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Can brain natriuretic peptide, S100b, and interleukin-6 prognosticate the neurological consequences in Egyptian patients presented with supratentorial intracerebral hemorrhage?

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ABSTRACT

Background: Biomarkers in supratentorial intracerebral hemorrhage (SICH) enhance the prognosis of the disease. This study aimed to assess the prognosticative grade of S100 calcium-binding protein B (S100B), interleukin-6 (IL-6), and the pro-brain natriuretic peptide (pro-BNP) in SICH outcome prediction.

Methods: Blood samples of 50 SICH patients were analyzed for the biomarkers. The patients were classified into two groups with and without intraventricular hemorrhage (IVH). The following scales including Glasgow Coma Score (GCS), the Barthel index (BI), intracerebral hemorrhage (ICH) score, ICH volume, National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Score (mRS), and length of stay were used to evaluate the severity.

Results: The severity scores (NIHSS, GCS, BI, mRI) were significantly higher in SICH patients with IVH versus SICH patients without IVH (P = 0.002, 0.008, 0.001, and 0.03, respectively). Serum levels for a pro-BNP and S100b are significantly higher in SICH patients with IVH versus SICH patients without IVH (P = 0.02 and 0.027, respectively). Multivariate correlations between demographic (age), biomarkers panel (IL-6, S100b, and pro-BNP), and clinical and severity scores (ICH score, ICH volume, length of hospital stay [LOS], BI, mRS, GCS, and NIHSSS) in all studied patients showed a highly significant correlation between ICH score and pro-BNP (P = 0.04). There was a highly significant correlation between LOS and IL-6 (P = 0.003).

Conclusion: Pro-BNP, IL-6, and S100b are greatly associated with the presence of IVH that, in turn, correlated well with poor clinical outcome measures.

Keywords: Interleukin-6, Outcome, Pro-brain natriuretic peptide, S100 calcium-binding protein b, Supratentorial intracerebral hemorrhage

INTRODUCTION

A relatively common and overwhelming disease is the primary supratentorial intracerebral hemorrhage (SICH) accompanied by variable prognosis despite the great advancement in its related neurological and neurosurgical management.[7] While immediate detection of SICH is easy by computed tomography (CT), the prospective expectation continues to be difficult to anticipate, especially at the early onset

of the disease, particularly when there is a need to stop the medical care for unfavorable patients by their physicians. This vague misleads to a dilemma of patient prognosis, from complete recovery to long-term care in patients with persistent vegetative state, stressing the necessity for complementary outcome means which lead to the early medical choices in patients with acute SICH. Conventionally, there are many variables such as the age of the patient and the hematoma characteristics (size, location, and ventricular extension) in early-onset SICH that has been used to anticipate the prognosis.[19,26] Nonetheless, those classical outcome parameters remain defective to give an actual evaluation for the prognosis in patients with SICH. While the hematoma mass effect leads to neuronal lesions that play a crucial role in the prognosis of SICH, the advances in intensive care showed improvement survivals among some patients from this primary lesion, and the deterioration was due to a secondary lesion like cerebral edema. Accordingly, neuroinflammation plays a crucial role in the pathogenesis of cerebral edema that leads to neuronal damage, and eventually, can anticipate the functional outcome.[24] Therefore, the prognosis of SICH can be expected from biomarkers of neuronal damage and inflammation; likewise, an alternative parameter of neuropathophysiology could anticipate the functional outcome. Biomarkers reflective for neuronal potentiation by astrocytic activation, like S100 calcium-binding protein B (S100b), showed a significant increase after ischemic stroke and subarachnoid hemorrhage (SAH).[34,37,44] In addition, S100b is known to be used as a predictive biomarker in the ischemic stroke and is an indicator of the possibility of hemorrhagic transformation and prognosis.[13,17,25,29] Moreover, many studies have shown that there is a correlation between S100b levels and long-term outcome in subarachnoid hemorrhage and SICH.[10,45] Several studies have demonstrated that there is an increase in brain natriuretic peptide (BNP) levels after acute brain lesions, such as SAH, ischemic stroke, and traumatic brain injury. Yet, the importance of BNP in cases with SICH is unclear. However, there is an evolving proof showing that BNP could have a role in the recovery from an acute brain lesion, mostly by increasing cerebral blood flow.[18,28,36,40,51]

Elevated serum level of interleukin-6 (IL-6) is known to be associated with a variety of brain pathologies including ischemic stroke,[48] SAH,[9] and intracerebral hematoma.[11]

In this study, we assess the predictive value of the biomarker panel of S100b, IL-6, and pro-BNP, in the functional outcome after SICH, rather than conventional clinical and/or radiological methods.

MATERIALS AND METHODS

Participants

The present prospective study included 50 patients with SICH who were admitted to the neurosurgery/neurology departments over a 12-month period at Mansoura Emergency University Hospital, Egypt. The diagnosis was based on clinical assessment and computed tomographic (CT) head scanning immediately after the onset of the condition. All patients were assessed by taking a medical history, history of previous cerebrovascular strokes, hypertension, diabetes mellitus, and renal or hepatic disorders.

Ethical approval

A consent whether informed or written was obtained from each patient and the ethical committee also approved the study.

Clinical assessment scales

Clinical examination besides the neurological severity scales for the assessment of functional outcome at the discharge time was evaluated by Glasgow Coma Score (GCS), the Barthel index (BI), intracerebral hemorrhage score (ICHS), National Institutes of Health Stroke Scale (NIHSS), and Modified Rankin Score (mRS). GCS, BI, NIHSS, mRS, and ICHS results were tabulated. The ICHS is a validated 6-point score to evaluate risk in patients with SICH and includes initial GCS, hematoma location, and volume, whether intraventricular hematoma is present or not, and the age.[20] Regarding the NIHSS score, it is a measurable scale for cerebral stroke that shows the level of consciousness, neglect, language function, eye movements, visual field, facial palsy, sensory function, motor strength, and coordination. The assessment can be done quickly, and the NIHSS score can be estimated by neurologists and non-neurologists by good training.[33] Regarding the GCS, it is a clinical scale that gives a dependable, objective method of estimating the conscious level of a patient for primary and follow-up assessment. The patient is evaluated by the scale criteria, and the estimated points give a patient score between 3 (denoting deep unconsciousness) and 15 (denoting fully conscious).[52]

Radiology evaluation

Within the initial 24 h after hospital admission, the studied group of patients was scanned using brain computed tomography and checked for hemorrhagic volume (cm^3), presence of intraventricular hemorrhage (IVH), and midline shift (MLS). On discharge from Mansoura University Hospital, we used the following functional assessment scales; BI, length of hospital stay (LOS), and mRS, by a blinded observer evaluation method as they are the best for biomarker panel data. All studied patients showed CT-proven supratentorial ICH before taking the blood samples. Regarding the CT scans evaluation, a blinded neuroradiologist used the well-known simplified ellipsoid volume equation method described by Kothari *et al*.[30] The septum pellucidum MLS was evaluated

by a blinded neuroradiologist. Any MLS more than 2 mm was considered significant.

Laboratory assessments

About 8 ml venous blood was withdrawn from each patient and divided as follows: 2 ml into EDTA tube for complete blood picture, 1.8 ml into the citrated tube for prothrombin time and APTT, and the remaining blood into the plain tube to get sera for routine investigations and the remaining sera were divided into three aliquots which were stored frozen at −20°C till the time of assay of specific investigations: S100 protein, IL-6, and N-terminal-pro-BNP. The routine laboratory investigations included complete blood picture, random blood sugar, liver, kidney function tests, and coagulation tests: PT and APTT. All routine laboratory chemical tests were done by fully automated chemistry analyzer Cobas c 311 (Roche Diagnostic GmbH Mannheim, Germany). A complete blood picture was done by Cell Dyn 1800, Abbott, USA. Coagulation tests were done by Siemens reagents using the Coatron Coagulometer, Germany. Quantitative determination of IL-6 was done by the enzyme-linked immunosorbent assay (ELISA) technique using RayBio Kit, Cat # ELH-IL6-001, USA.[5] The assay had a sensitivity of <3 pg/ml. Quantitative determination of S100 protein was done by the ELISA technique using DiaMetra Kit Ref: DK0074, Italy.[35] The assay had sensitivity up to 35.27 pg/ml and measuring range up to 5000 pg/ml. Assay of NT-pro-BNP was done by an electrochemiluminescence immunoassay using Elecsys 2010 (Roche Diagnostic GmbH, Mannheim, Germany). The assay had a measuring range of 3–35,000 pg/ml.[41]

Statistical analysis

The mean and standard deviation were used for the description of continuous variables, while percentages were used for categorical variables. The linear regression curve was used to express the correlation of CT outcomes to the biomarkers panel. The relationship between the biochemical markers panel and functional patient scores was assessed by the linear regression analysis for the BI. The mRS was evaluated as a dichotomous outcome, while the BI was evaluated as a continuous variable. Logistic regression analysis was done for mRS. Multivariate assumptions were used. The two-way interactions between covariates were used for additive effects. The tolerance and variance inflation tests were used to show the collinearity between the predictors. The SAS software version 9.3 or JMP 7.0.1 was used for the execution of those statistics.

RESULTS

General characteristics

The studied patients' group comprised 50 patients with predominant male gender, with male-to-female ratio of 16:9 ≅ 1.7:1 patient. The mean age (in years) of the studied group was 60.7 ± 11.5. The studied SICH patients were subdivided into two groups based on the presence or absence of IVH.

Severity scores results

The severity scores (NIHSS, GCS, BI, and mRS) were significantly higher in SICH patients with IVH when compared with SICH patients without IVH (P = 0.002, 0.008, 0.001, and 0.03, respectively), while the LOS score did not show any statistical significance [Table 1].

Laboratory results

Serum levels for a panel of blood biomarkers (pro-BNP and S100b) were significantly higher in SICH patients with IVH when compared with SICH patients without IVH (P = 0.02 and 0.027, respectively). The IL-6 did not show any statistical significance [Table 2].

Correlations between clinical data, laboratory results, and severity scores

Multivariate correlations between demographic (age), biomarkers panel (IL-6, S100b, and pro-BNP), and clinical and severity scores (ICH score, ICH volume, LOS, BI,

Table 1: Severity scores in SICH patients without IVH versus those with IVH.

Severity score mean±SD	SICH without IVH N=40	SICH with IVH N=10	Test of significance (*P*)
NIHSSS	9.73±3.8	21.8±9.1	0.002*
GCS	13.9±1.6	9.9±3.9	0.008*
LOS score	5.4±3.4	6.3±3.0	0.3
BI	66.3±13.1	26.5±15.7	0.001*
mRS	2.53±1.0	4.1±1.0	0.03*

*Significant (test is considered significant when $P \leq 0.05$),
SICH: Supratentorial intracerebral hemorrhage, IVH: Intraventricular hemorrhage, LOS: Length of hospital stay score, BI: Barthel index, mRS: Modified Rankin Score, GCS: Glasgow Coma Score, NIHSSS: National Institutes of Health Stroke Scale Score, N: Number

Table 2: Serum levels of IL-6, S100b, and pro-BNP in SICH patients without IVH versus those with IVH.

Parameter pg/ml median (range)	SICH patients without IVH	SICH patients with IVH N=10	Test of significance (*P*)
Pro-BNP	46.1 (5.9–2428)	243 (72.7–2994)	0.02*
IL-6	5.1 (2.4–11.5)	5.85 (4.2–11.2)	0.16
S100-B	61 (2.3–109.4)	92 (35–1370)	0.027*

*Significant (test is considered significant when $P \leq 0.05$),
SICH: Supratentorial intracerebral hemorrhage, IVH: Intraventricular hemorrhage, IL-6: Interleukin-6, BNP: Brain natriuretic peptide, N=Number

mRS, GCS, and NIHSSS) in all studied patients showed a highly significant correlation between ICH score and pro-BNP (P = 0.04). Moreover, there was a highly significant correlation between LOS and IL-6 (P = 0.003) [Table 3].

DISCUSSION

Many studies have shown that there is a correlation between the biochemical marker panels and the prognosis in various acute onset brain lesion pathogenesis, such as ischemic stroke,[44,48] traumatic brain injury,[6] and SAH.[9,47] Moreover, it showed a promising advantage in the diagnostic and prognostic accuracy that expressed a higher value with a panel of the biochemical markers than a single one.[32] Therefore, the use of laboratory biomarkers panels with the classical clinical and radiological methods gave additional prognostic information that helps in decision-making, especially in hypoxic encephalopathy after cardiac arrest,[12,46] and as an alternative parameter in many studies, for instance in SAH,[9] and ischemic infarction.[43,48] Therefore, this study showed that S100b and pro-BNP are highly statistically correlated with prognostic clinical scales in discharged SICH patients and this adds supplementary prognostic value in addition to the classical methods. During the acute neuronal injury, the microglia and Schwann cells release S100b in the cerebrospinal fluid and then into the blood with breakage in the blood–brain barrier (BBB). Accordingly, serum S100b is an indicator of both neuronal injury and BBB dysfunction.[2,27] In addition, S100b is stable and not affected by hemolysis allowing dependable laboratory results. Finally, the short half-life of S100b allows the applicable results to represent the current pathophysiological situation and gives valuable time for intervention in emergency neurological situations.[8] The BNP is considered as a neurohormone elaborated initially as a pro-hormone then enzymatically induced BNP and the aminoterminal part. It is produced mainly from the cardiac ventricles in reaction to high wall tension.[38,53] Serum BNP is increased with heart failure,[39] also BNP levels showed a marked increase in acute onset brain insult.[40] BNP has many effects such as vasodilation, inhibition of the sympathetic nervous system, and modifications of the electrolytes and fluid balance by its action of diuretic and natriuretic properties.[14,16,31] Many studies have shown that there are elevations of BNP after SAH,[18,36,56] ischemic stroke,[28,40] and traumatic brain injury.[51] The elevation of BNP after acute onset brain insults is correlated with an augmentation in cerebral blood flow, although it is still vague whether this is an adjusting reaction[3,21,42] or a harmful response from cerebral ischemia.[49,50] Few studies have discussed the role of biomarkers in patients with ICH. Many published data have shown the relationships in certain serological markers to differentiate between ischemic and hemorrhagic cerebral stroke,[4,32] and also the expectation of hematoma progression, like matrix metalloproteinases.[1] The well-known serum biomarkers used to evaluate neurological prognosis after ICH are IL-11 and S100b.[15,22] Weglewski *et al*. stated that there is a time course for S100b serum level to increase then decrease after ICH.[54] Moreover, in patients with ICH, the initial worsening, and long-term prognosis for up to 3 months, was associated with S100b serum levels on admission. Delgado *et al*. stated that elevated serum level of S100b after spontaneous ICH is closely correlated to the initial ICH volume. Nevertheless, initial ICH volume is the best predictor for early deterioration and worse neurological outcome using multivariate analysis.[10] Dziedzic *et al*. stated that acute ICH triggers elevated levels of serum IL-6 and IL10 which correlate with initial ICH volume and shift of midline structures which, in turn, correlates well with the final functional neurological outcome.[11] In this study, we could not find a statistically significant correlation between serum level of IL-6 and any of the utilized clinical evaluation scales at hospital discharge which is contrary to the results of Dziedzic *et al*., although we could acknowledge a statistically significant correlation between the IL-6 and the LOS that could be explained by other early hospital-related infectious complications rather than direct relation

Table 3: Correlations between demographic, laboratory markers, and clinical scores in all studied subjects (n=50).

Item	Age	ICHS	NIHSSS	GCS	ICHV	LOS	BI	mRS	Pro-BNP	S100-B	IL-6
Age		0.7	0.6	0.9	0.2	0.2	0.7	0.45	0.4	0.4	0.9
ICHS	0.7		0.00**	0.00**	0.001**	0.2	0.00**	0.01*	0.04*	0.2	0.3
NIHSSS	0.7	0.00**		0.00**	0.00**	0.2	0.00**	0.001**	0.2	0.4	0.4
GCS	0.9	0.00**	0.00**		0.008**	0.3	0.00**	0.008*	0.09	0.5	0.4
ICHV	0.2	0.001**	0.00**	0.008*		0.6	0.001**	0.02*	0.6	0.5	0.5
LOS	0.2	0.1	0.3	0.3	0.6		0.4	0.2	0.9	0.7	0.003**
BI	0.7	0.00**	0.00**	0.00**	0.001**	0.4		0.00**	0.1	0.4	0.3
mRS	0.5	0.01*	0.008*	0.008*	0.02*	0.2	0.00**		0.4	0.4	0.1

*Significant (test is considered significant when P≤0.05), **Highly significant (P≤0.005), LOS: Length of hospital stay score, BI: Barthel index, mRS: Modified Rankin Score, GCS: Glasgow Coma Score, NIHSSS: National Institutes of Health Stroke Scale Score, IL-6": Interleukin-6, BNP: Brain natriuretic peptide, ICHS: Intracerebral hemorrhage score, ICHV: Intracerebral hemorrhage volume

to the primary brain insult. This explanation was found to be in line with the results of other investigators.[55] In the current research, we found a positive significance statistical correlation between serum level of both pro-BNP and S100b after SICH in Egyptian patients and the functional neurological outcome at hospital discharge. Even if either of them is used in association with the classical clinical prognostic scores, like the ICH score, this will increase the prediction of the functional outcome.[20] Furthermore, there is a correlation between these serum biomarkers representing focal inflammatory reaction and MLS that represent cerebral edema.[23] In the current study, the nonsignificant correlation between both biomarkers (BNP and S100b) and classical prognostic parameters (GCS and hematoma volume) suggested that the serum biomarkers represent the secondary inflammatory effect more than the primary lesion of the mass effect [Table 3]. In the current study, we have been faced with several restrictions during data gathering that could be explained by, relatively small number of patients included in this study, so the interpretation of the study results should be dealt with caution. To be implemented in clinical practice, it should be validated by further future wider scale studies. Nevertheless, the study endpoint clinical scales were assessed at the time of SICH patient hospital discharge which could be modified after a good period of successful rehabilitation program which, in turn, could change the functional neurological outcome but at a more prolonged period of clinical follow-up. We believe that adding a follow-up biomarker level after several days of initial hospital admission could influence the global prognostic value achieved if combined with the initial measurement at the first 24 h and then correlated to the classical clinical-radiological prognosticator previously discussed. Even though the biomarker pro-BNP in this study correlates with ICHS which, in turn, correlates with the functional neurological outcome, IL-6 correlates with LOS in this study, the presence of IVH correlates with higher morbidity and mortality among the clinical severity scores [BI, NIHSS, GCS, and mRS; Table 1] that, in turn, correlate well with both S100b and pro-BNP in our study [Table 2]. From the previously discussed data, one can elucidate the probable valueability of initial biomarker assessment expecting the future functional outcome of our SICH patients. There is a lot of controversy regarding the withdrawal of care that could be influenced by regional laws and religious issues. For instance, Egyptian law does not allow for the withdrawal of care in terminally ill patients although it is an acceptable bylaw in other countries.[22] Based on our current data and supported by other references, worse neurological and functional outcome could be expected from laboratory biomarkers at an early stage of hospital admission, especially when combined with clinical-radiological prognosticators that could influence the decision of care withdrawal, particularly in SICH patient with IVH, a decision prohibited by law in our region although allowed elsewhere.[22]

CONCLUSION

Pro-BNP, IL-6, and S100b are greatly associated with the presence of IVH that correlated well with poor clinical outcome measures by NIHSSS, GCS, BI, and mRS. Moreover, these contribute to the prognostic biomarkers data over the severity scales that integrate both the clinical and radiographic characteristics. Nevertheless, those laboratory biomarkers added more prognostic value when conjoined with clinical severity scores, especially ICH score and pro-BNP. Further investigation of serial serum biomarkers measurements could be of value over a prolonged period, especially with the addition of cognitive function evaluation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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