Emergency department point-of-care biomarkers and day 90 functional outcome in spontaneous intracerebral hemorrhage: A single-center pilot study

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Abstract. Spontaneous intracerebral hemorrhage (sICH) results in high morbidity and mortality rates, thus identifying strategies for timely prognosis and treatment is important. The present study aimed to analyze the relationship between emergency department point-of-care (POC) blood biomarkers and day 90 functional outcome (FO) in patients with acute (<8 h) sICH. On-site POC determinations, including complete blood count, glucose, cardiac troponin I, D-dimer and C-reactive protein, and derived inflammatory indexes were performed for a cohort of 35 patients. The primary endpoint was a favorable day 90 FO (modified Rankin Score ≤3). Secondary endpoints included early neurological worsening (ENW), day 7/discharge neurological impairment, day 90 independence assessment (Barthel Index <60), hematoma enlargement and perihematomal edema (PHE) growth. A favorable three-month FO was reported in 16 (46%) participants. Older age, previous history of ischemic stroke and initial imagistic parameters, including intraventricular hemorrhage, enlarged contralateral ventricle and cerebral atrophy, significantly predicted an unfavorable FO. The admission D-dimer similarly predicted day 90 FO and the independence status, along with ENW and a more severe day 7/discharge neurological status. The D-dimer also correlated with the initial neurological status and PHE. PHE growth correlated with granulocytes, systemic immune-inflammation index and glycemia. The results suggested that a lower admission D-dimer could indicate an improved day 90 FO of patients with sICH, while also anticipating the development of PHE growth and ENW.

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Introduction

Spontaneous intracerebral hemorrhage (sICH) has a disproportionate socioeconomic impact considering its low incidence rate (26% of all incident strokes in 2017, with higher prevalence rates in East European countries) (1). An aging population and repeated unsuccessful research endeavors for curative treatment contribute to its high mortality and morbidity, resulting in a 1-month case fatality of 40% with only 12% of patients regaining long-term functional independence (2). At present, the focus is on improving early outcome prediction to individualize patient management, and to also identify individuals at risk before sICH occurs, as to date, no reliable premonitory onset markers have been determined. Therefore, biomarker testing is an area of interest, as it is minimally invasive, low cost and could potentially enable accurate risk stratification and outcome estimation. Routinely, the standard hematologic evaluation consists of complete blood count (CBC), including platelet (PLT) count, coagulation profile and serum glucose (3,4). As sICH is a time-sensitive condition, readily available point-of-care (POC) devices reduce delays and facilitate prompt management.

Over the past decade, the role of inflammation in sICH progression and neurological impairment has been further clarified (5,6), and inflammatory biomarkers are currently regarded as potential prognostication tools. CBC upon admission, which includes hemoglobin (Hb), red blood cells and their distribution width (RDW), and derived inflammatory indexes, such as neutrophils-to-lymphocytes ratio (NLR), lymphocytes-to-monocytes ratio (LMR), platelets-to-lymphocytes ratio (PLR) and C-reactive protein (CRP), have been

associated with mortality (5,7-11). Moreover, early neurological worsening (ENW) (12), hematoma volume expansion and the expansion of the surrounding edema (5,13,14), and day 90 functional outcome (FO) (6,13,15-19) have also been reported to be associated with mortality. Furthermore, systemic immune-inflammation index (SII) has been recently reported as a relevant predictor of poor hospital discharge outcome (20).

Leukocyte count has been consistently associated with larger ICH volumes (5), but no consensus has been reached as to ICH progression, infection risk and mortality (11). Higher admission neutrophils have been associated with larger baseline volumes (21), mortality (10,22,23) and morbidity (10,23). With regard to monocyte (MON) count, increased admission levels are associated with poor outcome and mortality (5), but not with ICH volume (21), as MON are thought to contribute to secondary injury (13). Admission lymphopenia has been correlated with higher stroke severity, larger baseline hematoma volume and intraventricular extension, along with infection risk and 3-month mortality rate (5). NLR and LMR mirror post-ICH proinflammation and immunosuppression (12), as higher NLR has reflected larger baseline volumes, stroke severity, severe perihematomal edema (PHE) growth and poor 3-month outcome (5), and lower LMR has indicated neurologic deterioration and day 90 mortality (12).

CRP has been significantly linked with hematoma growth (HG), ENW, mortality and 3-month outcome (5,7,9,24). Its early presence at the hemorrhagic site could be due to local synthesis or transformation of the circulating liver-synthetized pentameric form (24).

Regarding Hb, anemia is associated with larger ICH volumes (25), increased HG (26) and worse outcomes (26-28). RDW is another inexpensive, automatically generated hematology parameter that is impacted by inflammation and is currently associated with day 30 FO (29).

Moreover, stroke is considered a systemic condition that induces cardiac, lung and immune dysfunctions (5,30); therefore, cardiac biomarkers, such as troponin I (cTnI), have been linked to stroke severity (31), in-hospital mortality (30,32) and unfavorable outcomes (33,34). On the other hand, D-dimer levels have been associated with an increased risk (35,36) and severity (37) of hemorrhagic stroke, and an increased hematoma volume (37), although it has not been proved sufficiently accurate for molecular stroke diagnosis (38). Furthermore, admission hyperglycemia has also been related to mortality (6,8) and day 90 FO (6).

The emergency department (ED) provides a unique opportunity for POC testing, both for standard and additional biomarkers (e.g., cTnI, D-dimer and CRP). When addressing time-sensitive conditions such as sICH, targeted escalation of the standard protocol could benefit these hyperacute patients. The contribution of additional POC testing could enable early risk stratification strategies to be identified and facilitate improvements in outcomes for patients with sICH. Nevertheless, information about the applicability of POC testing on cerebral hemorrhage is scarce.

The present study aimed to assess the predictive role of ED-based POC biomarkers (standard and additional) and derived inflammatory indexes on day 90 FO in patients with acute sICH.

Materials and methods

Patient recruitment. The design and enrolment processes of this prospective, single-center, ED-based pilot study have been previously published (39). To summarize, adult patients presenting with acute sICH (<8 h from onset) to the ED of the County Emergency Hospital (Cluj-Napoca, Romania) were recruited over 18 months (December 2017 to June 2018) provided that Glasgow Coma Scale (GCS) was ≥8 and no exclusion criteria were met. The exclusion criteria were as follows: Identifiable secondary ICH causes, thromboembolic/ischemic disease, seizures, severe pre-ICH disability [modified Rankin Scale (mRS)≥4], coagulopathy, treatment with heparin, low-molecular-weight heparin, glycoprotein IIb/IIIa antagonists or oral anticoagulants, pregnancy/breastfeeding, scheduled neurosurgical/hemostatic treatment, enrolment in other studies within the last 30 days or terminal disease. The study protocol was approved by the Institutional Review Board of the 'Iuliu Haţieganu' University of Medicine and Pharmacy Cluj-Napoca (approval no. 441/24.11.2016). The procedures and interventions in the present study were in accordance with the principles stated by the Declaration of Helsinki. All participants or legal representatives provided written informed consent.

Data sources/measurements. Demographic, clinical and laboratory data were documented upon ED admission. The routine management of patients with acute sICH in our department and the study of specific interventions are present in Fig. 1. ED-based POC whole-blood analyzers included the Fujifilm Dry-Chem NX500 biochemistry analyzer and the Swelab Alfa Plus hematology analyzer. CBC included granulocytes [GRA; composed of neutrophiles (NEU) and the largest proportion of eosinophils (EOS)] and mid-size (MID) population of cells (composed of mid-size population of MON, basophils, EOS, blasts and other immature cells). Calculated hematology indexes included the following ratios: NLR (incorporating GRA values), LMR (incorporating MID values) and PLR, alongside SII [calculated as NEU x PLT/(lymphocytes (LYM) x1,000)] and incorporating GRA results. An ED-based PathFast™ fully automatic chemiluminescence enzyme immunoassay was used to study additional biomarkers, including cTnI, D-dimer and high sensitive CRP (hs-CRP).

Patients were clinically assessed on days 2 and 7 (or on discharge). Follow-up telephone interviews on day 90 included FO (mRS) and independence on daily living activities [Barthel Index (BI)].

Diagnosis and imagistic controls were performed on a General Electric Optima 64 scanner (Cytiva). The hemorrhage volume was measured using manual segmentation with the inclusion of the entire visible lesion area. The post-processing analysis was performed on a General Electric AW Server 2.0 workstation by two independent radiologists, blinded for patient outcome.

Statistical analysis. In this analysis, the primary endpoint was day 90 FO. A favorable outcome was considered as an mRS of 0-3, whereas an mRS of 4-6 was considered as an unfavorable outcome. Secondary clinical endpoints included ENW [defined as a GCS decrease of ≤2 points or a National Institute

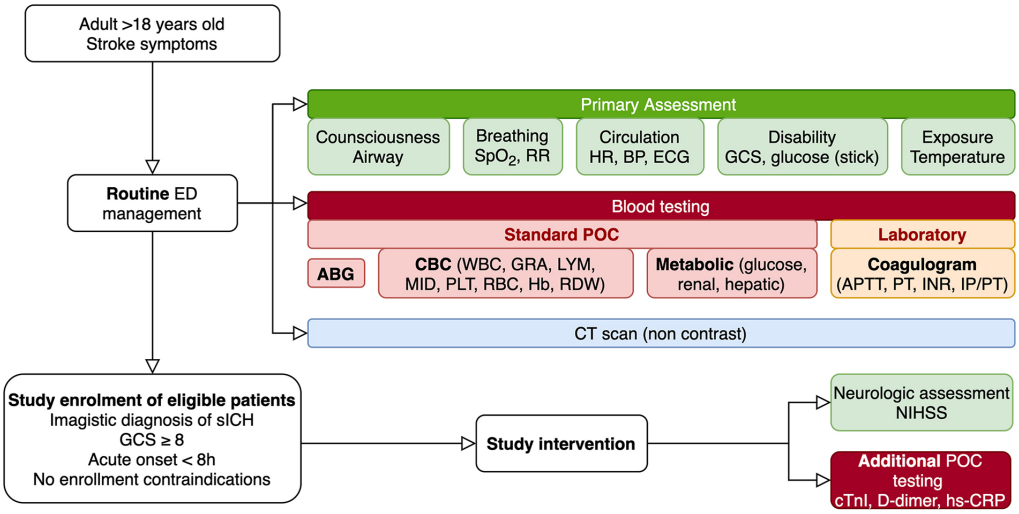

Figure 1. Routine ED baseline assessment of patients with sICH and study specific interventions. ED, emergency department; SpO_2, peripheral oxygen saturation; RR, respiratory rate; HR, heart rate; BP, blood pressure; ECG, electrocardiogram; GCS, Glasgow Coma Scale score; POC, point-of-care; ABG, arterial blood gases; CBC, complete blood count; WBC, white blood cells; GRA, granulocytes; LYM, lymphocytes; MID, mid-cell population; PLT, platelets; RBC, red blood cells; Hb, hemoglobin; RDW, red cell distribution width; APTT, activated partial prothrombin time; PT, prothrombin time; INR, international normalized ratio; IP/PT, prothrombin index/prothrombin time; CT, computer tomography; sICH, spontaneous intracerebral hemorrhage; NIHSS, National Institute of Health Stroke Scale; cTnI, cardiac troponin I; hs-CRP, high-sensitive C reactive protein.

of Health Stroke Scale (NIHSS) increase ≥4], day 7/discharge neurological impairment (NIHSS ≤15), and day 90 assessment of quality of life and independence. Radiological endpoints included HG (change in baseline hematoma volume of >33% or >6 ml by day 2) and PHE growth [difference in the largest PHE linear dimension between the diagnostic and control computed tomography (CT) scans].

Statistical analyses was performed using MedCalc® Statistical software (version 19.6; MedCalc Software byba). Quantitative data was assessed for normality of distribution using the Shapiro-Wilk test, and presented as the median and 25-75th percentiles. Qualitative data are presented as the frequency and percentage. Comparisons between groups were analyzed using the Mann-Whitney U test or χ^2 test. Spearman's rho was used to assess correlations between variables. P<0.05 was considered to indicate a statistically significant difference.

Results

A cohort of 39 patients was recruited, with 35 completing the in-hospital follow-up and 23 (66%) alive on day 90. All deaths were registered within the first month and in-hospital mortality was 23%.

Baseline characteristics of the cohort according to day 90 FO are presented in Table I. Older age, previous history of ischemic stroke, and the presence of intraventricular hemorrhage (IVH), enlarged contralateral ventricle (ECV) and cerebral atrophy on the initial CT scan significantly predicted an unfortunate FO scoring on day 90 follow-up. Median baseline hematoma volume and PHE did not differ significantly between surviving [hematoma volume, 9.15 cm^3 (6.69-22.18); PHE, 8.35 mm (6.81-11.58)] and deceased [hematoma volume, 16.83 cm^3 (9.2-31.89); PHE, 9.35 mm (6.50-13.25)] day 90 outcome groups (P=0.234 and P=0.470, respectively).

Baseline POC biomarker values and calculated indexes according to day 90 mRS are presented in Table II. Higher values in the unfavorable outcome group were documented for RDWa, GRA, NLR, PLR, SII, hs-CRP and D-dimer, but the differences were only significant for D-dimer (P<0.001). When further considering day 90 independence on daily living activities, D-dimer values were significantly higher (P=0.032) in the dependent patients [BI <60; 3.610 μg/ml FEU (0.900-5.010) vs. 0.758 μg/ml FEU (0.383-0.890)] compared with those in the day 90 independent group. Negative correlations were documented between admission D-dimer and admission GCS (rho=-0.342; P=0.044) and day 90 independence status (rho=-0.670; P=0.001).

ENW was documented in 9/35 patients, with only two alive by day 90, equally divided between outcome groups. Baseline median hematoma volume and PHE did not differ significantly (P=0.051 and P=0.094, respectively) between those with [hematoma volume, 24.60 cm^3 (14.16-70.00); PHE, 10.50 mm (9.23-20.63)] and without ENW [hematoma volume, 9.20 cm^3 (5.99-21.25); PHE, 7.5 mm (6.00-10.40)]. All ENW patients received antibiotic treatment by day 7 (ATB 7) and a modest correlation between ENW and ATB 7 was observed (rho=0.367, P=0.033). In patients who developed ENW, white blood cell [WBC; 10.60x10^9/l (8.00-15.25)], GRA [7.30x10^9/l (5.95-11.60)] and D-dimer [3.73 μg/ml FEU (1.22-5.01)] values were significantly higher compared with those in patients without ENW [WBC, 8.10x10^9/l (6.60-10.60); GRA, 5.30x10^9/l (3.90-7.55); D-dimer, 0.86 μg/ml FEU (0.63-1.63)] (P=0.042, P=0.025 and P=0.024, respectively). D-dimer was also significantly higher in the 8/35 patients with a worse day 7 neurological status, defined as NIHSS score ≥16 [2.01 (1.20-5.01) vs. 0.84 (0.59-1.93); P=0.017). By contrast, SII values were not significantly higher in either ENW group [0.45 (0.33-0.86) vs. 0.83 (0.37-1.36); P=0.265], nor in those patients with a worse day 7 neurological status [0.45 (0.32-1.01) vs. 0.49 (0.37-0.81); P=0.315].

The median length of hospital stay was 15 days. Two participants required neurosurgery and another one required

Table I. Baseline clinical and imagistic characteristics.

Characteristic	Day 90 FO		P-value
	Favorable (n=16)	Unfavorable (n=19)	
Median age (range), years	62 (57-68.5)	75 (73-81)	<0.001
>70	3 (18.8)	17 (89.5)	<0.001
Male, n (%)	11 (68.8)	8 (42.1)	0.217
Hypertension, n (%)	12 (75.0)	15 (78.9)	1.000
>2 antihypertensive drugs	7 (43.8)	10 (52.6)	0.854
Diabetes mellitus, n (%)	6 (37.5)	4 (21.1)	0.454
Dyslipidemia, n (%)	7 (43.8)	7 (36.8)	0.945
Statin use prior to admission, n (%)	4 (25)	6 (31.6)	0.723
Antiplatelet agent, n (%)	4 (25.0)	5 (26.3)	1.000
Smoking (former/active), n (%)	11 (68.8)	8 (42.1)	0.217
GCS, median (range)	15 (14; 15)	13 (12; 15)	0.080
NIHSS score, median (range)	8.5 (6.2; 14.5)	15 (6; 21)	0.288
Median SBP (range), mmHg	164.5 (154.5-192.5)	163 (147.2-174.2)	0.174
>170 mmHg, n (%)	7 (43.8)	8 (42.1)	1.000
Median HR (range), beats/min	81.5 (71.5-97.5)	75 (65-86)	0.267
Atrial fibrillation, n (%)	1 (6.2)	0 (0)	0.457
Hematoma location, n (%)			0.581
Supra-tentorial lobar	2 (12.5)	4 (21.1)	
Supra-tentorial deep	14 (87.5)	13 (68.4)	
Supra-tentorial mixte	0 (0)	1 (5.3)	
Infratentorial	0 (0)	1 (5.3)	
Hematoma volume, cm^3, n (%)			0.316
<30	14 (87.5)	14 (73.7)	
30-60	2 (12.5)	2 (10.5)	
>60	0 (0)	3 (15.8)	
Median perihematomal edema (range), mm	9.07 (7.16-28.21)	21.47 (6.97-32.86)	0.371
IVH, n (%)	1 (6.2)	8 (42.1)	0.022
MLS >10 mm, n (%)	3 (18.8)	10 (52.6)	0.086
Mass effect, n (%)	12 (75.0)	17 (89.5)	0.379
CVC, n (%)	12 (75.0)	16 (84.2)	0.677
ECV, n (%)	1 (6.2)	8 (42.1)	0.022
Periventricular leucoaraiosis, n (%)	5 (31.2)	13 (68.4)	0.064
Lacunarism, n (%)	8 (50.0)	16 (84.2)	0.071
Cerebral atrophy, n (%)	4 (25.0)	16 (84.2)	0.001
Median length of hospital stay (range), days	15 (11.5-16.75)	14 (8-19)	0.715
Discharge disposition			0.741
Family care	9 (56.2)	12 (63.2)	
Rehabilitation/lower rank hospital	1 (6.2)	2 (10.5)	

FO, functional outcome; mRS, modified Rankin Scale; TIA, transient ischemic attack; SBP, systolic blood pressure; HR, heart rate; GCS, Glasgow coma scale; IVH, intraventricular hemorrhage; MLS, midline shift; CVC, contralateral ventricle compression; ECV, enlarged contralateral ventricle; NIHSS, National Institute of Health Stroke Scale.

advanced intensive care unit (ICU) airway management. By day 7, medical complications occurred in 20 (57%) participants, all of whom were undergoing antibiotic treatments. A day 90 favorable outcome was reached in only 25% patients. No significant POC biomarker differences were documented between patients with and without day 7 antibiotic treatment.

Control CT scans were performed for 29/35 participants (83%). Only 7 controls were performed within the first 48 h (median time of 6 days and 13 h since the onset of symptoms). Any hematoma expansion occurred in 15/29 participants [median 2.46 cm^3 (1.78-11.18 cm^3)], yet the criteria for HG was fulfilled in only 6 (40%) patients, with 4 dying before the

Table II. Comparison of admission POC biomarkers according to day 90 outcome.

	Day 90 FO		
POC biomarker	Favorable (n=16)	Unfavorable (n=19)	P-value
Hb, g/dl	13.85 (12.75-15.07)	13.40 (12.70-14.80)	0.417
RBC, x10^{12}/l	4.55 (4.33-4.91)	4.55 (4.08-4.94)	0.729
RDWa, fl	60.30 (58.13-65.38)	63.20 (58.20-66.40)	0.943
WBC, x10^9/l	9.35 (6.45-11.58)	9.30 (6.70-11.30)	0.895
GRA, x10^9/l	5.40 (3.80-8.60)	6.20 (4.70-8.30)	0.667
LYM, x10^9/l	2.15 (1.33-2.68)	1.80 (1.40-2.20)	0.127
MID, x10^9/l	0.85 (0.60-1.10)	0.80 (0.60-1.30)	0.934
PLT, x10^9/l	168.50 (140.00-221.50)	162.00 (150.00-192.00)	0.740
NLR	2.26 (1.82-3.70)	3.14 (2.79-5.14)	0.145
LMR	2.11 (1.71-4.33)	2.11 (1.20-3.25)	0.486
PLR	92.94 (55.2-125.00)	95.21 (72.5-116.48)	0.655
SII	0.39 (0.25-1.15)	0.53 (0.36-0.88)	0.868
hs-CRP, mg/l	2.49 (0.89-4.01)	3.27 (0.68-5.20)	0.446
cTnI, ng/ml	0.003 (0.002-0.070)	0.003 (0.001-0.006)	0.181
D-dimer, μg/ml FEU	0.75 (0.38-0.89)	2.31 (0.92-5.01)	<0.001
Glucose, mmol/l	146 (143-168)	140 (119-183)	0.585

Data are presented as the median (range). FO, functional outcome; POC, point-of-care; WBC, white blood cells; GRA, granulocytes; LYM, lymphocytes; MID, mid-cell fractions; PLT, platelets; NLR, neutrophils-to-lymphocytes ratio; LMR, lymphocytes-to-monocytes ratio; PLR, platelets-to-lymphocytes ratio; SII, systemic immune-inflammation index; Hb, hemoglobin; RBC, red blood cells; RDW, red cells distribution width; hs-CRP, high sensitive C reactive protein; cTnI, cardiac troponin I.

follow-up. A median PHE growth of 3.65 mm (1.38-8.38 mm) was documented in 25 participants (12/19 unfavorable outcome group). Moderate or weak negative correlations were detected between POC inflammatory markers and indexes and PHE growth (rho=-0.511, P=0.005 for WBC; rho=-0.548, P=0.002 for GRA; rho=-0.373, P=0.047 for SII; rho=-0.378, P=0.043 for glucose). D-dimer was correlated with admission PHE (rho=0.398, P=0.018).

Cut-off values of the variables mostly associated with the primary outcome were calculated, namely age, admission GCS and D-dimer. As such, an unfavorable day 90 FO was indicated by age ≥72 years [area under the curve (AUC) 0.908 (95% confidence interval (CI), 0.761-0.979), Se 84.2 (60.4-96.6), Sp 93.7 (69.8-99.8), P<0.001)], GCS ≤13 [AUC 0.661 (95% CI 0.482-0.812), Se 52.63 (28.9-75.6), Sp 81.25 (54.4-96.0), P=0.0598)] and D-dimer >0.905 μg/ml fibrinogen equivalent unit [FEU; AUC 0.845 (95% CI 0.683-0.945), Se 84.21 (60.4-96.6), Sp 87.50 (61.7-98.4), P<0.001]. The receiver operating characteristic curve of admission D-dimer predicting day 90 FO is presented in Fig. 2.

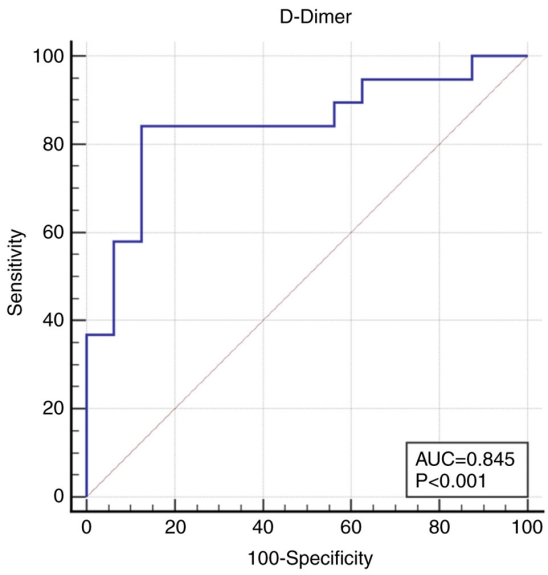

Figure 2. Receiver operation characteristic curve of admission D-dimer predicting day 90 functional outcome. Cut-off, 0.905 μg/ml fibrinogen equivalent units. AUC, area under curve.

Discussion

In this observational cohort of patients with spontaneous ICH, lower admission D-dimer indicated an improved day 90 FO and independence status. Increased age, previous stroke and certain initial imagistic parameters, including IVH, ECV and cerebral atrophy, implied an unfavorable outcome. The results indicated that D-dimer may also anticipate the development of ENW, and modestly reflect admission PHE, whereas certain inflammatory markers may correlate with PHE growth.

Our POC results of baseline D-dimer supported previously published data on the use of D-dimer in prognosing day 90 unfavorable FO (40,41), with an admission level of 0.905 μg/ml FEU predicting a poor 3-month outcome with a

sensitivity and specificity of ~85%. Previous reports identified values ~0.5 mg/l FEU as estimating a poor outcome (41,42). Nevertheless, the correlation between D-dimer and 3-month dependence status should be investigated further to verify the results of the present study. The mechanism through which D-dimer impacts the sICH prognostic value is yet to be established, as it is traditionally a hypercoagulability marker and more recently has been considered for potential application in ischemic stroke diagnosis (43). Evidence of elevated D-dimer as expression of increased fibrinolysis, hence contributing to a hypocoagulable status and extensive hemorrhages, is rather scarce (35,36,44). The present study consistently associated D-dimer with clinical endpoints, including admission neurological status expressed as GCS, throughout the entire follow-up period, alongside baseline PHE. Nevertheless, a correlation with ICH volume was not identified in the present study, despite being frequently reported in previous studies (37,40,41). With ICH volume as a known determinant of admission neurological status and ENW (40,44,45), a larger cohort might associate D-dimer with baseline volume and the evolution of neurological status, thus supporting the hypocoagulability theory.

ICH induces a state of systemic and peripheral inflammation, thus increasing circulating WBC and recruiting certain molecules within the affected area, which amplifies local damage (13,22). Previous studies have reported results for several inflammatory biomarkers and calculated indexes (Hb, absolute RDW, GRA, LYM, PLT, NLR, PLR) that contribute to the existing data on FO prognostication (5,6,17,19,28,29,46,47), but the cohort assessed in the present study did not display statistically significant results, only in-line tendencies with previously published evidence. Furthermore, moderate negative correlations were determined between WBC, GRA, SII and PHE growth. However, these were not consistent with existing theories on the contribution of acute inflammation to PHE enlargement (13), and subsequently to an unfavorable FO (6,13,15,16). This contradiction might reside in the modest sample size of the current analysis and of the fact that the GRA population was reported as a substitute for NEU, the former also including EOS alongside NEU. Recent evidence has shown a significant increase in peripheral WBC, GRA and MON population in patients with acute ICH, whereas the LYM population has decreased (48). The contribution of EOS to sICH prognostication is not completely understood; however, Chen *et al* (14) correlated EOS count with increased risk of HE. Moreover, the short interval from symptom onset to CBC sampling in the present cohort (39) might have prevented the documentation of the activation of local and systemic inflammation (13,22,48). In the present study, MID was documented as a surrogate for MON, but its values incorporate multiple cell populations. SII is a parameter that is documented in regard to hospital discharge outcome of patients with sICH (20); NEU and LYM reflect inflammation, whilst PLT reflect vascular permeability. As such, SII components could depict local PHE metabolism. The results of the present study were in line with previous data on larger SII values in the unfavorable FO subgroup (20), without reaching statistical significance. Furthermore, there was no association with day 7 neurological status (as a proxy for the reported discharge FO) (20) or day 90 FO, which indicated that the timing of the most effective inflammatory panel requires further investigation.

As all reported individual inflammatory markers (WBC, GRA, LYM, MID and CRP) failed to predict day 90 FO, the analysis on calculated indexes (NLR, LMR, PLR and SII) produced similar results. Subsequently, further extensive research is required to validate whether such POC derived indexes can impact outcome prognostication in a similar manner as previous evidence has indicated (5,12,17,46).

At present, the results regarding CRP are inconclusive, despite existing evidence of its association with HG, ENW, mortality and 3-month outcome (5,7,9,24), including in-hospital mortality data reported on a consistent ED-based cohort (9). Currently, hs-CRP assays can only measure plasma pentameric CRP, thus failing to incorporate the extent of the neuroinflammatory response to ICH (24). Furthermore, a pre-existing subliminal inflammatory status, though not detected as an infection or chronic inflammation, might affect the coagulation function and the vessel wall pathophysiology, contributing to persistent vessel leakage.

PLT and PLR are well-known indicators of mortality (8,49) and increase the chances of a negative day 90 FO (6,17-19). Although a similar 25% of each study group was under antiplatelet medication when sICH occurred, the present analysis only documented a moderate negative correlation of PLT with admission ICH volume and day 7 neurological status, in spite of previous discussions on its implications within the existing inflammatory process accompanying sICH (19). Nevertheless, Zhang and Shen (19) demonstrated that ICU rather than ED admission PLR values are relevant for outcome estimation.

In regard to Hb levels, lower mean admission values were recorded in the unfavorable outcome group, without statistical significance or without meeting the criteria of the definition of anemia (39). RDW is another inexpensive automatically generated hematology parameter that is impacted by inflammation (29), and our results indicated a modest correlation with admission PHE, but this was not associated with day 90 FO.

If sICH is considered as having a systemic impact, then metabolic and cardiac biomarkers could indicate its amplitude. However, random admission hyperglycemia did not reflect the severity of sICH (50), nor was it associated with day 90 FO estimation (6), in spite of the modest negative correlation with PHE growth. Mean admission cTnI levels did not differ among outcome groups and the analysis conducted in the present study did not correlate this parameter with any of the study endpoints. Previous studies on troponin levels have concluded that peak serum cTnI values rather than admission values reflect a poor outcome, including mortality (33,34). Therefore, we speculate that the results of the present study suggest further investigating POC testing.

To the best of our knowledge, the present study was one of the few studies on POC testing in acute sICH within an ED, yet its value is limited due to its one-center location and modest sample size, meaning that the current results require further investigation in order to be validated in sICH management. As the sICH population is of an increasing age, D-dimer interpretation should be considered cautiously. The heterogeneity of control CT scan acquisition is another restraint, as the timing of the second scan varied greatly

and, as such, ICH and PHE progression were not reflected uniformly. Therefore, serial sampling of inflammatory biomarkers and a more restrictive protocol for control scans might identify the most relevant time point for a predictive inflammatory panel.

In conclusion, several biomarkers showed modest correlations with the progression of sICH and the day 90 FO, advocating for extensive research on the contribution of ED POC routine biomarkers as outcome assessment tools in hemorrhagic stroke. D-dimer could be a promising maker, as lower admission values could indicate an improved day 90 FO and anticipate the development of PHE growth and ENW. The predictive utility of D-dimer on independence status is a novelty at the present moment and further research is needed to validate the current observations in the acute care setting.

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Availability of data and materials

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

Authors' contributions

EMM, AG and LPD conceptualized the study. EMM, AG, ML, CC and LPD performed the experiments. Formal analysis was conducted by EMM and SCV. Investigations were performed by EMM, AG, ML, CC and LPD. Resources were accrued by EMM, AG and LPD. The original draft preparation was carried out by EMM. Reviewing and editing of the manuscript were performed by EMM, AG, SCV, ML, CC and LPD. AG and LPD provided supervision. EMM and AG confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of the 'Iuliu Haţieganu' University of Medicine and Pharmacy (approval no. 441/24.11.2016). All patients or legal representatives provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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