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# Neutrophil-to-leukocyte ratio and admission glycemia as predictors of short-term death in very old elderlies with lobar intracerebral hemorrhage

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## Abstract:

**BACKGROUND:** The incidence of spontaneous intracerebral hemorrhage (SICH) is highest in very old elderlies ( $\geq 75$  years). The increasing use of antithrombotic drugs is shifting the epidemiology of SICH towards predominance of lobar subtype, suggesting an incremented propensity of bleeding associated with underlying cerebral amyloid angiopathy. With population aging and antithrombotic use, a parallel raise of proportion of lobar SICH is occurring. Improvement of prognostication in this specific age group and SICH type is needed. Routine blood biomarkers can contribute to prediction of short-term mortality after SICH.

**OBJECTIVE:** Our aim was to investigate the contribution of routine blood biomarkers for short-term mortality (30-days) in elderly patients with lobar SICH.

**METHODS:** Retrospective analysis of consecutive 130 patients with  $\geq 75$  years and lobar SICH. The outcome was 30-day mortality. Logistic regression analysis was used to investigate whether admission routine biomarkers can be used as predictors.

**RESULTS:** The case fatality was 40.8%. Admission glycaemia level, neutrophil to lymphocyte ratio and mean platelet volume were significantly different between groups ( $p = 0.001$ ,  $p = 0.024$ ,  $p = 0.038$ , respectively). There was no significant difference in all other routine biomarkers. On multivariate analysis, admission higher mean BG level (odds ratio [OR]: 1.010, 95% confidence interval [CI]: 1.001-1.019,  $p = 0.026$ ) and neutrophil to lymphocyte ratio (OR: 1.070, 95%CI: 1.008-1.136,  $p = 0.027$ ) emerged as predictors.

**CONCLUSION:** In very old patients with lobar SICH, higher BG level and neutrophil to lymphocyte ratio are associated with increased risk of short-term death.

## Keywords:

Blood biomarkers, elderly patients, short-term death, spontaneous intracerebral hemorrhage

## Introduction

Stroke is a leading cause of mortality and permanent disability in developed societies.<sup>[1,2]</sup> The risk of spontaneous intracerebral hemorrhage (SICH), the severest of all stroke types, increases with advanced age, with the highest incidence

occurring in persons over 75 years of age.<sup>[3-5]</sup> In the very old, the use of antithrombotic drugs for secondary prevention has been associated with a higher risk of SICH, particularly of lobar subtype, suggesting an incremented propensity of bleeding associated with underlying asymptomatic cerebral amyloid angiopathy (CAA).<sup>[5,6]</sup> Indeed, in the absence of macrovascular causes, CAA emerges as the main cause SICH in elderly patients.<sup>[5,7]</sup> With progressive aging

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of the population and expansion of antithrombotic use for ischemic stroke events (anticoagulants or antiplatelets), a parallel raise of the number of lobar SICH cases in the very old is occurring. For these reasons, improvement of prognostication in this specific age group and type of SICH is certainly needed. Routine blood biomarkers can contribute to the improvement of prognostication in stroke.<sup>[8-10]</sup> The behavior of these biomarkers reflects the complex systemic response to SICH, from inflammation, activation of the sympathetic nerve system to dysregulation of the immune system.<sup>[11]</sup> For instance, elevated red blood cell distribution width (RDW) in intracerebral hemorrhage (ICH), mainly of lobar location, was demonstrated to be associated with an increased risk of mortality.<sup>[12]</sup> Similarly, admission high blood glucose (BG) level was associated with early and long-term mortality after ICH.<sup>[13]</sup> These studies, however, involved a nonselected SICH population with mixed aged and etiology populations. Despite the growing number of elderly patients with stroke, the number of studies addressing the role of routine blood biomarkers in patients with advanced age remains extremely low.<sup>[14]</sup> Therefore, we investigated the contribution of several routine blood biomarkers for short-term (30 days) vital prognosis in elderly patients ( $\geq 75$  years) with presumable CAA-related lobar SICH.

## Methods

A retrospective evaluation of consecutive case series of spontaneous lobar SICH from January 2009 to December 2018 was carried out. The institutional database from the only stroke unit serving the region of Algarve, Southern Portugal, was the main source of data. Only patients with spontaneous lobar SICH, defined as hematoma originating at the cortex and cortical-subcortical junction, with  $\geq 75$  years, having the main residence in the Algarve were included. Exclusion criteria include nonlobar location, macrovascular causes of SICH (cerebral vein thrombosis, cavernoma, tumor, malformation, and hemorrhagic transformation), and neurosurgical treatments. Brain computed tomography, angiography, and/or magnetic resonance were used to investigate the alternative causes of bleeding. The following variables were extracted: age, gender, social insertion income, number of previous hospitalizations, admission modified Rankin Scale (mRS), Glasgow Coma Scale, BG level, hypertension, atrial fibrillation, dementia, previous medications, radiological findings (volume and presence of intraventricular dissection), severity assessed by the ICH score, selected intrahospital complications, and admission serum biomarkers (RDW, neutrophils, lymphocytes, platelets, mean platelet volume [MPV], platelet distribution width, international normalized ratio, troponin I, D-dimer, sodium, potassium, blood urea

nitrogen, creatinine, and C-reactive protein [CRP]). The outcome was vital status at 30 days after stroke onset. To reduce the risk of biased results due to missing data,<sup>[15]</sup> variables with more than 20% of missing data were excluded. The 30-day mortality (short-term death) was the outcome of this study.

This study was approved by the Institutional Ethics Committee. Informed consent was waived due to its retrospective nature.

Statistical analysis of the data was performed using the specific software (SPSS for Windows, SPSS Inc., Chicago, Illinois, USA, version. 28). Bivariate and multivariate analyses were performed to evaluate the correlation of selected variables with 30-day death using Pearson's Chi-squared or Fisher's exact tests for categorical variables and the Student's *t*-test or Mann-Whitney *U*-test for continuous variables, as appropriate. Logistic regression with the inclusion of statistically significant variables ( $P < 0.05$ ) was used to verify the independent association between specific biomarkers and the outcome of patients with lobar SICH.

## Results

A total of 130 cases of lobar ICH were included in the study. A pilot study was carried out to verify whether the variables of interest were consistently obtained after hospital arrival. The following variables were eliminated ( $\geq 20\%$  of missing data): B-type natriuretic protein, fibrinogen, albumin, hemoglobin A2, glycated hemoglobin, and serum lipids.

Table 1 presents the general characterization and comparison of sociodemographic, clinicoradiological, and admission routine biomarkers between deceased and survivors of spontaneous lobar SICH.

Most cases occurred in the left hemisphere ( $n = 73, 56\%$ ). The frequency of anatomic distribution of predominant lobar affection was as follows: frontal ( $n = 48, 36.9\%$ ), parietal ( $n = 36, 27.7\%$ ), temporal ( $n = 29, 22.3\%$ ), and occipital ( $n = 6, 4.6\%$ ). Multiple simultaneous hematomas in more than three lobar locations occurred in 11 (8.4%) patients. Overall, the mean volume was 29.1 ml (range: 5.0–71.2 ml).

The short-term case fatality was 40.8%. There were no significant differences on sociodemographic (age and gender), prior to ICH functional neurological impairment (mRS and previous hospitalizations), and risk factors, including the use of anticoagulants. The group of deceased patients had a higher proportion ( $P < 0.05$ ) of intraventricular hemorrhage, hematoma volume, ICH score  $>3$ , and infectious complications. None

**Table 1: General characterization and comparison of sociodemographic, clinicoradiological, and admission routine biomarkers between deceased and survivors of spontaneous lobar intracerebral hemorrhage**

Characteristics	Total population (n=130)	Survivors (n=77)	Deceased (n=53)	P
Demographic characteristics				
Male, n (%)	67 (51.5)	37 (55.2)	30 (44.8)	0.338
Age (year), mean±SD	82.1±4.8	82±4.8	82.3±4.7	0.679
Previous hospitalizations ≤2, n (%)	114 (87.7)	69 (60.5)	45 (39.5)	0.422
mRS pre-ICH >2, n (%)	18 (13.8)*	11 (61.1)	7 (38.9)	0.849
ICH risk factors, n (%)				
Dyslipidemia	76 (58.5)	42 (55.3)	34 (44.7)	0.275
Hypertension	118 (90.8)	68 (57.6)	50 (42.4)	0.358
Diabetes mellitus	33 (25.4)	18 (54.5)	15 (45.5)	0.526
Atrial fibrillation	24 (18.5)	14 (58.3)	10 (41.7)	0.921
Hypocoagulation, n (%)				
Vitamin K antagonists	24 (18.5)	12 (50)	12 (50)	0.316
Novel oral anticoagulants	2 (1.5)	2 (100)	0	0.072
Dementia	38 (29.2)	25 (65.8)	13 (34.2)	0.328
Radiological findings, n (%)				
≥30 cc of volume	63 (48.5)	18 (28.6)	45 (71.4)	<b>&lt;0.001</b>
Intraventricular dissection	54 (41.5)	17 (31.5)	37 (68.5)	<b>&lt;0.001</b>
ICH score >3, n (%)	35 (26.9)*	2 (5.7)	33 (94.3)	<b>&lt;0.001</b>
GCS, mean±SD	12±3.2	13.7±1.3	9.5±3.4	<b>0.000</b>
Treated in the stroke unit, n (%)	80 (62.5)	56 (70)	24 (30)	<b>0.003</b>
Intrahospital complications, n (%)				
Hyperactive delirium, yes	44 (33.8)	28 (63.6)	16 (36.4)	0.465
Respiratory tract infection, yes	43 (33.1)	19 (44.2)	24 (55.8)	<b>0.014</b>
Urinary tract infection, yes	34 (26.2)	25 (73.5)	9 (26.5)	<b>0.048</b>
Blood biomarkers				
BG, mean±SD	153.7±64	137±51.9	177±72	<b>0.001</b>
RDW, mean±SD	14.3±1.5	14.1±1.1	14.5±1.8	0.216
Neutrophils, mean±SD	75±14.1	74.1±9.7	76.3±18.7	0.431
Lymphocytes, mean±SD	17.2±12.9	17.1±7.8	17.3±18	0.937
Neutrophil/lymphocyte ratio, mean±SD	7.8±9.2	6.1±5.5	10.4±12.5	<b>0.024</b>
Platelets, mean±SD	208.7±77.9	209.5±68.6	207.7±90.4	0.898
MPV, mean±SD	10.4±1.4	10.2±1.3	10.9±1.3	<b>0.038</b>
PDW, mean±SD	14.8±2.8	14.5±2.6	15.3±3	0.082
Sodium, mean±SD	138±3.9	138±3.8	137.9±4	0.891
Potassium, mean±SD	4.2±0.6	4.2±0.5	4.1±0.7	0.250
BUN, mean±SD	25±15.3	23.5±12.7	27±18.2	0.212
Creatinine, mean±SD	1.1±0.9	1.1±1	1.2±0.8	0.576
Troponin I, mean±SD	20.9±92	110.5±219.2	77.5±105.2	0.864
<0.001, n (%)	10 (7.7)	7 (70)	3 (30)	0.721
CRP, mean±SD	21.9±48.3	27.9±55.8	39.4±58.1	0.344
Admission ≤6 h after stroke onset, n (%)	55 (43.7)	13 (23.6)	42 (76.4)	0.737

\*One missing value. Boldfaced values - variables with  $P < 0.05$ . BUN: Blood urea nitrogen, CRP: C-reactive protein, GCS: Glasgow Coma Scale, ICH: Intracerebral hemorrhage, MPV: Mean platelet volume, mRS: modified Rankin Scale, PDW: Platelet distribution width, RDW: Red blood cell distribution width, SD: Standard deviation, BG: Blood glucose, IQR: Interquartile range (Q3–Q1)

of the patients received palliative care. Survivors were more often treated at the stroke unit. Regarding admission biomarkers, the deceased patient group had high admission BG level (mean: 177 mg/dl vs. 137 mg/dl,  $P = 0.001$ ), neutrophil-to-lymphocyte ratio (mean: 10.4 vs. 6.1,  $P = 0.024$ ), and MPV (mean: 10.9 vs. 10.2,  $P = 0.038$ ). There was no significant difference in all other biomarkers, including the RDW and CRP [Table 1]. On multivariate analysis [Table 2], in addition to the ICH score and respiratory tract infection,

admission higher BG level with an odds ratio (OR) = 1.010, 95% confidence interval (CI) = 1.001–1.019,  $P = 0.026$  and neutrophil-to-lymphocyte ratio with OR = 1.070, 95% CI = 1.008–1.136, and  $P = 0.027$  emerged as predictors of short-term death in elderly patients with lobar ICH.

## Discussion

The study of prognostic biomarkers in the very old

**Table 2: Multivariate analysis of predictors of short-term death in elderlies with spontaneous intracerebral hemorrhage**

Characteristics	P	OR	95% CI	
			Lower	Upper
Treated in the stroke unit	0.086	3.357	0.843	13.362
ICH score	<b>&lt;0.001</b>	38.479	7.706	192.132
Admission blood biomarkers				
BG	<b>0.026</b>	1.010	1.001	1.019
Neutrophil/lymphocyte ratio	<b>0.027</b>	1.070	1.008	1.136
MPV (fL)	0.900	1.029	0.656	1.614
Intrahospital complications				
Respiratory tract infection	<b>0.010</b>	4.716	1.443	15.384
Urinary tract infection	0.120	3.164	0.741	13.502

Boldfaced values - variables with  $P < 0.05$ . ICH: Intracerebral hemorrhage, MPV: Mean platelet volume, OR: Odds ratio, CI: Confidence interval, BG: Blood glucose

with SICH is among the most neglected areas of research.<sup>[16]</sup> The epidemiological shift with an increasing proportion of lobar SICH and the associated very high short-term mortality further emphasizes the need of early identification of patients at risk. Indeed, more than two out of five elderlies with lobar SICH died within the 1<sup>st</sup> month. Improvement of detection of at-risk patients is, therefore, fundamental to stratify the intensity of acute care, which has been shown to improve short-term functional and vital prognosis.<sup>[17]</sup> Our study demonstrated, in a community representative cohort of very old lobar SICH patients, that admission BG level and neutrophil-to-lymphocyte ratio can be useful biomarkers to help in the prediction of short-term death. These findings are consistent with what has been reported in the literature on the general SICH population. Higher admission BG levels were associated with early and long-term mortality after SICH.<sup>[13]</sup> Likewise, higher admission neutrophil-to-lymphocyte ratio was also associated with poor prognosis in patients with SICH.<sup>[18]</sup> There is evidence showing that higher BG may increase brain edema, inflammatory reaction, free radical injury, and excitotoxic or apoptotic cell death after stroke.<sup>[13]</sup> On the other hand, BG also reflects the magnitude of sympathetic or stress response, with patients experiencing intense responses having higher BG.<sup>[13]</sup> The neutrophil-to-lymphocyte ratio is used as an inflammatory biomarker.<sup>[18]</sup> Reactive elevation of neutrophils is linked with a secondary brain injury, and a decrease in lymphocytes is associated with exhausted immune host defense.<sup>[18]</sup> After SICH onset, the acute raise of toxic neutrophils increases the release of neurotoxicity factors, further damaging the blood-brain barrier after SICH.<sup>[18]</sup>

Our study reinforces the utility of routine and universally available blood biomarkers to aid vital short-term prognosis in elderly patients with lobar SICH. There are, however, some limitations that are worthwhile discussing. Unfortunately, the overall prior to SICH

health status was not considered in our study. This may impact the study results as very old patients do have specific physiological characteristics and present more often with several comorbidities that can determine the role of different blood biomarkers.<sup>[19]</sup> Indeed, the Charlson Comorbidity Index and frailty were shown to be strongly correlated with acute stroke outcomes in the elderly.<sup>[20-22]</sup> Nevertheless, as in previous similar studies, prior functional neurological status (mRS) or conditions such as dementia and diabetes mellitus did not emerge as predictors of short-term death.<sup>[23-25]</sup> We also did not address specifically if prior to stroke primary health care interventions, for instance, regular exercise, tobacco use, blood pressure control, or even the use of statins,<sup>[26]</sup> contributed to the outcome. APOE genotyping was not performed and could have improved the diagnosis confidence of CAA as the underlying cause of lobar SICH.<sup>[27,28]</sup> The small sample size most probably reduced the statistical power to demonstrate the role of factors such as the MPV, troponin I, or CRP.

## Conclusion

Although necessary in some circumstances, studies based on the comparison of outcomes or biomarkers between very old and young stroke patients, or with all general stroke population, may hold back clinicians and researchers to go further in terms of understanding the specificities of stroke in the very old. If consistently validated in more studies, biomarkers such as BG and neutrophil-to-lymphocyte ratio can certainly contribute to better prognostication and identification of elderly patients with a higher risk of worse outcomes after SICH.

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## Conflicts of interest

There are no conflicts of interest.

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