Original Research

NEUROLOGY

Feasibility of a pilot study on point-of-care biomarkers in spontaneous intracerebral hemorrhage in an emergency setting

Eugenia–Maria Mureșan[1], Adela Golea[2], Sorana D. Bolboacă[3], Lăcrămioara Perju-Dumbravă[1]

1) Department of Neurosciences, Iuliu Hatieganu Univesrity of Medicine and Pharmacy, Cluj-Napoca, Romania

2) Department of Surgery, Emergency Medicine Division, Iuliu Hatieganu Univesrity of Medicine and Pharmacy, Cluj-Napoca, Romania

3) Department of Medical Education, Medical Informatics and Biostatistics, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract

Background and aims. Stroke is a worldwide leading cause of death and disability and spontaneous intracerebral hemorrhage (sICH) has significant economic and social impact, regardless of recent efforts towards outcome-bettering acute interventions. The aim of the study was to assess the feasibility of a prospective observational research regarding point-of-care (POC) biomarkers in sICH, conducted in a level one emergency department (ED).

Methods. Patients with acute (<8 hours) sICH were enrolled in this study. Patients presenting a Glasgow Coma Scale score <8, secondary causes of intracerebral hemorrhage, seizures, recent ischemic events, known thromboembolic disease, anticoagulant treatment, severe pre-stroke disability, terminal disease, scheduled neurosurgery/hemostatic treatment were excluded. Feasibility was defined as ED inclusion and follow-up rates, time-to-inclusion, and frequency of missing data. Baseline demographic, imaging and POC biochemical status of the study group were documented, including inflammatory (complete blood count, C-reactive protein), metabolic (glucose, hepatic, and renal function) and cardiovascular markers (cardiac troponin I, D-dimer).

Results. The inclusion rate was 2.16 patients/month with a final sample of 35 patients out of 239 potentially eligible patients. The median time from symptom onset to ED presentation was 128 minutes (IQR 96-239), with 21/35 patients having presented within the first 3 hours from ictus. Median times between symptoms' onset to Computer Tomography (CT) scan and ED presentation to CT scan were 170 minutes (IQR 126-317) and 25 minutes (IQR 17-62), respectively. The median time from patient's presentation to CBC result was 12 minutes (IQR 6.5-20), with 21/35 study participants having the results available within 15 minutes from ED arrival. The median cohort age was 72-years, with a 19/16 male/female ratio. Hypertension was the most frequent risk factor (77%), along with ischemic heart disease (31%) and diabetes (29%). One-third of the hypertensive patients did not undergo blood pressure lowering treatment. Median values of POC biomarkers on ED admission were within normal range.

Conclusions. It was feasible to determine point-of-care biomarkers in spontaneous intracerebral hemorrhage on admission in ED, despite the urgency of the medical condition.

Keywords: cerebral hemorrhage, point-of-care systems, emergency service, biomarkers, feasibility study

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Address for correspondence:
adela.golea@umfcluj.ro

Background and aims

Emergency medicine (EM) is considered a developing medical specialty, having its beginnings in the 1960s in the U.S.A., Canada, and the United Kingdom [1]. Later, the need for standardized emergency care led to its recognition as an independent specialty and the worldwide formation of professional societies. Romania is amongst the European countries where the EM specialty is officially recognized and celebrates 28 years of existence in 2021. Emergency physicians are providing 24/7 care in advanced and intermediate care hospitals, addressing not only life-threatening conditions, but also stable patients in need of urgent care.

Among life-threatening conditions, stroke (ischemic or hemorrhagic) has been the focus of continual advancement, particularly considering the benefit of thrombolysis for the ischemic one. Regarding hemorrhagic stroke and intracerebral hemorrhage (ICH) in particular, definitive therapies are still being sought in the hope of bettering functional outcome [2,3]. Though responsible for only 10 - 20% of total stroke cases [4], ICH is considered a devastating condition not only in terms of the patient's direct impairment but also as an economic and social burden [5]. Research efforts have been focused during the last decade on identifying biomarkers that could lead to functional outcome improvement of hemorrhagic stroke patients, along with risk stratification and prognosis.

Inflammatory status on admission was one of the contributing factors to an unfavorable outcome in sICH patients [6], as stroke is generally affecting systems such as cardiac, pulmonary, and immune system [7]. C-reactive protein (CRP), an acute phase inflammatory marker, has been associated with increased mortality [8-10], poor outcome [9] or hematoma volume [10] and growth [11]. D-dimer, a product of fibrin degradation, proved to be a risk factor for mortality [8,12,13] and early neurological deterioration (END) [14] and was associated with parenchymal hematoma volume [12, 13]. Reports on cardiac troponin elevations (with subtypes I and T considered as largely offering identical information [15] are still controversially linked with mortality in spontaneous ICH (sICH) [9,16,17], yet have been shown as an indicator of poor outcome in subarachnoid hemorrhage [15].

If considering the nature of the emergency department (ED), with personnel regularly attending to new patients in need of diagnosis and immediate care, implementing prospective research protocols is a tremendous challenge even for the most experienced physicians. In Romania, only 20 prospective research protocols have been published as having recruited patients directly from ED. The PubMed search performed on May 22nd, 2020 (search strategy "(emergency department) AND (prospective) AND (Romania)" over 10 years period) retrieved 15 valid observational studies (two hundred and ninety-one titles and abstracts have been screened). Five additional articles have been identified on previous similar searches.

The 20 studies were conducted in 9 hospitals from 5 teaching medical centers and an additional non-teaching hospital. Nine articles reported results as part of international research [18-26]. Research topics included resuscitation [21,26-30], cardiovascular and respiratory pathologies (syncope [31,32], acute heart failure [22], asthma [25], and dyspnoea [24,33], infectious diseases [19,20], with 1 regarding the paediatric population [19], pre-hospital [18,23], toxicology [34-36], trauma [37], and upper gastrointestinal bleeding [38,39].

Our ED has implemented one research protocol [29,30] and has been part of another international research group [24,25].

Bearing in mind the above, the input of point-of-care biomarkers (POC) in risk stratification and outcome prognosis of patients presenting with sICH should be assessed throughout ED-based research.

The primary objective of the present study was to evaluate the feasibility of a prospective ED research protocol by assessing inclusion and follow-up rates, alongside time-to-inclusion and frequency of missing data. The POC evaluation of the cohort's biochemical status was the secondary objective of our study.

Methods

Study design and setting

Emergency Management of Spontaneous Intracerebral Hemorrhage – Biomarkers (EsICH-bio, registered at ClinicalTrials.gov – NCT02935985) was a prospective observational study that recruited sICH patients presenting to the ED of County Emergency Hospital Cluj-Napoca, Romania over a time frame of 18 months (12.12.2016 - 11.06.2018). The medical facility is a 1,542 beds teaching hospital in the North-West of Romania, providing medical care for 3.46% of the country's population [40]. The EsICH-bio study protocol was approved by the Ethics Committee of "Iuliu Haţieganu" University of Medicine and Pharmacy of Cluj-Napoca, Romania, (441/24.11.2016) and endorsed by the Ethics Committee of the hospital. The study procedures and interventions are following the principles stated by the Declaration of Helsinki.

Patients with an imaging diagnosis of acute sICH (defined as hyperdense parenchymal hemorrhagic collection of no detectable secondary cause) were

recruited from the ED, based on a phone alert system. Informed consent was obtained from patient/proxy (or the emergency procedure (EP) form signed by an investigator and a physician not related to the study team) prior to participant's clinical assessment (including mRS - modified Rankin Scale and NIHSS - National Institute of Health Stroke Scale). A team of EM physicians (7 out of 63 attendings and residents) who received prior training (including mRS and NIHSS) completed the enrolment of the eligible patients and performed the clinical evaluation. The participation of the EM physicians was on a voluntary basis, with no financial compensations available.

Venous blood samples for the study of POC biomarkers were collected following clinical assessment, including cardiac troponin subtype I (cTnI), high-sensitive CRP (hs-CRP) and D-dimer. POC blood measurements were performed for all participants as part of the primary ED assessment and consisted of complete blood count (CBC): white blood cells (WBC), granulocytes (GRA), lymphocytes (LYM), mid-cell fractions (MID) and platelets (PLT), glucose, hepatic, and renal function. Data collection also included medical and medication history (containing cardiovascular risk factors such as age, gender, history of hypertension, diabetes mellitus, cigarette smoking, hyperlipidemia, symptomatic ischemic heart disease, and previous ischemic/ hemorrhagic stroke events), pre-treatment vital signs, medical management variables, surgical/ intensive care unit interventions, and medical complications.

The enrolment and follow-up processes are presented in table I. After ED enrolment, participants were clinically assessed on days 2 and 7 (or discharge) on neurology/ neurosurgery wards by members of the recruiting team. Telephone surveys were conducted on days 90 and 180, collecting data on functional outcome (mRS), disability (Barthel Index), quality of life (EuroQoL - Quality of Life), cognition (Telephone Interview for Cognitive Status-modified) and mood (Zung Self-Rating Depression Scale).

Feasibility criteria comprised inclusion and follow-up rates (on days 90 and 180), onset/ ED admission to inclusion timeframes (reported as symptom onset/ ED admission landmark to CT scan acquisition/ imaging diagnosis, routine blood panel (defined as time of the CBC results) and sampling of study specific biomarkers) and frequency of missing data. Secondary objective was the POC evaluation of the baseline biochemical status of the study cohort.

Additionally, a retrospective data collection was performed regarding patients with non-traumatic ICH who were not included in EsICH-bio, with the aim of documenting potentially eligible patients lost due to no phone alert of the research team.

Table I. EsICH-bio patient enrolment and follow-up.

Evaluation	Screening (ED)	Day 1 (ED)	Day 2 (neuro)	Day 7 or discharge (neuro)	Day 90 ± 7 (phone)	Day 180 ± 7 (phone)
Head CT	☑					
Clinical evaluation	☑		☑	☑		
Consent	☑					
Blood samples		☑				
NIHSS	☑		☑	☑		
mRS		☑			☑	☑
Disability (BI)					☑	☑
EQ 5D-5L					☑	
Cognition (TICS-m)					☑	
Mood (Short ZDS)					☑	

Legend: NIHSS – National Institute of Health Stroke Scale; mRS – modified Rankin Scale; BI – Barthel Index; EQ 5D-5L – EuroQoL - Quality of Life; TICS-m – Telephone Interview for Cognitive Status-modified; ZDS – Zung Self-Rating Depression Scale.

Participants

The enrollment process *included* adult (age over 18) patients diagnosed with sICH within the first 8 hours from ictus, for whom contact details had been documented and informed consent was obtained. *Exclusion criteria* consisted of secondary causes of ICH (e.g., trauma, known arterio-venous malformations, aneurysms, hemorrhagic transformation of ischemic stroke, thrombosis, thrombolysis, tumors, infections), Glasgow Coma Scale (GCS) <8 points, known thromboembolic disease, history of coagulopathy, recent ischemic events (e.g., stroke, myocardial infarction, peripheral arterial disease within the last 12 months), history of seizures, severe pre-ICH disability (mRS ≥4), current treatment with heparin, LMWH, GPIIb/IIIa antagonists or oral anticoagulants, pregnancy or breastfeeding, scheduled neurosurgical intervention in the next 24 hours, scheduled hemostatic treatment, enrolment in other studies within the last 30 days, or terminal disease.

Point-of-care devices

All POC determinations have been conducted on analyzers currently used in advanced care Romanian ED (operated by ED nurses): Swelab Alfa Plus hematology analyser, Fujifilm Dry-Chem NX500 whole blood biochemistry analyser, and PathFast™ Mitsubishi Kagaku Iatron, Inc. analyser (for cTnI, hs-CRP and D-dimer). Personnel processing blood samples was not blinded to participants' diagnosis.

For study POC biomarkers (cTnI, hs-CRP and D-dimer), a total of 5 determinations were sampled previously to the participants' study enrolment due to case management reasons and it has been decided to accept those values as relevant for future analysis.

Imaging

Initial and control CT scans were performed on a General Electric Optima 64 scanner (GE Healthcare, Boston, Massachusetts, USA). Non-enhanced head CT images were acquired in the caudo-cranial direction (from the skull base to the vertex) using the following parameters: matrix, 512x512; collimation, 20×0.625 mm; 120 kV; 250 effective mAs, using a dose reduction algorithm (ASIR) of 50%; rotation time, 1s/ rotation tube, at table speed 15 mm/ rotation, with a pitch of 0.56. The images were reconstructed as axial, coronal and sagittal 3-mm-thick images; the 3 mm width images were reconstructed with 3 mm increment. The post processing analysis was performed on a General Electric AW Server 2.0 workstation. The hemorrhage volume was measured by using manual segmentation with the inclusion of the entire area where the lesion was seen.

Two independent radiologists assessed diagnostic and control scans, blinded to patients' outcome. Consensus results were used for following analysis.

Statistical analysis

Statistical analysis was performed with Statistica (StatSoft, USA, v. 8). Descriptive statistics are reported as the number, percentage and associated 95% confidence intervals (reported in squared brackets) using an exact formula similar to that presented by Jäntschi [41] were reported for qualitative data. The value of media, first to third quartile in round brackets, and range as minimum to maximum value in curly brackets were reported for quantitative data.

Results

During the study period, 77,134 patients were treated in the ED of County Emergency Hospital Cluj-Napoca, Romania. Three hundred and seventy-five subjects had suggestive clinical aspects and an imaging ICH diagnosis (0.50% [0.45% to 0.54%]). Sixty-four percent of imagistic ICH subjects suffered a sICH [59% to 69%].

Thirty-nine subjects were included in the study (16% [12% to 22%]) and thirty-five remained under observation (90% [77% to 97%]); one withdrew and three underwent neurosurgery within 24 hours from inclusion (see Figure 1). The inclusion rate was 2.16 patients/ month. No patient refused the ED enrollment, though the EP was used in 12 cases (34.3%) and in another 21 (60%) the legal representative's consent was initially obtained in the ED. On day 90, 1/35 participants was not available for the telephone follow-up, compared to 4/35 participants on day 180.

ED admission and inclusion times are presented in figure 2. The median time from symptom onset to ED presentation was 128 minutes (IQR 96 to 239), with 21/35 patients having presented within the first 3 hours from ictus. All participants had a diagnostic CT scan performed in our ED, with a median time of 170 minutes (IQR 126 to 317) between symptom onset and CT scan acquisition. ICH imaging diagnosis was available in a median time of 25 minutes (IQR 17 to 62) from presentation. More than half of the participants (18/35) underwent the imaging investigation in the first 30 minutes from their arrival, with 9 of them within the first 20 minutes. Regarding symptom onset to POC sampling time, the median values for routine and study specific biomarkers were 150 min (IQR 117 to 259) and 237 minutes (IQR 193 to 384), respectively. The median times from patients' ED presentation to CBC results and study sampling were 12 minutes (IQR 6.5 to 20) and 100 minutes (IQR 74 to 139), respectively. 21/35 participants had routine POC panel results available within 15 minutes from ED arrival.

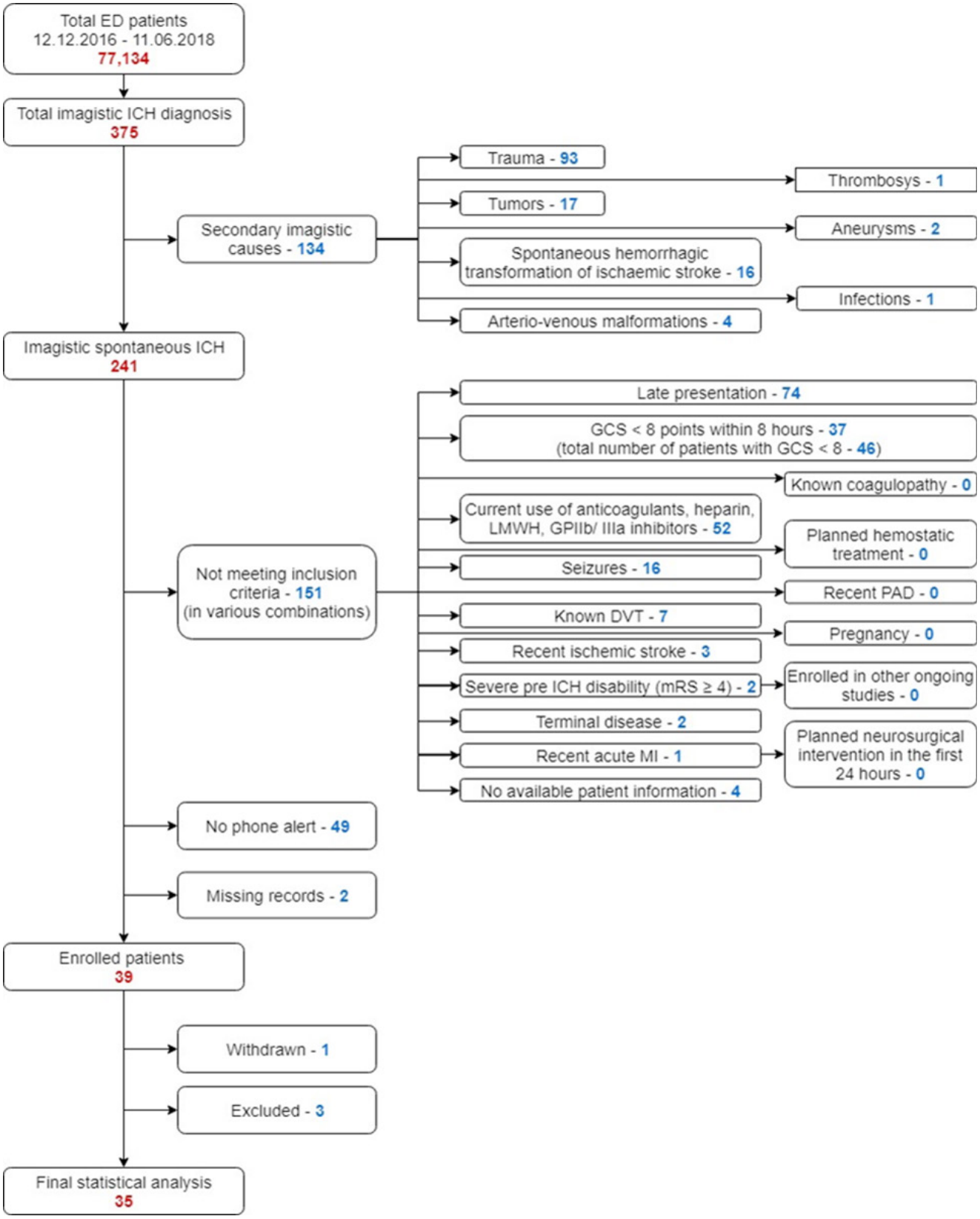

Figure 1. EsICH-bio STROBE diagram.

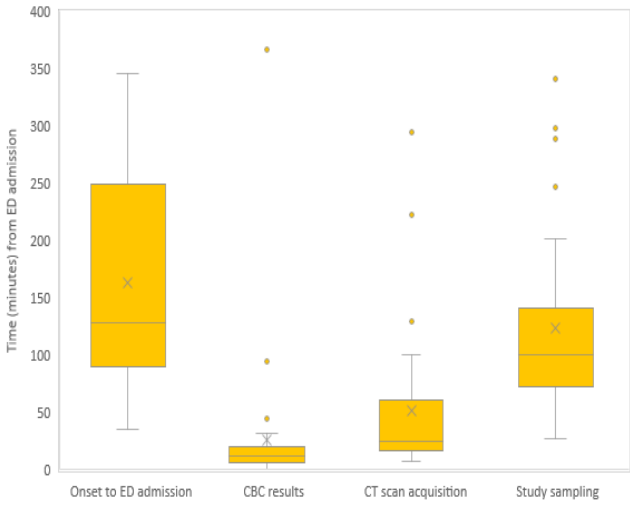

Figure 2. Spontaneous intracerebral hemorrhage admission and inclusion times within the emergency department (ED) (the × corresponds to the mean value, the horizontal line in the box to the value of median, the box to the 25th and respectively 75th percentile and the whiskers to the maximum and minimum values).

During the ED enrollment, no missing data were recorded on items incorporated into the objectives of the study (neurological assessment, study biomarkers and routine blood panel), yet interest is not constantly paid to certain cardiovascular risk factors such as alcohol consumption and smoking (missing data 22.8% and 11.4%, respectively). Moreover, hematoma description is currently unstandardized, with items such as volume or 3-dimensions characterization being completely overlooked by the on-call radiologist. Fever was not documented on any participant, yet a high percentage of missing data on ED enrollment was observed on this item (37%).

The demographics and past medical history of the investigated cohort are illustrated in table II. The participants had a mean age of 69.9 years (10.4 years standard deviation), with 6/35 participants (17.1%) older than 80. Most frequently documented risk factors were hypertension, ischemic heart disease and diabetes mellitus. One-third of the hypertensive patients did not undergo any blood pressure (BP) lowering treatment.

Neurological status on admission was documented as GCS and NIHSS scores. The GCS values ranged from 8 to 15, with 4 participants scoring a 10 or lower GCS. Upon enrolment, 4 participants had SBP values higher than 200 mmHg. During the first 24 hours from ictus, 30/35 participants (86%) required 3 or more BP lowering agents, with one patient requiring 10 pharmacological forms. The most frequently used BP lowering medication were enalapril, furosemide, and metoprolol, whilst calcium channel blockers were only used in 3 patients. No participant had a pre-stroke dependency greater than 2 on the mRS; 5 out of the 35 participants had a pre-stroke mRS of 1. The clinical characteristics of the participants on ED admission are presented in table III.

Table II. Demographic data of study participants.

	Total cohort (n=35)
Demographics	
Age, years, median (IQR)	72 (61.5-78)
>70 years, n (%)	18 (51.4)
Male, n (%)	19 (54.3)
Ethnic origin	
Romanian, n (%)	27 (77.1)
Hungarian, n (%)	8 (22.9)
Medical history and general risk factors	
Previous ischemic stroke or TIA, n (%)	8 (22.9)
Previous IHD, n (%)	11 (31.4)
Hypertension, n (%)	27 (77.1)
Diabetes mellitus, n (%)	10 (28.6)
Smoking status	
Former, n (%)	13 (37.1)
Active, n (%)	2 (5.7)
Never, n (%)	16 (45.7)
Alcohol intake	
Past, n (%)	2 (5.7)
Occasionally, n (%)	8 (22.9)
Frequent/daily, n (%)	10 (28.6)
Medication history	
Antiplatelet agent, n (%)	9 (25.7)
Antihypertensive	
Treatment = yes, n (%)	20 (57.1)
>2 drugs, n (%)	10 (28.6)
Lipid lowering agent, n (%)	10 (28.6)

Legend: TIA: transient ischemic attack; IHD: ischemic heart disease.

Table III. Clinical characteristics of study participants on ED (study) admission.

	Total cohort (n=35)
SBP (mmHg), median (IQR)	167 (157-184)
>170 mmHg, n (%)	17 (48.6)
DBP (mmHg), median (IQR)	89 (79-101)
Heart rhythm	
Heart rate (bpm)	76 (69-87.5)
Atrial fibrillation, n (%)	1 (2.9)
NIHSS score, median (IQR)	11 (6.5-19)
≥ 15, n (%)	14 (40.0)
GCS, median (IQR)	15 (12.5-15)
Pre-stroke dependence (mRS), median (IQR)	0 (0-0)
Temperature (°C), median (IQR)	36.4 (36.2-36.6)

Legend: SBP: systolic blood pressure; DBP: diastolic blood pressure; bpm: beats per minute; NIHSS: National Institute of Health Stroke Scale; GCS: Glasgow Coma Scale; mRS: modified Rankin Scale.

Paraclinical characteristics of the study cohort (Table IV) comprises CT scan aspects, and POC biomarkers values, both routine panel and study biomarkers. Hematoma location was most frequently supra-tentorial deep, with a median volume of 12.5cm^3 (IQR 7.26 to 25.52). Perihematoma edema (PHE) was present in all participants, with a median value of 9.00 mm (IQR 6.5 to 11.75).

Table IV. Baseline paraclinical characteristics of study participants on ED (study) admission.

	Total cohort (n=35)
CT scan - Hematoma characteristics	
Hematoma location	
Supra-tentorial Lobar, n (%)	6 (17.1)
Supra-tentorial Deep, n (%)	27 (77.1)
Infra-tentorial, n (%)	1 (2.9)
Combination of above locations, n (%)	1 (2.9)
Hematoma volume (cm^3)	
< 30, n (%)	28 (80.0)
30 – 60, n (%)	4 (11.4)
> 60, n (%)	3 (8.6)
IVH, n (%)	9 (25.7)
Midline shift > 10 mm, n (%)	13 (37.1)
Mass effect, n (%)	29 (82.9)
Periventricular leucoaraiosis, n (%)	18 (51.4)
Lacunarism, n (%)	24 (68.6)
Cerebral atrophy, n (%)	20 (57.1)
Compression of contralateral ventricle, n (%)	28 (80)
Enlarged contralateral ventricle, n (%)	9 (25.7)
POC routine panel	
WBC (×10^9/L), median (IQR)	9.30 (6.7-11.3)
GRA (×10^9/L), median (IQR)	5.9 (4.1-8.3)
LYM (×10^9/L), median (IQR)	1.9 (1.4-2.4)
MID (×10^9/L), median (IQR)	0.8 (0.6-1.3)
PLT (×10^9/L), median (IQR)	162 (146-211)
Hb (mg/dL), median (IQR)	13.60 (12.7-14.85)
Blood glucose (mg/dL), median (IQR)	146 (122-168)
Renal function	
Creatinine (µmol/L), median (IQR)	0.70 (0.60-0.90)
BUN (mg/dL), median (IQR)	17.5 (13.8-21.4)
Hepatic function	
ASAT (U/L), median (IQR)	26.00 (21.75-32.25)
ALAT (U/L), median (IQR)	23.00 (14.00-31.00)
POC study biomarkers	
hs-CRP (mg/L) median (IQR)	2.49 (0.679-4.17)
cTnI (ng/mL) median (IQR)	0.003 (0.001-0.006)
D-dimer (µg/ml FEU) median (IQR)	0.91 (0.665-2.82)

Legend: PHE: perihematoma edema; IVH: intraventricular hemorrhage; WBC: white blood cells; GRA: granulocytes; LYM: lymphocytes; MID: mid-cell fractions; PLT: platelets; Hb: hemoglobin; BUN: blood urea nitrogen; ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase.

Discussion

Our results support the feasibility of ED-based enrolment in prospective research, with inclusion and follow-up rates resembling previously published ones [3,42]. Though sICH patients are diligently and promptly managed once admitted to ED, late and irregular presentations in every third patient greatly limits enrolment opportunities. Nevertheless, ED POC testing provides a generous array of information on biological parameters, which theoretically could contribute to risk stratification and outcome improvement.

Thirty-nine patients were included over a period of 18 months, reaching similar inclusion and follow-up rates as other sICH reports [42]. If factoring in the 49 patients lost due to lack of study team activation, the inclusion rate could have doubled. Considering that none of the eligible patients refused ED enrollment and follow-up rates remained solid, we could speculate that ED is a favorable enrollment site for patients suffering of acute neurological conditions. Withal, certain aspects require immediate attention, if inclusion rate is to properly reflect the unique opportunity offered by an ED-based research enrollment.

The high proportion of no phone alert is of great concern. Apart from shortage of experienced EM researchers, a level one Romanian ED addresses all acute conditions, thus the workload is frequently considerable and prevents the on-call EM physician from dedicating time to patient screening and enrolment. As observed (figure 2), standard ED management for ICH patients is expeditious, yet the completion of the enrollment process and study sampling is prolonged (3.95 to 4.03 hours from stroke onset), even though still within previously published reports, ranging from 2 to 11.9 hours [10,43,44]. In contrast, items such as time from stroke onset to CT scan are lower in EsICH-bio cohort (3.48h vs. 6.9h) [45]. Subsequently, further efforts (e.g., training, academic and/or professional recognition of both physicians and nurses) should be made as to increase the effective participation of EM professionals in prospective research.

The peculiarities of the Romanian emergency system and general medical education of the population are reflected by figure 2. Late presentations (30.7% of the potentially eligible cohort) probably mirror the population's lack of education on stroke recognition. Furthermore, EMS are regionally based, with all patients transferred to the nearest ED, thus generating an additional delay due to the second ambulance transfer to a stroke centre. As of May 2018, a national stroke protocol [46] enables a pre-hospital and ED fast-track for each dispatch recognized stroke suspicion, aiming to shorten thrombolysis time.

Failure to document all required data when conducting an ED-based enrolment could be an expected side-effect of such a busy working environment. The current analysis emphasizes ED personnel's ability to prioritize the collection of indispensable study data, whilst

overlooking items not customary used in their daily practice. Additionally, lack of standardized imaging interpretation potentially generates communication difficulties and even if of little benefit to research purposes, a uniformed diagnosis format would ensure better transparency in interdisciplinary collaboration. Electronic medical records could reduce frequency of missing data and empower evidence-based research, yet future studies are needed to quantify the overall impact of digitalization.

Educational efforts targeting EMS, ED physicians and the general population could shorten arrival times, enlarge enrollment ratio, and reduce missing data and interpretation errors, hence increasing prospects of a better outcome and contributing to a pertinent analysis of the Romanian sICH population. Networking and multi centre cooperation should be the focus of future initiatives, as access to a larger pool of critical patients would contribute to establishing pathways and risk scores.

As part of the secondary endpoint of the present study, demographical and POC biochemical data on ED enrolment were reported. The cohort's mean age was higher than previous data [3], with the preponderance of advanced age participants. Smoking and alcohol drinking are risk factors linked with the development of acute stroke [10], short-term mortality [45] and increase of hematoma volume [47]. Though of undisputed relevance for sICH long-term management, these risk factors are frequently overlooked in our ED, as little can be influenced during the hyperacute management, with alcohol drinking being more frequent than smoking in our cohort. The prevalence of ischemic heart disease, stroke (including transient ischemic attacks) in the EsICH-bio cohort was greater than previous reports [3]. Diabetes mellitus, a factor of resistant hypertension [16], is known to be associated with in-hospital mortality of hemorrhagic stroke [48] and was recorded in almost one third of our cohort, alongside median baseline glycemic values similar to a previous report [49]. Admission hyperglycemia is an independent risk factor for early mortality [13,50], especially in non-diabetic patients [50].

Baseline ED vital signs included lower median values for both systolic and diastolic BP and HR [3,47,51]. Lack of compliance to BP lowering treatment was numerous among the cohort, despite being a known modifiable risk factor and predictor of mortality and outcome. Admission HR over 85 bpm has been reported as being associated with increased mortality and worse mRS [16].

Routinely ED accessible POC biomarkers generate a comprehensive biological panel for any critical patient and we believe that sICH patients would benefit greatly if these data would be used for risk stratification and outcome prognostication. Inflammation seems to play a considerable part in sICH progression [7]. High WBC and neutrophils (NEU) admission values have been linked with admission hematoma volume and intraventricular hemorrhage (IVH), END, death or major disability [10,11,44,50,52-54]. According to Kim et al. [45], a leukocytes value above 9,400/mm^3 poses a 2.4-fold increase risk of short-term mortality. Admission anemia has also been associated with larger ICH volumes [52], whilst admission lymphopenia is correlated with higher stroke severity, larger baseline hematoma volume and IVH, along with infection risk and 3-months mortality [7]. Nevertheless, our cohort's mean values are within accepted normal laboratory limits and not reaching published thresholds for prognostication utility. A similar conclusion can be extended to hs-CRP [10] and cardiovascular POC biomarkers, D-dimer [13] and cTnI [16].

However, certain new observations must be mentioned. Present results offer granulocytes as a surrogate for NEU and the question of POC granulocytes time-related augmentation arises, if considering the one reported on NEU [53]. Monocytes are substituted by MID, which include eosinophils among others, whose contribution to sICH evolution is still uncharted [55]. Therefore, larger cohorts are required for validating the impact of POC testing in acute sICH.

Our study has some limitations. Firstly, and probably most important, is the single center location of this study. As very little data is available on the Romanian ED stroke population, multicenter research is needed to establish a detailed epidemiological profile, aiming to identify risk factors and probable complications. Secondly, the lack of resources for establishing a dedicated ED research team affected the inclusion ratio. As so, future prospective research should address this issue, if to take advantage of the large pool of eligible participants. Due to the particular setting of the hosting medical facility (ED, neurology and neurosurgery departments functioning in different locations), the degree of planned neurosurgical intervention could not be documented accurately, as 3 initially eligible patients worsened by the time they reached the neurosurgical ward and required immediate intervention (and were subsequently excluded from study). Lastly, 2 of the 241 potentially eligible patients' charts could not be accessed for the retrospective analysis due to administrative reasons.

Conclusions

Our study indicates that a prospective observational trial in sICH patients is feasible in the ED, with possible significant gains for improving urgent care of the critical pathologies currently stabilized within these departments. Reported inclusion and follow-up rates should encourage future ED-based prospective studies, in spite of prolonged arrival times leading to frequent late presentations. Current standard practices of on-paper medical records contribute to significant missing data.

Emergency department point-of-care devices can be easily accessible tools in the hyperacute management of sICH, a condition still seeking impactful strategies to reduce its economic and societal impact.

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