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RESEARCH

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The role of blood protein biomarkers in acute ischemic stroke prognosis

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Abstract

Background Stroke is one of the most frequent causes of mortality and disability, blood protein biomarkers are used to determine patients at high risk for a severe illness and to estimate the outcome. This study aimed to detect the relation between serum levels of C-reactive protein, matrix metalloproteinase 9, S100 calcium-binding protein B, brain natriuretic peptide, D-dimer and stroke severity and outcome in acute ischemic stroke patients.

Results One hundred eighty-six patients with acute ischemic stroke participated and were subjected to complete general, neurological examination, assessment of stroke severity clinically and radiologically using National Institute of Health Stroke Scale (NIHSS), and Alberta Stroke Program Early CT (ASPECT) score and assessment of functional outcome using (modified Rankin Scale). C-reactive protein, matrix metalloproteinase 9, S100 calcium-binding protein B, brain natriuretic peptide and D-dimer were assessed. Higher C-reactive protein was found in patients with ASPECT score ≤ 7 and in patients with cerebral edema, seizures and was positively correlated with stroke severity according to NIHSS and modified Rankin Scale. C-reactive protein serum level at onset was negatively correlated with NIHSS at onset and is a significant predictor for mortality. D-dimer was negatively correlated with NIHSS. S100 calcium-binding protein B was significantly elevated in patients who developed hemorrhagic transformation.

Conclusions Serum C-reactive protein level can be used as a predictor for mortality and higher S100 calcium-binding protein B was detected in patients with hemorrhagic transformation.

Keywords Biomarkers, C-reactive protein, Matrix metalloproteinase 9, S100 calcium-binding protein B, Brain natriuretic peptide, d-Dimer, Ischemic stroke

Background

Stroke is a common global cause of disability and mortality [1]. It has a diverse etiology that include unmodifiable risk factors, such as age, genetics, and sex in addition to risk factors that can be modified as, hypertension, Diabetes Mellitus, dyslipidemia, smoking, and sedentary lifestyle [2].

Stroke prognosis can be influenced by several prognostic factors such as age, stroke severity, comorbid conditions, and associated complications, in addition to the influence of interventions for instance, thrombolysis, stroke unit care, and rehabilitation [3].

Biomarkers could help in predicting prognosis in acute ischemic stroke including patient response to treatment, occurrence of complications, and long-term functional outcomes [4].

Some of these biomarkers are indicators of either brain tissue damage or the inflammatory process accompanying the ischemic stroke [5]. S100 calcium-binding protein B (S-100B), matrix metalloproteinase (MMP) and brain natriuretic peptide (BNP) are markers of ischemic brain injury, whereas C-reactive protein (CRP) is one of the markers implicated in the inflammatory and immune responses accompanying ischemic stroke. In addition, molecules involved in acute thrombosis such

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as fibrinogen and D-dimer have been linked to ischemic stroke [6].

We aimed to find a possible correlation—in a sample of Egyptian acute ischemic stroke patients—between serum biomarkers, and stroke severity, complications, and short-term outcome.

Methods

A total of 186 patients with acute ischemic stroke were included in this cross-sectional observational study, which was conducted on acute ischemic stroke patients at the Neurology Department's Stroke Unit between May 2021 and April 2022. The follow-up period was extended to July 2022. Informed written consent to participate in the study was obtained from participants.

Inclusion criteria: Both sexes with age above 18 years, diagnosed as acute ischemic stroke clinically and confirmed by computed tomography (CT) brain within 3 days of onset of stroke symptoms.

Exclusion criteria: Transient ischemic attacks, patients with intracerebral, subarachnoid hemorrhage or venous infarctions, patients with other neurological disorders mimicking stroke such as hypoglycemic coma, diabetic ketoacidosis, Todd's paralysis, patients with hematological, inflammatory, auto-immune diseases or cancer that had high levels of serum inflammatory markers.

Patients underwent the following:

Meticulous clinical assessment: detailed history taking, general and neurological examination. Assessment of initial stroke severity was done using National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) on admission and by the Alberta Stroke Program Early CT Score (ASPECT score). According to NIHSS patients were divided into minor < 5, moderate 5–15, moderate to severe 16–20 and severe stroke 21–42 [7].

Assessment of functional outcome was done using modified Rankin Scale (mRS) on discharge and after 3 months. We grouped patients according to mRS into 3 groups: good outcome (mRS 0–3), poor outcome (mRS 4–5) and mortality (mRS 6).

Laboratory workup included complete blood picture and erythrocyte sedimentation rate, blood glucose level, glycated hemoglobin level, liver function tests, renal function tests, lipid profile, serum electrolyte (sodium, potassium and calcium), coagulation profile (prothrombin time (PT), prothrombin concentration (PC), international normalized ratio (INR)), uric acid, vasculitic profile was done in stroke in young patients and if positive these patients were excluded, and blood protein biomarkers: C-reactive protein (CRP) level**,** serum calcium-binding protein Beta (S100B), matrix Metalloproteinase 9 (MMP-9) brain natriuretic peptide (BNP) and D-dimer using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) within 3 days of onset of stroke symptoms except for CRP it was withdrawn within first 24 h of admission to exclude its elevation due to hospital acquired infections.

Radiological Workup: Computed tomography (CT) brain using 16-slice CT scanner (Siemens, Somatom go.Top, Germany) was done to all patients on admission to confirm diagnosis, assess ASPECT score, and to exclude patients according to the exclusion criteria.

In addition, follow-up CT brain was done to detect hemorrhagic transformation and cerebral edema. Hemorrhagic transformation is classified according to the European cooperative acute stroke study (ECASS II) into four subtypes:

Hemorrhagic transformation type 1 (HT1) demonstrated as small hyperdense petechiae affecting less than one third of the vascular territory. Hemorrhagic transformation type 2 (HT2) is a hyperdensity within the infarct zone affecting more than one-third of the vascular territory without mass effect. Parenchymal hematoma type 1 (PH1) is a homogeneous hyperdensity affecting less than 30% of the infarct zone with mass effect while parenchymal hematoma type 2 (PH2) is a homogeneous hyperdensity affecting more than 30% of the infarct zone with significant mass effect [8].

The statistical software for the social sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA) was used to code and enter the data. For quantitative data, the mean, standard deviation, median, minimum, and maximum were used; for categorical data, frequency (count) and relative frequency (percentage) were used. To compare quantitative variables, the non-parametric Kruskal–Wallis and Mann–Whitney tests were utilized [9]. Using the Chi square (X2) test, categorical data were compared. When the anticipated frequency is less than 5, an exact test was utilized instead [10]. The Spearman correlation coefficient, used to determine correlations between quantitative variables, was used [11]. Statistics were considered significant for p values less than 0.05. Univariate analysis for predictors was conducted using the T test and Mann–Whitney U test.

Results

The age of the patients was between 23 and 85 years with a mean age 59.15 ± 12.08 years, the patients included 107 (57.5%) males and 79 (42.5%) females. Seventy-one (38.17%) patients presented with acute ischemic stroke within window (4.5 h), 61 of them received recombinant tissue plasminogen activator (rtPA) and 10 of them underwent mechanical thrombectomy, while 115 (61.83%) patients presented out of window. NIHSS onset score ranged from (2–27) and ASPECT score ranged from 3 to 10.

Regarding the hospital course, mean length of hospital stay (LOS) was10.84 ± 8.76 days with median 8.00, 46 (24.7%) patients were admitted to intensive care unit (ICU) with mean ICU duration 16.52 ± 13.33 days with median 13.00 and 13 (6.98%) patients died.

Risk factors, stroke severity assessment on admission, complications that occurred during hospital course results are shown in Tables 1, 2, and 3, respectively.

On comparing the level of protein biomarkers between patients according to stroke severity assessed by NIHSS onset severity, higher mean D-dimer serum level was found in patients with lower NIHSS onset severity (p value 0.05), regarding ASPECTS score the mean CRP serum level was higher with ASPECTS scores ≤ 7 (p value 0.018).

Comparison of serum levels of biomarkers (CRP, d-dimer, MMP-9, S100B, BNP) between patients who received thrombolytic therapy, underwent mechanical thrombectomy and those who received medical treatment did not show statistical significance between the groups (p value 0.791, 0.591, 0.225, 0.306, 0.647, respectively), as shown in Table 4.

As regards complications, statistically significant higher mean serum CRP level was found in patients who developed cerebral edema, seizures, hemorrhagic transformation, urinary tract infection UTI, and pneumonia (p value 0.001, 0.028, 0.019, 0.001, 0.001), respectively, while mean D-dimer serum level was significantly higher in those who developed pneumonia (p value 0.04), as shown in Table 5.

Patients with higher mean S100B serum level had significantly higher incidence of hemorrhagic transformation (83.89 ± 113.85 ng/L) while in patients without hemorrhagic transformation was 76.89 ± 121.48 ng/L (p value = 0.049), whereas hemorrhagic transformation grading was significantly associated with higher mean CRP serum level (43.86 ± 47.98 mg/L, 84.50 ± 81.22 mg/L, 94.50 ± 78.22 mg/L and 131.94 ± 80.88 mg/L in HT-1, HT-2, PH-1 and PH-2, respectively) (p value = 0.019), as shown in Table 5.

Patients who had poor functional outcome on discharge (mRS 4–5), had a mean CRP serum level higher than those with good functional outcome on discharge (mRS 0–3) (70.86 ± 52.56 mg/L versus 51.53 ± 49.38 mg/L) and it was the highest in patients who deceased (mRS = 6) (194.00 ± 67.81 mg/L) (p value = 0.001).

This statistically significant relation was not noticed between any of the serum biomarkers and mRS after 3 months, as shown in Table 6.

Correlations between biomarkers and stroke severity as regards NIHSS at onset and ASPECT score showed that serum levels of CRP were positively correlated with NIHSS at onset (p value = 0.002), while both d-dimer levels and MMP-9 levels showed statistically significant negative correlation with NIHSS at

Table 1 Risk factors among patients

Risk factors		Frequency	Percent
Diabetes mellitus		58/186	31.2
Hypertension		92/186	49.5
Atrial fibrillation		52/186	28.0
Ischemic heart disease		39/186	21.0
Rheumatic heart disease		12/186	6.5
Smoker		64/186	34.4
Addiction		9/186	4.8.0
Cerebrovascular insults	First presenting stroke	135/186	72.6
	Previous strokes Or TIA	42/186	22.6
	Recurrent strokes and TIA	9/186	4.8
	Total	186/186	100.0

TIA transient ischemic attack, there is overlap in risk factors

Table 2 Stroke clinical assessment on admission as regards NIHSS, mRS

Clinical assessment		Frequency	Percent %
Stroke severity by NIHSS score	Minor < 5	8/186	4.3
	Moderate 5–15	134/186	72.0
	Moderate to severe 16–20	42/186	22.6
	Severe 21–42	2/186	1.1
Modified Rankin Scale (mRS) at Onset	mRS 0	0/186	0
	mRS 1	1/186	0.5
	mRS 2	8/186	4.3
	mRS 3	37/186	19.9
	mRS 4	99/186	53.2
	mRS 5	41/186	22.0
	mRS 6	0/186	0

NIHSS National Institute of Health Stroke Scale, *mRS* Modified Rankin Scale

Table 3 Complications that occurred during hospital course

Complications		Frequency	Percent%
Hemorrhagic Transformation	• HT-1	10/186	5.4
	• HT-2	12/186	6.5
	• PH-1	1/186	0.5
	• PH-2	8/186	4.3
	• Total	31/186	16.7
Cerebral Edema		30/186	16.1
Decompressive Craniectomy		2/186	1.1
Pneumonia		38/186	20.4
Intubation		11/186	5.9
Tracheostomy		6/186	3.2
Urinary tract infection		42/186	22.6
rtPA Complications	• Bleeding per orifices	5/186	2.7
	• Allergic Reaction	2/186	1.1
DVT		3/186	2.1
Bulbar Symptoms		53/186	28.5
Gastrostomy		5/186	2.7
Another Stroke		6/186	3.2
Seizures		11/186	5.9
Mortality		13/186	7.0

HT hemorrhagic transformation, *PH* parenchymatous hematoma, *rtPA* recombinant tissue plasminogen activator, *DVT* deep venous thrombosis

onset (p value = 0.05, 0.038, respectively). Serum CRP level was negatively correlated with ASPECT score (p value = 0.008).

There was a statistically significant positive correlation between serum CRP levels and MMP-9 with hospital stay duration, ICU duration (p value 0.002,0.001 and 0.019, 0.019), respectively**,** while BNP revealed a statistically significant positive correlation with ICU duration only (p value = 0.05), as shown in Table 7.

Serum CRP level revealed a statistically significant positive correlation with mRs at onset, on discharge and 3-month follow-up (p value = 0.001, 0.001, 0.004), respectively, as shown in Table 8.

Logistic regression analysis revealed that mean CRP serum level was a significant predictor that is accompanied by higher risk for mortality, where one unit increase in CRP was associated with 2.5% higher risk of mortality, as shown in Table 9.

Discussion

Cerebrovascular stroke, whether ischemic or hemorrhagic, is one of the leading causes of morbidity and mortality, so the presence of measurable biomarkers can help in predicting the prognosis and identifying high risk patients [12].

Elevated CRP may indicate tissue damage, stroke severity or a systemic inflammatory response to infection [13]; therefore, the association between CRP levels and stroke severity and outcome was assessed, and after excluding infections, it was found that the mean CRP serum level was significantly higher in patients with a lower ASPECTS score (≤7), and this finding is consistent with Wang and colleagues 2020 [14] and Marta-Enguita and colleagues [15] which stated that higher CRP concentration was associated with larger infarct volumes, greater neurological deficit and worse functional outcomes.

On the contrary, Rezaeitalab and colleagues [16] found that serum CRP levels at baseline and follow-up were not correlated to the ASPECTS score. The differences in results between studies could be attributed to genetic variations between study populations, and that the timing of biomarkers assessment and measurement, either on admission or follow-up could affect the correlation between biomarker levels and stroke outcome.

In this study, CRP serum levels were positively correlated with NIHSS at onset, length of hospital stays and ICU duration. This came in agreement with Cai and colleagues [17] who reported that high levels of CRP on admission are associated with higher risk of neurological worsening and longer hospital stay.

Moreover, CRP serum levels were higher in patients with poor functional outcome on discharge (mRS 4–5) in comparison with those with good functional outcome on discharge (mRS 0–3) and was also positively correlated with mRs at onset, on discharge and follow-up after 3 months, this came in agreement with Wang and colleagues 2020 [14] and Lee and colleagues [18] which

Table 4 Comparison between patients regarding stroke treatment and serum levels of biomarkers

Stroke treatment	CRP Mean ± SD	D-Dimer Mean ± SD	MMP-9 Mean ± SD	S100B Mean ± SD	BNP Mean ± SD
a) Medical treatment	62.11 ± 55.22	6.58 ± 11.02	769.71 ± 173.67	93.43 ± 201.47	16.64 ± 19.32
b) Thrombolytic Therapy (rtPA)	69.08 ± 69.81	9.06 ± 17.15	724.85 ± 180.34	120.62 ± 244.18	15.45 ± 19.48
c) Mechanical Thrombectomy	90.25 ± 90.18	4.80 ± 5.50	778.68 ± 156.03	85.91 ± 80.59	20.01 ± 22.27
p value	0.791	0.591	0.225	0.306	0.647

rtPA recombinant tissue plasminogen activator, *CRP* C-reactive protein, *MMP-9* matrix Metalloproteinase 9, *S100B* serum calcium-binding protein Beta, *BNP* brain natriuretic peptide

Table 5 Protein biomarkers, stroke severity and complications

	CRP	d.Dimer	MMP-9	S100β	BNP
1) NIHSS onset severity					
a) Minor stroke < 5	37.21 ± 24.31	15.41 ± 24.39	760.10 ± 157.67	38.83 ± 14.30	6.19 ± 3.34
b) Moderate stroke 5–15	60.35 ± 56.28	5.43 ± 6.94	751.03 ± 171.12	84.83 ± 140.38	8.36 ± 8.38
c) Moderate to severe stroke 16–20	85.76 ± 78.12	5.13 ± 6.47	746.71 ± 186.35	55.66 ± 55.07	5.97 ± 4.07
d) Severe stroke 21–42	150.00 ± 100.41	3.82 ± 0.10	889.58 ± 61.74	72.71 ± 3.75	6.53
p value	0.085	0.05*	0.761	0.367	0.620
2) Neurological complications					
a) Cerebral edema	117.89 ± 84.08	4.53 ± 3.94	765.08 ± 217.06	78.83 ± 135.18	7.55 ± 8.83
p value	0.001*	0.632	0.408	0.804	0.854
b) Seizures	113.59 ± 77.46	7.17 ± 8.99	778.59 ± 183.34	122.45 ± 264.37	7.60 ± 6.76
p value	0.028*	0.915	0.909	0.426	0.609
c) Occurrence of hemorrhagic transformation	86.39 ± 77.63	3.89 ± 2.04	712.36 ± 203.34	83.89 ± 131.85	6.35 ± 4.87
p value	0.123	0.195	0.191	0.049*	0.476
d) Hemorrhagic transformation grading					
-HT-1	43.86 ± 47.98	2.94 ± 0.76	711.48 ± 221.32	105.75 ± 217.38	6.80 ± 4.67
-HT-2	84.50 ± 81.22	4.84 ± 2.84	640.39 ± 173.88	67.52 ± 81.74	6.64 ± 6.31
-PH-1	94.50 ± 78.22	170.00 ± 170.00	3.35 ± 3.35	845.92 ± 845.92	8.49 ± 8.49
-PH-2	131.94 ± 80.88	3.70 ± 1.00	804.71 ± 213.38	37.87 ± 13.99	4.90 ± 0.86
p value	0.019*	0.177	0.191	0.350	0.641
3) Non-neurological complications					
a) Pneumonia	49.62 ± 46.18	5.71 ± 8.74	744.78 ± 165.97	79.99 ± 134.56	7.60 ± 7.48
p value	0.001*	0.040*	0.157	0.416	0.827
b) UTI	52.19 ± 50.07	5.38 ± 8.26	744.09 ± 169.59	79.23 ± 135.37	7.73 ± 7.66
p value	0.001*	0.274	0.162	0.608	0.993

* statistically significant (*P* values less than 0.05)

CRP C-reactive protein, *MMP-9* matrix Metalloproteinase 9, *S100B* serum calcium-binding protein Beta, *BNP* brain natriuretic peptide, *NIHSS* National Institute of Health Stroke Scale, *HT* hemorrhagic transformation, *PH* parenchymatous hematoma, *UTI* urinary tract infection

Table 6 Protein biomarkers and mRS

mRs discharge	CRP	d.Dimer	MMP-9	S100β	BNP
Good outcome (0–3)	51.53 ± 49.38	6.23 ± 9.69	753.67 ± 169.45	84.58 ± 143.60	8.03 ± 7.53
Poor outcome (4–5)	70.86 ± 52.56	4.90 ± 4.73	734.37 ± 184.53	55.61 ± 39.37	7.46 ± 8.01
Mortality (6)	194.00 ± 67.81	4.28 ± 1.84	791.93 ± 174.68	64.64 ± 78.00	4.85 ± 1.81
p value	**0.001***	**0.536**	**0.584**	**0.828**	**0.761**

* statistically significant (*P* values less than 0.05)

mRS modified Rankin Scale, *CRP* C-reactive protein, *MMP-9* matrix Metalloproteinase 9, *S100B* serum calcium-binding protein Beta, *BNP* brain natriuretic peptide

stated that CRP levels were correlated with good outcomes at 30 and 90 days. Patients with lower level of CRP had more favorable functional outcomes at 90 days and a higher likelihood of survival rate compared to patients with higher CRP level.

These correlations between CRP serum levels and stroke severity either clinically (NIHSS, mRS, length of hospital stay) or radiologically (ASPECT score) could be because elevated CRP level is not only an indicator of the severity of brain damage but also a cause, as following cerebral ischemia, acute phase proteins including C-reactive protein are released, causing secondary ischemic brain damage [13].

Table 7 Correlation between serum protein biomarkers, hospital stay duration and ICU duration

	Hospital stay duration		ICU duration	
	Correlation coefficient	***p* value**	**Correlation coefficient**	***p* value**
CRP	0.443	0.002*	0.607	0.001*
d-Dimer	0.029	0.694	0.190	0.205
MMP-9	0.172	0.019*	0.348	0.019*
S100B	0.00	0.997	0.106	0.494
BNP	0.041	0.578	0.272	0.05*

* statistically significant (*P* values less than 0.05)

CRP C-reactive protein, *MMP-9* matrix Metalloproteinase 9, *S100B* serum calcium-binding protein Beta, *BNP* brain natriuretic peptide, *ICU* intensive care unit

Table 8 Correlation between serum CRP and modified Rankin Scale at onset, on discharge and at 3-month follow-up

CRP	**mRs at onset**	**mRs on discharge**	**mRS at 3-month follow-up**
Correlation coefficient	0.280	0.325	0.219
p value	0.001*	0.001*	0.004*

* statistically significant (*P* values less than 0.05)

mRS modified Rankin Scale, *CRP* C-reactive protein

Table 9 Logistic regression analysis

	***p* value**	***B* (regression coefficient)**	**95% CI for *B***
Constant	0.999	− 22.338	
CRP	0.001	0.025	1.037–1.014

CRP C-reactive protein

The current study explored the association between initial mean CRP serum levels and development of post-stroke complication. Mean CRP serum levels were higher in patients who developed non-neurological complication (pneumonia, UTI) during the hospital course. This finding is supported by Tinker and colleagues [19] and Koton and colleagues [20] who stated that plasma CRP levels detect early development of stroke-associated infections. However, Hou and colleagues [21] found no association between CRP serum level and pulmonary or urinary tract infection.

The association between initial mean CRP serum levels and the development of cerebral edema can be because CRP can cause blood brain barrier disruption, resulting in brain edema [22] and supported by the fact that high serum CRP level was correlated with early neurological deterioration, in patients with cardioembolic stroke, due to cerebral edema [23] In line with these results, Modrego and colleagues [24] concluded that baseline CRP levels could predict cerebral edema in patients with ischemic stroke.

In addition, the role of neuroinflammatory process in the pathogenesis of seizures has been well documented [25]. Acute ischemic stroke triggers an inflammatory response that results in elevated CRP levels [13]. This inflammatory response leads to neuronal hyper-excitability ultimately enabling the onset of epilepsy [26, 27], therefore supporting the finding of this study that CRP serum levels were associated with the occurrence of seizures and is further supported by the fact that increased levels of high sensitivity CRP (hs-CRP) were associated with post-stroke epilepsy [22].

Post-ischemic inflammatory responses cause blood–brain barrier disruption leading to hemorrhagic transformation, and subsequently worse prognosis of patients with acute ischemic stroke [28] accordingly in this study patients with hemorrhagic transformation particularly those with parenchymal hematoma type 2 (PH2) had higher mean CRP levels than those without hemorrhagic transformation, this goes along with Sasanejad and colleagues [29] who found that serum level of CRP at admission had a significant association with the risk of all hemorrhagic transformation.

In the current study, logistic regression analysis revealed that CRP serum level was a significant predictor of mortality, this finding is consistent with Jiang and colleagues [30] and Yu and colleagues [31] who also found that CRP serum level independently predict mortality.

Although D-dimer can be used in ischemic stroke patients as its level is correlated to the size or severity of stroke and prognosis [32]. In this study, D-dimer serum levels showed negative correlation with NIHSS severity at onset. This came in contrary to Abbas and colleagues [33] and Yao and colleagues [34] who found D-dimer serum levels were positively correlated with NIHSS especially on first- and seventh-day post-stroke.

This might be because aberrations in homeostasis after cerebral ischemia are related to the mechanisms of ischemia not the degree of neurological injury. In this study large artery thrombosis and lacunar infarcts are collectively predominant, where the thrombus is rich in platelets that lead to the production of d-dimer levels within the normal range [35], and that in lacunar infarcts the thrombus is small to produce large amounts of d-dimer and because of the other mechanisms that lead to lacunar infarcts other than thrombosis such as vascular degeneration [36] also because in this study there was a high percentage of cardioembolic stroke patients, some of whom were previously diagnosed with atrial fibrillation (AF) and were on anticoagulant drugs as warfarin or new oral anticoagulants (NOACs) which altered

the D-dimer level, causing lower levels of D-dimer than expected, giving rise to false-negative results [37].

MMP-9 causes breakdown in the blood–brain barrier (BBB) subsequently leading to entrance of inflammatory cells and fluid into the brain, causing hemorrhage, vasogenic edema and neuronal cell death [38], so explaining the findings of the current study that serum Matrix metalloproteinase (MMP)-9 level was positively correlated with hospital stay and ICU duration. This is supported by the findings that high serum MMP-9 levels in acute ischemic stroke were associated with mortality, major disability, and severe brain edema which could explain prolonged hospital stay [39, 40]. This finding came in contrast to the findings of Hoda and colleagues [41] who showed no significant association between MMP-9 and hospital stay in acute ischemic stroke patients.

In addition, although it is generally accepted that MMP-9 is increased following stroke, there is argument about the cells that secret MMP-9, whether they are resident brain cells, cells of the vasculature or circulating immune cells, such as neutrophils [42]; therefore, it may not reflect the exact stroke severity due to the central and peripheral secretion of MMP-9 following stroke; accordingly in this study, MMP-9 was negatively correlated with NIHSS at onset. This was contradictory to Krishnamoorthy and colleagues [43] who found that plasma MMP-9 levels were positively correlated with NIHSS scores at baseline, 12, 24, and 48 h. Whereas Lu and colleagues [44] found no correlation between MMP-9 levels and NIHSS scores suggesting that MMP-9 may not be a reliable indicator of stroke severity and the extent of necrotic tissue.

The calcium-binding protein S-100B is a well-known biomarker of blood–brain barrier disruption. This blood–brain barrier disruption leads to hemorrhagic transformation and cerebral edema in patients who have ischemic strokes [45]. In the current study, mean S100B serum levels were significantly higher in patients who developed hemorrhagic transformation (HT). This agreed with Honegger and colleagues [45] and Dagonnier and colleagues [46] which also showed elevated median S100B levels in patients with HT, also elevated S100B concentration has been associated with increased risk of hemorrhage in rtPA treated patients.

BNP is released from the damaged brain tissue after injury [47], and its amount rises as tissue damage worsens, indicating the severity of stroke [48]. In the current study, the BNP serum level was positively correlated with ICU duration. This agreed with Pan and colleagues [49] and Fukuhara and colleagues [50] that showed that higher serum BNP may reflect the severity of an ischemic stroke and is a risk for heart failure, which may necessitate prolonged treatment and longer ICU stays, furthermore the pre-thrombolytic BNP level may serve as a reliable marker for predicting mortality in ischemic stroke patients and was correlated with poor outcomes and mortality at 3 months.

Conclusions

CRP serum levels are associated with more severe stroke, post-stroke complications and worse short-term outcome. S 100 B is also associated with higher incidence of hemorrhagic transformation, accordingly blood protein biomarkers may have a prognostic value in stroke patients, so, helping in modifying the treatment plans and strategies to minimize disability and improve functional outcome.

However, the current study had several limitations. First, serum blood biomarkers were only evaluated once at baseline; subsequent measurements, which may be required to account for changes in serum levels over time and their relationships to outcomes of strokes, were not performed. Second, the modified Rankin scale was not consistently gathered during the study using either home visits or phone calls. Finally, biomarkers were measured in plasma, not in cerebral spinal fluid, and it is yet unknown if peripheral serum levels correspond to equivalent alterations in the central nervous system.

Abbreviations

ASPECTS	Alberta Stroke Program Early CT Score
BNP	Brain natriuretic peptide
CRP	C-reactive protein
CT	Computed tomography
DVT	Deep venous thrombosis
ELISA	Enzyme-linked immunosorbent assay
HT	Hemorrhagic transformation
Hs-CRP	High sensitivity C-reactive protein
ICU	Intensive care unit
LOS	Length of hospital stay
MMP-9	Matrix metalloproteinase 9
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
PH	Parenchymatous hematoma
rTPA	Recombinant tissue plasminogen activator
S-100 B	S100 calcium-binding protein B
TIA	Transient ischemic attack

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Author contributions

ME: research idea, data acquisition, data analysis and interpretation, and manuscript writing and reviewing, AS and RHM: data acquisition, data analysis and interpretation, GH and AS: data interpretation and manuscript writing and reviewing. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

Permission from the research ethics committee, Faculty of Medicine, Cairo University was obtained on 10th of November 2020. Informed written consent to participate in the study was obtained from participants.

Consent for publication

Not applicable.

Competing interests

The authors have no conflict of interests to disclose.

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