2.0 (0.4-10.5)	NI
Follow-up GRAEB-score, pr. point	1.3 (1.2-1.5)	NI	1.5 (1.2-1.9)	NI
Delayed IVH	10.3 (3.2-33.3)	NI	2.6 (0.2-26.6)	NI
IVH expansion, per GRAEB point	11.0 (4.4-27.2)	1.7 (1.2-2.3)	5.5 (1.1-26.3)	2.3 (1.3-4.2)
SAH on follow-up scan	3.4 (1.6-7.3)	2.8 (0.8-9.3)	2.6 (0.7-9.5)	NI
Delayed SAH	3.4 (0.6-21.3)	NI	NA	NA
Hydrocephalus	5.3 (1.7-16.3)	1.4 (0.3-6.6)	2.6 (0.2-26.6)	NI
Midline shift, per. mm	1.3 (1.1-1.4)	1.1 (0.9-1.3)	1.2 (0.9-1.4)	NI

*We adjusted for admission haematoma volume, admission GRAEB-score. †We adjusted for admission GRAEB-score. NI – Not included in the model due to insignificance or representation by other values (collinearity). NA – Not assessed due to incomplete representation.

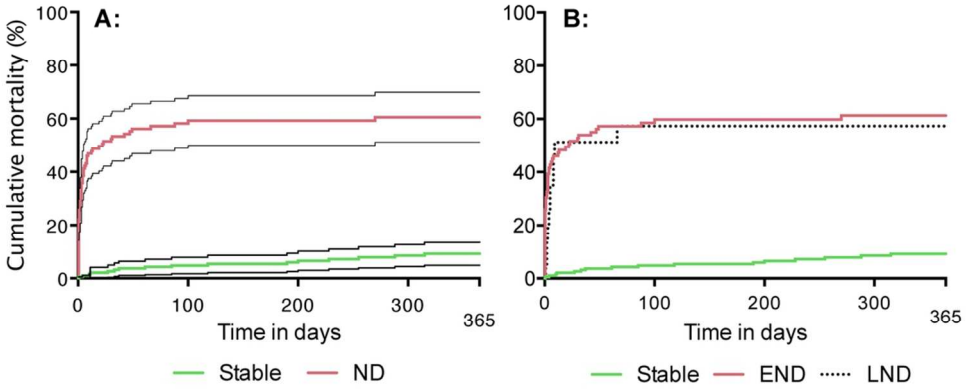
FIGURE LEGENDS:

Figure 1: Study outline and prevalence of neurological deterioration during the first week. Panel A describes the incidence of END during the fist 24 hours, and panel B describes the incidence of LND during the following 6 days.

Figure 2: Survival curves displaying mortality during the first year. Panel A represents cumulative mortality (±95% CI) of the patients stable and with neurological deterioration during the first week. Panel B represents cumulative mortality separated into patients with END, LND, and stable during the first week.



Study outline and prevalence of neurological deterioration during the first week. Panel A describes the incidence of END during the fist 24 hours, and panel B describes the incidence of LND during the following 6 days.
193x137mm (300 x 300 DPI)



Survival curves displaying mortality during the first year. Panel A represents cumulative mortality (±95% CI) of the patients stable and with neurological deterioration during the first week. Panel B represents cumulative mortality separated into patients with END, LND, and stable during the first week.
97x42mm (300 x 300 DPI)

Supplementary Materials

Prediction and prognostication of neurological deterioration in patients with acute ICH – a hospital-based cohort study

Ovesen et al. 2015

Supplemental Methodology:

Patients:
The acute stroke service of Bispebjerg Hospital covers a well-defined catchment area consisting of the entire Capitol Region of Denmark (approximately 1.7 million inhabitants), and receives acute patients from this area every day, all year - as well as patients possibly eligible for intravenous thrombolysis on even dates by direct referral from paramedics, general practitioners, and other hospitals in the region. On arrival of an acute ICH patient, the on-call neurosurgeon in a neighbouring hospital (distance 3 km) is consulted based on the admitting physician's discretion. The surgeon reviews CT images electronically, and a consensus-decision is made regarding instant surgical intervention or repeated contact in case of neurological deterioration. Patients admitted on vitamin-K antagonistic oral anticoagulation treatment and with an international normalized ratio (INR) > 1.7 are treated with prothrombin complex concentrate (PCC) and phytomenadion in order to reverse the anticoagulation effect; patients on factor Xa inhibitors are treated with PCC alone, and haemodialysis is considered in patients on directs thrombin-inhibitor treatment.

Patient Characteristic Definitions:
Prior stroke or transitory ischemic attack (TIA) was defined as a previous diagnosis of stroke or TIA. Hypertension (BP > 140/90mmHg) was defined as a history of untreated hypertension, the use antihypertensive medication on admission, or a diagnosis of hypertension during admission/outpatient clinic. The weekly consumption of alcohol was defined as excessive, if exceeding 252 g for men and 168 g for women. Active or prior smoking was defined as present use of tobacco or at least 3-pack years of prior use. The Charlson Index consists of 19 medial conditions each assigned a prognostic weight. The index is calculated by summing the weights. As the original score also includes cerebrovascular disease and hemiplegia, this was only added to the score, if these conditions existed before onset of the present stroke. The Charlson Index can include an age component, but this was not assigned in this study, as age was a separate variable.

Radiology:
Radiological imaging was conducted using 64-section multi-detector computed tomography scanners (MDCT) (Brilliance-64, Philips Medical Systems, Best, the Netherlands). Helical CTA from the aortic arch to vertex was performed using 120 kVp, 400 mAs/slice, collimation 64 x 0.625 mm (isotropic voxel resolution), and 70 ml iodine intravenous contrast injection (Iohexol 350 mg/ml) via an antecubital vein monitored with automated contrast tracking.

Stroke In Progression (SIP) Score:
The SIP-score is a shortened version of the Scandinavian Stroke Scale designed for monitoring purposes of acute stroke patients in Denmark. The score monitors the progression of symptoms in the arm, hand, and leg on the affected side of the body. In addition the patients ability to speak is monitored:

Arm motor power - 6: raises arm with normal strength, 5: raises arm with reduced strength, 4: raises arm with flexion in the elbow, 2: can move but not against gravity, 0: Paralysis.
Hand power - 6: Normal power, 4: Reduced strength in full range, 2: Some movements, fingertips do not reach palm, 0: Paralysis.

Leg motor power - 6: raises leg with normal strength, 5: raises leg straight with reduced strength, 4: raises leg with flexion in the knee, 2: can move but not against gravity, 0: Paralysis.
Speech - 10: no aphasia, 6: limited vocabulary or incoherent speech, 3: more than yes/no, but not longer sentences, 0: only yes/no or less

Supplemental Tables:

Supplemental table 1: Baseline characteristics and associations to early and late neurological deterioration

	END	No END	p-value	LND	No LND	p-value
Male gender	45 (50,6%)	127 (60,5%)	0,126	13 (65,0%)	111 (60,3%)	0,811
Age, y	73 (64-81)	70 (61-80)	0,062	81 (62-84)	70 (61-79)	0,068
TTS, min	95 (73-132)	106 (80-144)	0,146	103 (88-129)	108 (81-146)	0.557
Medical History						
Prior stroke	17 (19,3%)	30 (14,3%)	0,298	3 (15,0%)	26 (14,1%)	1,000
Prior TIA	4 (4,5%)	6 (2,9%)	0,489	0 (0,0%)	6 (3,3%)	1,000
Hypertension	57 (66,3%)	153 (73,6%)	0,256	15 (75,0%)	136 (73,9%)	1,000
Charlson Score, points	1 (0-1)	0 (0-1)	0,266	1 (0,5-2)	0 (0-1)	0,003
Pre-stroke mRS, points	0 (0-0.0)	0 (0-0)	0,054	0 (0-0,5)	0 (0-0)	0,492
Active or prior smoking	29 (43,3%)	87 (48,1%)	0,567	7 (43,8%)	76 (47,8%)	0.799
Excessive alcohol use	7 (10,0%)	26 (14,0%)	0,248	3 (16,7%)	23 (14,2%)	0,728
Medication						
Antiplatelet therapy	25 (29,1%)	56 (26,7%)	0,669	4 (20,0%)	51 (27,7%)	0,600
Anticoagulation therapy	20 (22,7%)	20 (9,5%)	0,005	4 (20,0%)	16 (8,7%)	0,115
Antihypertensive therapy	44 (51,2%)	105 (50,0%)	0,898	12 (60,0%)	91 (49,5%)	0,481
Statin therapy	18 (20,9%)	47 (22,4%)	0,878	7 (35,0%)	40 (21,7%)	0,260
Admission stroke characteristics						
NIHSS, points	17 (11-22)	10 (5-16)	<0,0001	15 (13-20)	9 (5-15)	<0,0001
GCS, points	12 (10-14)	15 (13-15)	<0,0001	13 (11-14)	15 (13-15)	0,002
Blood pressure						
Systolic, mmHg	191,9 (37,1)	185,2 (27,6)	0,216	174,2 (20,9)	187,0 (27,5)	0,019
Diastolic, mmHg	105,6 (24,1)	100,4 (20,8)	0,083	101,7 (21,6)	100,9 (20,3)	0,928
Heart rate, min^{-1}	79,6 (16,3)	81,2 (16,9)	0,555	85,5 (20,1)	81,1 (16,4)	0,372
Body temperature, ^{o}C	36,4 (0,6)	36,7 (3,9)	0,568	36,6 (0,4)	36,8 (4,1)	0,698
Haematoma location			0,285			0,024
Lobar	41 (46,1%)	78 (37,1%)		13 (65,0%)	62 (33,3%)	
Basal ganglia	43 (48,3%)	113 (53,8%)		6 (30,0%)	104 (56,5%)	
Posterior fossa	5 (5,6%)	19 (9,0%)		1 (5,0%)	18 (9,8%)	
Initial haematoma volume	45,1 (18,0-88,9)	10,1 (3,5-24,0)	<0,0001	28,5 (12,5-44,1)	9,0 (3,0-21,1)	0,002

IVH (GRAEB score ≥1)	46 (51,7%)	52 (24,8%)	<0,0001	12 (60,0%)	36 (19,6%)	<0,0001
Admission GRAEB-score:			<0.0001			<0,0001
0 points	46 (51,7%)	158 (75,2%)		8 (40,0%)	148 (80,4%)	
1-5 points	17 (21,3%)	40 (19,0%)		8 (40,0%)	31 (16.8%)	
6-12 points	24 (27.0%)	12 (5,7%)		4 (20,0%)	5 (2.7%)	
SAH	33 (37,1%)	35 (16,7%)	<0,0001	5 (25,0%)	27 (14,7%)	0,326
Midline shift (mm)	2,0 (0,0-7,0)	0,0 (0,0-0,0)	<0,0001	0,0 (0,0-2,0)	0,0 (0,0-0,0)	0,103
Admission CTA	64 (71,9%)	159 (75,7%)	0,561	14 (70,0%)	140 (76,1%)	0,586
Spot sign	47 (73,4%)	29 (18,1%)	<0,0001	3 (21,4%)	25 (17,7%)	0,719
Follow-up CT	51 (57,3%)	112 (53,3%)	0,612	13 (65,0%)	97 (52,7%)	0,350
Admission biochemestry						
Hemoglobin, mmol/L	8,6 (7,9-9,3)	8,7 (8,1-9,3)	0,548	8,4 (7,5-8,9)	8,7 (8,1-9,4)	0,064
WBC count	8,1 (6,6-10,3)	7,9 (6,4-9,8)	0,449	9,0 (6,6-12,1)	7,8 (6,4-9,6)	0,345
Neurophil count	5,1 (4,0-7,2)	5,0 (3,7-6,9)	0,658	6,0 (3,7-9,2)	4,9 (3,6-6,7)	0,168
Platelet count	213,0 (173,0-240,0)	222,0 (180,0-273,0)	0,084	208,5 (170,5-283,5)	223,0 (181,0-273,0)	0,999
Glucose, mmol/L	7,3 (5,9-8,6)	6,4 (5,8-8,3)	0,017	6,4 (5,6-9,2)	6,4 (5,8-8,0)	0,753
APTT	26,0 (24,0-32,0)	27,0 (25,0-29,0)	0,958	27,0 (25,0-29,0)	27,0 (25,0-29,0)	0,764
INR	1,0 (1,0-1,2)	1,0 (1,0-1,1)	0,632	1,1 (1,0-1,2)	1,0 (1,0-1,1)	0,119

Data presented as frequency (%), mean (SD) and median (IQR) as appropriate. TTS – time to scan; mRS – modified Rankin Scale; NIHSS – National Institute of Health Stroke Scale; GCS – Glasgow Coma Scale; IVH – intraventricular haemorrhagic extension; SAH – subarachnoid haemorrhagic extension; WBC – white blood cell count; APTT – activated partial thromboplastin time; INR – international normalized ratio.

Supplemental table 2: Predictors of independent walking (mRS≤3) after 90 days among survivors and mortality during first year

	Independent walking			Mortality during first year		
	OR	95% CI	p-value	HR	95% CI	p-value
Age (per year)	0.96	0.93-0.99	0.025	1.04	1.02-1.06	0.001
Charlson Score (per point)	0.55	0.35-0.85	0.008	1.44	1.22-1.72	<0.001
Admission NIHSS (per point)	0.85	0.79-0.92	<0.001	1.09	1.04-1.14	<0.001
Haematoma location:						
Lobar	1	…	…	1	…	…
Basal ganglia	0.19	0.07-0.54	0.002	1.17	0.69-1.99	0.567
Posterior fossa	0.22	0.04-1.18	0.078	3.30	1.25-8.7	0.016
Initial haematoma volume (per mL)	0.97	0.95-0.98	0.001	1.01	1.00-1.01	0.007
Admission IVH	1.01	0.42-2.44	0.895	1.66	0.99-2.78	0.055
Surgical haematoma evacuation[1]	1.28	0.26-6.37	0.762	0.25	0.08-0.77	0.016
External ventricular drainage	0.59	0.10-3.58	0.563	0.42	0.15-1.17	0.097
Neurological deterioration	0.11	0.04-0.32	<0.001	6.99	3.54-13.8	<0.001

[1]Only surgery due to pending herniation was included.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p. 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p. 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p. 3
Objectives	3	State specific objectives, including any prespecified hypotheses	p. 4
Methods			
Study design	4	Present key elements of study design early in the paper	p. 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p. 4, 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	p. 4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p. 5,6, and supplementary methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p. 5,6, and supplementary methods
Bias	9	Describe any efforts to address potential sources of bias	p. 7,8
Study size	10	Explain how the study size was arrived at	p. 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p. 7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p. 7,8
		(*b*) Describe any methods used to examine subgroups and interactions	p. 7,8
		(*c*) Explain how missing data were addressed	p. 7,8
		(*d*) If applicable, explain how loss to follow-up was addressed	p. 7

		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	p. 8,9,10,11
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Supplemental table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	p. 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	p. 10,11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Please see tables
		(*b*) Report category boundaries when continuous variables were categorized	p. 7,8 and tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	p. 11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Please see discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	p. 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p. 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prediction and prognostication of neurological deterioration in patients with acute ICH – a hospital-based cohort study

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Prediction and prognostication of neurological deterioration in patients with acute ICH – a hospital-based cohort study

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Indexing terms: Intracerebral haemorrhage, Computed tomography angiography, Surveillance, Clinical neurology, Critical care.

Word count: 4816

ABSTRACT:

Objective: Patients with intracerebral haemorrhage (ICH) are at high risk of neurological deterioration (ND). We aimed at establishing predictors of early as well as late neurological deterioration and at exploring the impact of neurological stability during the first week on long-term prognosis.

Design: We conducted this study as a retrospective cohort study. ND was evaluated based on consciousness and severity of neurological symptoms. ND during the first 24 hours after admission was defined as early ND (END) and from 24 hours to 7 days as late ND (LND). Patients were followed up until February 2015.

Participants: We included 300 acute ICH-patients (≤4.5 hours from symptom-onset) admitted to our institution from March 2009 to January 2015.

Setting: Section of Acute Neurology, Department of Neurology, Bispebjerg Hospital is a specialized referral centre receiving acute stroke patients from the entire capitol region of Denmark.

Results: We found that spot sign on CT-angiography (OR 10.7 CI: 4.79-24.3) and extensive degree of interventricular haemorrhage (IVH) (OR 8.73 CI: 2.87-26.5) were independent predictors of END, whereas degree of comorbidity (Charlton Index), admission stroke severity, and degree of IVH predicted LND. On follow-up imaging, haematoma expansion was independently associated with END (OR 6.1 CI: 2.2-17.3), and expansion of IVH was independently associated with both END (OR 1.7 CI: 1.2-2.3 per point increase) and LND (OR 2.3 CI: 1.3-4.2 per point increase). ND during first week was associated with a one-year mortality of 60.5%, compared to 9.2% among the patients, who remained stable.

Conclusion: These results suggest that stability during the first week entails an optimistic prognosis. Relatively easy and effective risk-stratification of END and LND is possible on admission based on spot sign, IVH, and clinical parameters.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- The main strengths of this study are its fairly large sample size of acute ICH patients included consequently without selection; the large proportion of the patients worked up with CT-angiography in the acute setting allowing us to include the spot sign as a prognostic marker; and the detailed follow-up regarding outcome allowing very few people to be lost to follow-up.
- The major limitation of this study is the incomplete use of follow-up imaging 24 hours after stroke onset. Both patients with mild ICH and those with devastating strokes might be less likely to receive follow-up imaging. We choose to include all patients to keep the study population as unselected as possible.

INTRODUCTION:

Neurological deterioration in patients with ICH is common, as approximately 25% of patients deteriorate within the first two days following admission (1-5). However, even though the incidence of early neurological deterioration (END) is well-described, easy-to-use predictors allowing a better ultra-early risk-stratification in terms of identifying unstable patients are not well established. New imaging concepts as the CTA-based spot sign, which have proved to predict haematoma expansion, are likely a powerful tool in the acute risk-stratification of ICH-patients. Further, little is known about late neurological deterioration (LND), even through the existence of LND is well established among clinicians (4,6). Evidence indicates that the structural damage as well as secondary space-

occupying lesions in the brain occur predominantly during the very first days of illness (7-12) (provoking END and LND). Assuming minimisation of complications by means of adequate stroke unit care (including aspiration pneumonia, venous embolisms, urinary tract infections etc.) (13,14) - we propose that clinical neurological stability during the initial week after stroke onset will translate into an overall stability of the patient and hence a lower risk of long-term morbidity and mortality. Therefore, the aim of the present study was to establish predictors of END and LND present upon admission as well as the significance of the acute phase of illness on the long-term prognosis.

METHOD:

Department of Neurology, Bispebjerg Hospital maintains a database with on-going registration of consecutive patients with primary ICH admitted to the acute stroke unit within 4.5 hours after symptom onset. The present study was conducted as a retrospectively planned analysis based on this cohort including patients admitted to our acute stroke unit from March 2009 to January 2015. The number of arriving patients determined the sample-size. Patients were excluded, if deeply comatose on admission (Glasgow coma scale <5) - or if later diagnostic work-up revealed an underlying cause of the haemorrhage (final diagnosis not primary ICH). On arrival, patients underwent a standardized work-up including non-contrast computed tomography (NCCT), and a National Institute of Health Stroke Scale score (NIHSS) was obtained. Patients further underwent acute computed tomography angiography (CTA), if no contraindication to the procedure (allergy or significant kidney failure) was present. ICH patients were treated in accordance with guidelines from the European Stroke Organisation (15,16). Patients were continuously monitored, and vital values as well as Glasgow Coma Scale (GCS) and neurological symptoms (Stroke in Progression Score – SIP-score) were recorded at least every hour within the first 24 hours by the nursing staff. The SIP-score is a shortened version of the Scandinavian Stroke Scale and is used for monitoring

purposes of acute stroke patients (17) (Please see supplementary methods section). Follow-up imaging was scheduled to be performed approximately 24 hours after admission or earlier in case of neurological deterioration. When patients were assumed stable, they were transferred to rehabilitation in local hospital stroke units based on the abode of the patient. Local stroke units are monitored on quality, and all comply with the national standards regarding stroke unit care. A more detailed description of treatment procedures is presented in online supplement (Please see supplementary methods section).

Neurological Deterioration:

Neurological deterioration was defined as a decrease of ≥2 GCS points (18) or ≥4 SIP-score points, either lasting longer than 8 hours, requiring surgical intervention, or resulting in death. The cut point of 4 SIP-points was made based on the widely accepted 4 point NIHSS cut point (3,19) when defining neurological deterioration and the conversion formula between the Scandinavian Stroke Scale and NIHSS (20). Early neurological deterioration (END) was defined as occurring within the first 24 hours after admission (3,18,19,21) with the admission value of GCS and SIP-score as baseline reference. The presence of END was confirmed based on the documented GCS and SIP-score values along with medical chart descriptions. Late neurological deterioration (LND) was defined as occurring later than 24 hours after hospital admission, but within the first 7 days (6). LND was confirmed based on review of all medical chart data from day 1-7. Documented progression in the patient's condition equal to ≥2 GCS points or ≥4 SIP-score points with the GCS and SIP-score values at 24 hours after admission as reference and with no other obvious non-neurological cause such as infection or pulmonary embolism was defined as LND. Only patients, who were stable during the first 24 hours and non-surgically treated, were assessed for LND. If patients were discharged within the first week after symptom onset, patients were presumed

continuously stable. A consultant neurologist (HC) with extensive experience in stroke neurology assessed the medical charts to confirm LND.

Definitions of Patient Characteristics and Comorbidity:

Detailed descriptions on definition of patient characteristics are presented in online supplement (Please see supplementary methods section). Disability prior to stroke onset was graded using the modified Rankin Scale (mRS), and degree of comorbidity was graded using the Charlson Comorbidity Index (22).

CT and CT-angiographic Imaging and Analysis:

A senior consultant neuroradiologist (AFC) and two board-certified radiologists (IH and EK) reviewed all imaging in a systematic manner blinded to clinical data. We defined the presence of the spot sign as one or more 1 to 2 mm foci of enhancement within the haematoma on CTA source images (23) (imaging protocol details are presented in supplementary methods section). Haematoma volumes were calculated using the ABC/2-method (24). Significant haematoma expansion was defined as an increase in haematoma volume of ≥12.5mL between admission and follow-up NCCT. The volume and extent of the interventricular haemorrhage (IVH) were graded using the semi quantitative GRAEB-score (25). Subarachnoid extension of the haemorrhage (SAH) was defined as clearly visible blood in the subarachnoid space. Delayed IVH or SAH were defined as IVH or SAH on follow-up imaging, not present on admission imaging. Midline shift was measured as the distance from the septum pellucidum between the frontal horns of the lateral ventricles to a line connecting the anterior and posterior insertions of the falx cerebri on a CT slice containing the third ventricle (8). Hydrocephalus was defined as marked dilation of one or more of the ventricles.

Follow-up:

Patients were followed through the national electronic chart system. Outcome at 90 days was assessed based on records from the outpatient clinic or occupational therapy. Good outcome was defined as the ability to walk independently (mRS ≤3). Mortality of the patients was collected during the first year after the admission date or until February 20th 2015. Patients, who were not Danish citizens, were censored the day they left the country.

Ethical Statement:

As our ICH-database constitutes an observational cohort study based on medical records, it has been approved by the Danish Data Protection agency (file no. 2010-41-5205) in accordance with Danish law.

Statistics:

We compared normally distributed data using students-t-test, non-normally distributed data and ordinal scale data using Mann-Whitney-U test and categorical data using Chi-square test. We designed prediction models for END and LND using logistic regression. Baseline data that were significantly different between the two groups ($p < 0.05$) were added into the models and excluded in a backward stepwise manner. In the models, we included NIHSS as the estimator of admission neurological status due to its widespread international use. GCS or SIP-score was not additionally included due to collinearity concerns. Based on data from the follow-up imaging, we constructed two additional logistic models for END and LND. Radiological variables significantly different between the groups were included in the models. If measures of enlargement of radiological variables (e.g. absolute haematoma expansion) were used in the models, we also adjusted for

baseline variables (e.g. admission haematoma volume). Non-adjusted survival analysis during the first year after admission was undertaken using Kaplan-Meier curves stratified for neurological deterioration (ND) during the first 7 days. ND was used as a collective term of both END and LND. The independent effect of neurological deterioration on 90-days functional outcome and long-term mortality was assessed using logistic regression (good 90 days outcome) and Cox Proportional Hazard Model (long term mortality). We included age and gender, degree of comorbidity (Charlson score), factors known to be associated with ICH-outcome (26), and surgical procedures in the models. ND was entered as a time dependent variable to avoid the immortal time bias. $P<0.05$ was considered to be significant. Statistical analyses were performed in SPSS 20 statistical software (IBM Corp, Armonk, NY, USA).

RESULTS:

We included 300 patients with acute primary ICH in the cohort (figure 1). All patients received admission non-contrast CT (224 [74.7%] underwent acute CTA) with a median (IQR) delay from symptom onset of 103.0 (76.3-143.0) minutes. At least one follow-up non-contrast CT was performed in 163 (54.3%) patients with a median (IQR) delay from admission CT of 19 (10-25) hours. One patient underwent external ventricular drain installation immediately after admission without indication of END. This patient was excluded from further analysis. Five patients underwent surgical evacuation of the haematoma, and 3 underwent placement of external ventricular drainage without previous neurological deterioration. These patients were excluded from analysis at the time they underwent surgery.

Early Neurological Deterioration:

Of the 299 patients, 89 (29.7%) fulfilled the criteria of early neurological deterioration (figure 1). Among admission characteristics (supplemental table 1) END was most notably associated with higher NIHSS (17 [11-22] vs. 10 [5-16], p<0.0001), lower GCS (12 [10-14] vs. 15 [13-15], p<0.0001), higher admission haematoma volume (45.1 [18.0-88.9] mL vs. 10.1 [3.5-24.0] mL, p<0.0001), larger degree of midline shift (2.0 [0.0-7.0] mm vs. 0.0 [0.0-0.0] mm, p<0.0001), in addition to a higher frequency of IVH (51.7% vs. 24.8%, p<0.0001), SAH (37.1% vs. 16.7%, p<0.0001) and spot sign (73.4% vs. 18.1%, p<0.0001). END was significantly associated with pre-stroke oral anticoagulation treatment (22.7% vs. 9.5%, p=0.005) but not treatment with platelet inhibitors. Time from admission to reversal of anticoagulation treatment was commenced was similar for stable patients and patients suffering END. Of the patients with END, 20 (22.5%) required intubation with a median (IQR) time from symptom-onset of 3.00 (2.0-4.00) hours. Eleven (12.4%) patients with END underwent placement of external ventricular drain with a median (IQR) time to drain placement of 6.0 (4.0-17.0) hours. Seventeen (19.1%) of the patients with END underwent surgical removal of the ICH - all with the indication of pending herniation. Of the patients with END 34 (38.2%) had a do-not-resuscitate (DNR) order placed on their charts within the first 24 hours after admission compared to only 11 (5.2%) of the stable patients (P<0.0001). In multivariate analysis among the 224 patients with CTA on admission (table 1), the most notably predictors of END were the spot sign, anticoagulation treatment, and extensive IVH. This model provided excellent discriminative capability towards END (C-statistics = 0.87, CI: 0.82-0.92). If CTA-data were not considered (n=299), the significant predictors of END were oral anticoagulation treatment, extensive IVH, and more severe stroke symptoms (NIHSS) on admission. Patients with haematoma volumes below 10 mL were in low risk. This model also provided a good discriminative capability towards END (C-statistics = 0.82, CI: 0.77-0.88). On follow-up scan, significant haematoma expansion and expansion of IVH were independently associated with END

(Table 2). Of the 36 patients with END, who were alive and non-surgically treated after the initial 24 hours, 19 (52.8%) deteriorated further within the following 6 days.

Late Neurological Deterioration:

After the first 24 hours, 204 patients remained stable and non-surgically treated. During the next 6 days, 20 (9.6%) patients, who were stable during the initial 24 hours, suffered LND (figure 1). Patients with LND (supplemental table 1) most notably had significantly higher degree of comorbidity (median Charlson Score 1 [0.5-2] vs. 0 [0-1], p=0.003), higher admission NIHSS (15 [13-20] vs. 9 [5-15], p<0.0001), lower admission GCS (13 [11-14] vs. 15 [13-15], p=0.002), higher admission volume (28.5 [12.5-44.1] mL vs. 9.2 [3.0-21.1] mL, p=0.002), and higher frequency of IVH (60.0% vs. 19.6%, p<0.0001) compared to patients, who remained stable. In multivariate analysis, the significant predictors present on admission of LND were higher degree of comorbidity (Charlson Score), more extensive IVH, and higher admission NIHSS. This model provided excellent discriminative capability towards LND (C-statistics = 0.86, CI: 0.76-0.95). On follow-up scan, final extension of the IVH was associated with LND, and expansion of the IVH was an independent predictor when adjusted for extension of baseline IVH (Table 2). Of the patients with LND 12 (60.0%) had a DNR order placed on their charts with a median (IQR) delay of 3 days (0-4) after admission. Of the patients who remained stable during the entire first week only 7 (3.7%) had a DNR order placed on their charts with a median delay (IQR) from admission of 0 days (0-0).

Outcome:

After 90 days, 122 (72.2%) of the surviving patients, who remained stable during the first 7 days, were able to walk independently compared to 9 (20.5%) of the patients, who suffered ND (p<0.0001). Adjusted for significant prognostic factors (age, admission NIHSS, IVH, admission

haemorrhage volume, and haematoma location), comorbidity (Charlson Score), surgical procedures (surgical evacuation and instalment of external ventricular drainage) - ND was an important inverse predictor of good outcome (OR 0.11 CI: 0.04-0.32) (supplemental table 2).

One year after admission, 60.5% (CI: 51.2-69.8%) of the patients, who suffered ND during the first 7 days after admission, had died (Figure 2A). In comparison, only 9.2% (CI: 4.9-13.5%) of the patients, who remained stable during the first 7 days, had died ($p<0.0001$). The median survival of the patients, who suffered ND, was 20.0 days. Patient with END and LND suffered comparable mortality during first year (figure 2B). When the same significant prognostic factors as above were controlled for, neurological deterioration was established as an important predictor of long-term mortality (HR 6.99 CI: 3.54-13.8) (supplemental table 2). Other independent predictors of mortality during the first year were age, Charlson Score, admission NIHSS, posterior fossa location, and admission haematoma volume. We only included surgical treatment of patients with pending herniation, and it appeared to affect survival, however, it was not a predictor of good functional outcome.

DISCUSSION:

Patients, who remained stable during the first week after stroke onset, were highly likely to survive the first year. Haematoma expansion is a key driving force behind END, and factors that mark the patients as unstable within the first day were essentially risk factors of haematoma expansion – spot sign, larger haematomas, and anticoagulation treatment. Patients with smaller haematomas seemed to be protected from END. In addition, extensive haemorrhage into the ventricles of the brain marked the patients as unstable during the entire first week.

This study has several strengths. We believe that the generalizability of the data is high, as this study is based on consecutive patients with as little selection as possible as they were admitted based on catchment area. Patients are admitted fast track with early symptoms of stroke, independent of e.g. age or stroke severity. The electronic follow-up of patients allowed this to be almost complete, and only very few (all foreign citizens) were lost to follow-up. The large majority of patients in this study underwent acute CTA enabling us to investigate the spot sign as a risk factor of ND.

A weakness is the incomplete use of follow-up imaging, which could impose concerns of selection bias in the analysis of the follow-up images, however, the frequency of follow-up imaging was distributed equally among stable patients and patients suffering END or LND. It remains likely that the moribund patients, who might have concealed a large portion of haematoma expansion or IVH, as well as patients with mild symptoms were the groups most likely to be excluded from follow-up scan. Another weakness is the way in which LND was assessed. We did not possess consecutive GCS and SIP-score data further than the first day in most patients, and we thus needed to rely on medical chart data with documentation of GCS and the physicians' description of LND. However, physicians in Denmark are obligated to keep rigorous medical records, and because of this, we believe that even though it could provide information bias, it was an acceptable way to assess LND.

Our data are in consistence with other studies documenting a substantial risk of neurological deterioration during the first 24 to 48 hours. The relatively high fraction of patients undergoing END in our study is likely due to the exclusion of comatose and surgically treated patients (2-4) from other studies on END. LND is relatively poorly described in the literature. Mayer et al. (4) documented an incidence of LND relatively similar to ours. Sun et al. (6) found a higher incidence

of LND, but did not exclude patients suffering END. We demonstrated that patients, who already have suffered END, will be in high risk of continuing their trajectory of deterioration during the following days and consequently give rise to a higher risk of LND, if they are not excluded.

In a newly published meta-analysis (27), it was concluded that admission haematoma volume and IVH were associated with END, however, it was not shown that haematoma expansion was significantly related to END. Our study supports the notion that haematoma expansion is one of the key driving forces behind END. This study - as well as other studies - has found that patients with early predictors of haematoma expansion such as large haematoma (28), anticoagulation treatment, and spot sign (3,19) were more likely to undergo END. In addition, a few studies have shown a direct link between haematoma expansion and END (10,11,29). In this study, we found the spot sign to be an important predictor of END. The spot sign is a well-recognized predictor of early haematoma expansion. It is likely that much of the effect of other predictors of END (larger haematomas and anticoagulation therapy) is mediated at least in part by the spot sign. This was also observed in this study, as some of the predictors of END lost predictive effect, when the spot sign was considered in the model. This makes prediction of early neurological stability the perhaps most clinically useful utility of acute CTA, and spot sign assessment in patients with ICH should be recommended in all acute ICH patients.

That patients with IVH are in risk of END seems to be well established (27). Our data further support Sun et al. in the link between LND and IVH (6). It is highly likely that part of the process of both early and late neurological deterioration is driven by obstruction of the cerebrovascular fluid circulation and other harmful processes related to IVH (7,30,31). We encountered two phenomena not described in great detail in the literature – delayed IVH and expansion of the IVH volume. Both

of these have previously been described as independent predictors of poor outcome - to the best of our knowledge never before in relation to ND (32,33), though intuitively correlated. Our study indicates that the final IVH volume is predictive of LND. This emphasises the need for follow-up imaging in all patients with ICH allowing earlier intervention.

It is clear from our results that the first week constitutes the primary critical period regarding functional outcome and long-term mortality. Even after we controlled for other well-known predictors of mortality and poor outcome (26) as well as surgical treatment strategies, ND remained an important independent predictor of functional outcome and mortality. As the stability of the patients during the first week is very critical, when it comes to functional outcome and mortality, this study emphasizes the importance of targeting the underlying processes that drive the deterioration – haematoma expansion, obstruction of circulation in the fluid filled spaces, and comorbidities. We believe this study to possess excellent external validity. The trend today is towards a more fast track work-up of stroke patients due to the documented benefit of recanalization therapies in ischemic stroke. This entails that more and more patients with ICH also will be diagnosed early. We believe that our fairly unselected population and the few patients lost to follow-up makes our study a trustworthy picture of neurological deterioration in acute ICH-patients.

CONCLUSION:

The first week constitutes a very critical period with a relative high incidence of ND. Stability during the first week entails a good prognosis. END seems directly associated with haematoma expansion. Obstruction of the fluid filed spaces seems to be associated with both END and LND. Patients with a higher degree of comorbidity are in higher risk of LND.

CONTRIBUTORS: CO and HC contributed to the study concept and design. CO, AFC, IH, CKH and EK participated in the gathering of data. CO, AFC, SR and HC participated in the analysis and interpretation of the data. CO drafted the manuscript. All authors performed critical revision of the manuscript for important intellectual content.

COMPETING INTEREST: The authors declare that they have no conflict of interest.

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DATA SHARING STATEMENT: No additional data are available.

ETHICS: The Danish Data Protection Agency (file no. 2010-41-5205) has approved the registry**.**

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TABLES:

Table 1: Independent predictors of early and late neurological deterioration

	OR	95% CI	p-value
Early neurological deterioration – Patients with CTA on admission (n = 224)			
Anticoagulation treatment:	3.41	1.19-9.80	0.023
Admission GRAEB-score:			
0 points	1.00	…	…
1-5 points	2.02	0.76-5.40	0.161
6-12 points	8.73	2.87-26.5	<0.001
Admission haematoma volume:			
>60mL	1.00	…	…
10-59.9mL	0.43	0.18-1.06	0.066
<10mL	0.27	0.09-0.82	0.021
Spot Sign	10.7	4.79-24.3	<0.001
Early neurological deterioration – All patients (n = 299)			
Anticoagulation treatment:	3.87	1.65-9.11	0.002
Admission GRAEB-score:			

0 points	1.00	…	…
1-5 points	1.59	0.73-3.46	0.241
6-12 points	4.63	1.79-12.0	0.002
Admission SAH	2.24	1.03-4.87	0.042
Admission haematoma volume:			
>60mL	1.00	…	…
10-59.9mL	0.44	0.20-0.95	0.037
<10mL	0.20	0.07-0.56	0.002
Admission NIHSS (pr. point)	1.08	1.03-1.14	0.002
Late neurological deterioration – All patients at risk at day 1 (n = 204)			
Charlson Score (pr. point)	1.74	1.18-2.55	0.005
Haematoma location:			
Lobar	1.00	…	…
Basal ganglia	0.17	0.05-0.59	0.005
Posterior fossa	0.22	0.02-3.14	0.263
Admission GRAEB-score:			
0 points	1	…	…

1-5 points	4.81	1.42-16.3	0.012
6-12 points	22.2	3.66-134.8	0.001
Admission NIHSS (pr. point)	1.13	1.03-1.23	0.014

Variables offered to both END-models were Anticoagulation treatment, admission GRAEB-score, SAH on admission, serum glucose level, admission midline shift, admission haematoma volume, and admission NIHSS value (Spot sign presents only the first model). Variables offered to the LND-model were Charlson Score, admission NIHSS, admission haematoma volume, admission GRAEB-score, and admission midline shift.

Table 2: Follow-up imaging characteristics

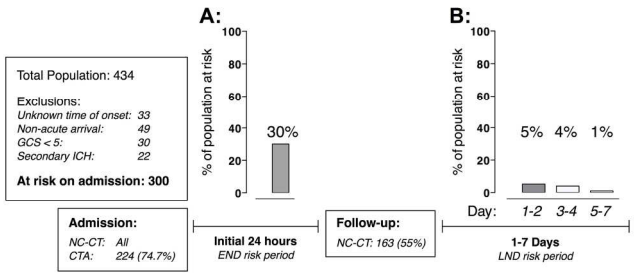
	Early neurological deterioration		Late neurological deterioration	
	Crude OR	Adjusted OR*	Crude OR	Adjusted OR †
Significant haematoma expansion, >12.5 mL	15.0 (6.3-35.5)	6.1 (2.2-17.3)	2.0 (0.4-10.5)	NI
Follow-up GRAEB-score, pr. point	1.3 (1.2-1.5)	NI	1.5 (1.2-1.9)	NI
Delayed IVH	10.3 (3.2-33.3)	NI	2.6 (0.2-26.6)	NI
IVH expansion, per GRAEB point	11.0 (4.4-27.2)	1.7 (1.2-2.3)	5.5 (1.1-26.3)	2.3 (1.3-4.2)
SAH on follow-up scan	3.4 (1.6-7.3)	2.8 (0.8-9.3)	2.6 (0.7-9.5)	NI
Delayed SAH	3.4 (0.6-21.3)	NI	NA	NA
Hydrocephalus	5.3 (1.7-16.3)	1.4 (0.3-6.6)	2.6 (0.2-26.6)	NI
Midline shift, per. mm	1.3 (1.1-1.4)	1.1 (0.9-1.3)	1.2 (0.9-1.4)	NI

*We adjusted for admission haematoma volume, admission GRAEB-score. †We adjusted for admission GRAEB-score. NI – Not included in the model due to insignificance or representation by other values (collinearity). NA – Not assessed due to incomplete representation.

FIGURE LEGENDS:

Figure 1: Study outline and prevalence of neurological deterioration during the first week. Panel A describes the incidence of END during the fist 24 hours, and panel B describes the incidence of LND during the following 6 days.

Figure 2: Survival curves displaying mortality during the first year. Panel A represents cumulative mortality (±95% CI) of the patients stable and with neurological deterioration during the first week. Panel B represents cumulative mortality separated into patients with END, LND, and stable during the first week.



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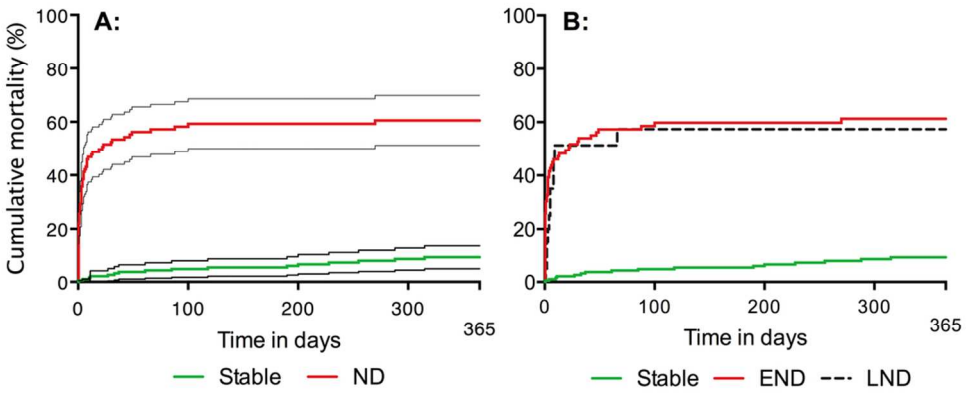

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Supplementary Materials

Prediction and prognostication of neurological deterioration in patients with acute ICH – a hospital-based cohort study

Ovesen et al. 2015

Supplemental Methodology:

Patients:
The acute stroke service of Bispebjerg Hospital covers a well-defined catchment area consisting of the entire Capitol Region of Denmark (approximately 1.7 million inhabitants), and receives acute patients from this area every day, all year - as well as patients possibly eligible for intravenous thrombolysis on even dates by direct referral from paramedics, general practitioners, and other hospitals in the region. On arrival of an acute ICH patient, the on-call neurosurgeon in a neighbouring hospital (distance 3 km) is consulted based on the admitting physician's discretion. The surgeon reviews CT images electronically, and a consensus-decision is made regarding instant surgical intervention or repeated contact in case of neurological deterioration. Patients admitted on vitamin-K antagonistic oral anticoagulation treatment and with an international normalized ratio (INR) > 1.7 are treated with prothrombin complex concentrate (PCC) and phytomenadion in order to reverse the anticoagulation effect; patients on factor Xa inhibitors are treated with PCC alone, and haemodialysis is considered in patients on directs thrombin-inhibitor treatment. Do-not-resuscitate (DNR) orders are in our institution placed on the patients chart by the treating physician in consensus with the patient or the patient's next of kin. It implies no resuscitation in case of cardiac/respiratory arrest and that the patient is not a candidate for mechanical ventilation should it be required. It does not necessarily imply discontinuation of on-going medical treatment

Patient Characteristic Definitions:
Prior stroke or transitory ischemic attack (TIA) was defined as a previous diagnosis of stroke or TIA. Hypertension (BP > 140/90mmHg) was defined as a history of untreated hypertension, the use antihypertensive medication on admission, or a diagnosis of hypertension during admission/outpatient clinic. The weekly consumption of alcohol was defined as excessive, if exceeding 252 g for men and 168 g for women. Active or prior smoking was defined as present use of tobacco or at least 3-pack years of prior use. The Charlson Index consists of 19 medial conditions each assigned a prognostic weight. The index is calculated by summing the weights. As the original score also includes cerebrovascular disease and hemiplegia, this was only added to the score, if these conditions existed before onset of the present stroke. The Charlson Index can include an age component, but this was not assigned in this study, as age was a separate variable.

Radiology:
Radiological imaging was conducted using 64-section multi-detector computed tomography scanners (MDCT) (Brilliance-64, Philips Medical Systems, Best, the Netherlands). Helical CTA from the aortic arch to vertex was performed using 120 kVp, 400 mAs/slice, collimation 64 x 0.625 mm (isotropic voxel resolution), and 70 ml iodine intravenous contrast injection (Iohexol 350 mg/ml) via an antecubital vein monitored with automated contrast tracking.

Stroke In Progression (SIP) Score:
The SIP-score is a shortened version of the Scandinavian Stroke Scale designed for monitoring purposes of acute stroke patients in Denmark. The score monitors the progression of symptoms in the arm, hand, and leg on the affected side of the body. In addition the patients ability to speak is monitored:

Arm motor power - 6: raises arm with normal strength, 5: raises arm with reduced strength, 4: raises arm with flexion in the elbow, 2: can move but not against gravity, 0: Paralysis.
Hand power - 6: Normal power, 4: Reduced strength in full range, 2: Some movements, fingertips do not reach palm, 0: Paralysis.
Leg motor power - 6: raises leg with normal strength, 5: raises leg straight with reduced strength, 4: raises leg with flexion in the knee, 2: can move but not against gravity, 0: Paralysis.
Speech - 10: no aphasia, 6: limited vocabulary or incoherent speech, 3: more than yes/no, but not longer sentences, 0: only yes/no or less

Supplemental Tables:

Supplemental table 1: Baseline characteristics and associations to early and late neurological deterioration

	END	No END	p-value	LND	No LND	p-value
Male gender	45 (50.6%)	127 (60.5%)	0.126	13 (65.0%)	11 (60.3%)	0.811
Age, y	73 (64-81)	70 (61-80)	0.062	81 (62-84)	73 (61-79)	0.068
TTS, min	95 (73-132)	106 (80-144)	0.146	103 (88-129)	95 (81-146)	0.557
Medical History						
Prior stroke	17 (19.3%)	30 (14.3%)	0.298	3 (15.0%)	2 (14.1%)	1.000
Prior TIA	4 (4.5%)	6 (2.9%)	0.489	0 (0.0%)	0 (0.3%)	1.000
Hypertension	57 (66.3%)	153 (73.6%)	0.256	15 (75.0%)	10 (73.9%)	1.000
Charlson Score, points	1 (0-1)	0 (0-1)	0.266	1 (0.5-2)	0 (0-1)	0.003
Pre-stroke mRS, points	0 (0-0.0)	0 (0-0)	0.054	0 (0-0.5)	0 (0-0)	0.492
Active or prior smoking	29 (43.3%)	87 (48.1%)	0.567	7 (43.8%)	7 (47.8%)	0.799
Excessive alcohol use	7 (10.0%)	26 (14.0%)	0.248	3 (16.7%)	2 (14.2%)	0.728
Medication						
Antiplatelet therapy	25 (29.1%)	56 (26.7%)	0.669	4 (20.0%)	51 (27.7%)	0.600
Anticoagulation therapy	20 (22.7%)	20 (9.5%)	0.005	4 (20.0%)	16 (8.7%)	0.115
Antihypertensive therapy	44 (51.2%)	105 (50.0%)	0.898	12 (60.0%)	91 (49.5%)	0.481
Statin therapy	18 (20.9%)	47 (22.4%)	0.878	7 (35.0%)	40 (21.7%)	0.260
Admission stroke characteristics						
NIHSS, points	17 (11-22)	10 (5-16)	<0.0001	15 (13-20)	9 (7-15)	<0.0001
GCS, points	12 (10-14)	15 (13-15)	<0.0001	13 (11-14)	15 (13-15)	0.002
Blood pressure						
Systolic, mmHg	191.9 (37.1)	185.2 (27.6)	0.216	174.2 (20.9)	187.0 (27.5)	0.019
Diastolic, mmHg	105.6 (24.1)	100.4 (20.8)	0.083	101.7 (21.6)	100.9 (20.3)	0.928
Heart rate, min^{-1}	79.6 (16.3)	81.2 (16.9)	0.555	85.5 (20.1)	81.1 (16.4)	0.372
Body temperature, ^{o}C	36.4 (0.6)	36.7 (3.9)	0.568	36.6 (0.4)	36.8 (4.1)	0.698
Haematoma location			0.285			0.024
Lobar	41 (46.1%)	78 (37.1%)		13 (65.0%)	62 (33.3%)	
Basal ganglia	43 (48.3%)	113 (53.8%)		6 (30.0%)	104 (56.5%)	
Posterior fossa	5 (5.6%)	19 (9.0%)		1 (5.0%)	18 (9.8%)	
Initial haematoma volume, mL	45.1 (18.0-88.9)	10.1 (3.5-24.0)	<0.0001	28.5 (12.5-44.1)	9.0 (3.0-21.1)	0.002

IVH (GRAEB score ≥1)	46 (51.7%)	52 (24.8%)	<0.0001	12 (60.0%)	36 (19.6%)	<0.0001
Admission GRAEB-score:			<0.0001			<0.0001
0 points	46 (51.7%)	158 (75.2%)		8 (40.0%)	148 (80.4%)	
1-5 points	17 (21.3%)	40 (19.0%)		8 (40.0%)	31 (16.8%)	
6-12 points	24 (27.0%)	12 (5.7%)		4 (20.0%)	5 (2.7%)	
SAH	33 (37.1%)	35 (16.7%)	<0.0001	5 (25.0%)	27 (14.7%)	0.326
Midline shift (mm)	2.0 (0.0-7.0)	0.0 (0.0-0.0)	<0.0001	0.0 (0.0-2.0)	0.0 (0.0-0.0)	0.103
Admission CTA	64 (71.9%)	159 (75.7%)	0.561	14 (70.0%)	140 (76.1%)	0.586
Spot sign	47 (73.4%)	29 (18.1%)	<0.0001	3 (21.4%)	23 (17.7%)	0.719
Follow-up CT	51 (57.3%)	112 (53.3%)	0.612	13 (65.0%)	98 (52.7%)	0.350
TTPCC, min	70 (51-83)	92 (42-114)	0.220	42 (30-91)	92 (60-144)	0.126
Admission biochemestry						
Hemoglobin, mmol/L	8,6 (7,9-9,3)	8,7 (8,1-9,3)	0,548	8.4 (7.5-8.9)	8.7 (8.1-9.4)	0.064
WBC count	8,1 (6,6-10,3)	7,9 (6,4-9,8)	0,449	9.0 (6.6-12.1)	7.9 (6.4-9.6)	0.345
Neurophil count	5,1 (4,0-7,2)	5,0 (3,7-6,9)	0,658	6.0 (3.7-9.2)	4.9 (3.6-6.7)	0.168
Platelet count	213,0 (173,0-240,0)	222,0 (180,0-273,0)	0,084	208.5 (170.5-283.5)	222.0 (181.0-272.0)	0.999
Glucose, mmol/L	7,3 (5,9-8,6)	6,4 (5,8-8,3)	0,017	6.4 (5.6-9.2)	6.4 (5.8-8.0)	0.753
APTT	26,0 (24,0-32,0)	27,0 (25,0-29,0)	0,958	27.0 (25.0-29.0)	27.0 (25.0-29.0)	0.764
INR	1,0 (1,0-1,2)	1,0 (1,0-1,1)	0,632	1.1 (1.0-1.2)	1.0 (1.0-1.1)	0.119

Data presented as frequency (%), mean (SD) and median (IQR) as appropriate. TTS – time to scan; mRS – modified Rankin Scale; NIHSS – National Institute of Health Stroke Scale; GCS – Glasgow Coma Scale; IVH – intraventricular haemorrhagic extension; SAH – subarachnoid haemorrhagic extension; TTPCC – Time from admission to Prothrombine Complex Concentrate administration; WBC – white blood cell count; APTT – activated partial thromboplastin time; INR – international normalized ratio.

Supplemental table 2: Predictors of independent walking (mRS≤3) after 90 days among survivors and mortality during first year

	Independent walking			Mortality during first year		
	OR	95% CI	p-value	HR	95% CI	p-value
Age (per year)	0.96	0.93-0.99	0.025	1.04	1.02-1.06	0.001
Charlson Score (per point)	0.55	0.35-0.85	0.008	1.44	1.22-1.72	<0.001
Admission NIHSS (per point)	0.85	0.79-0.92	<0.001	1.09	1.04-1.14	<0.001
Haematoma location:						
Lobar	1	…	…	1	…	
Basal ganglia	0.19	0.07-0.54	0.002	1.17	0.69-1.99	0.57
Posterior fossa	0.22	0.04-1.18	0.078	3.30	1.25-8.7	0.016
Initial haematoma volume (per mL)	0.97	0.95-0.98	0.001	1.01	1.00-1.01	0.001
Admission IVH	1.01	0.42-2.44	0.895	1.66	0.99-2.78	0.055
Surgical haematoma evacuation[1]	1.28	0.26-6.37	0.762	0.25	0.08-0.77	0.016
External ventricular drainage	0.59	0.10-3.58	0.563	0.42	0.15-1.17	0.094
Neurological deterioration	0.11	0.04-0.32	<0.001	6.99	3.54-13.8	<0.001

[1]Only surgery due to pending herniation was included.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p. 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p. 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p. 3
Objectives	3	State specific objectives, including any prespecified hypotheses	p. 4
Methods			
Study design	4	Present key elements of study design early in the paper	p. 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p. 4, 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	p. 4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p. 5,6, and supplementary methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p. 5,6, and supplementary methods
Bias	9	Describe any efforts to address potential sources of bias	p. 7,8
Study size	10	Explain how the study size was arrived at	p. 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p. 7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p. 7,8
		(*b*) Describe any methods used to examine subgroups and interactions	p. 7,8
		(*c*) Explain how missing data were addressed	p. 7,8
		(*d*) If applicable, explain how loss to follow-up was addressed	p. 7

		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	p. 8,9,10,11
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Supplemental table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	p. 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	p. 10,11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Please see tables
		(*b*) Report category boundaries when continuous variables were categorized	p. 7,8 and tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	p. 11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Please see discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	p. 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p. 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.