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Serum S100β as a predictor of severity and outcomes for mixed subtype acute ischaemic stroke

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ABSTRACT

Introduction: Serum S100β levels are mostly used for predicting outcomes of large vessel stroke (LVS). Its application for mixed subtypes of acute ischaemic stroke (AIS) is limited.

Methods: Patients with mixed subtype of AIS, aged over 18 years, who presented within 24 hours of stroke onset were consecutively enrolled. Serum S100β levels at presentation ($S100\beta_b$) and 72 hours ($S100\beta_{72hrs}$), and corresponding National Institutes of Health Stroke Scale ($NIHSS_b$ and $NIHSS_{72hrs}$, respectively) were assessed. Stroke outcomes were evaluated by modified Rankin Scale (mRs) at 30 days (mRs_{30}) and 90 days (mRs_{90}). Correlations between $S100\beta_b$, $S100\beta_{72hrs}$ and difference between the two ($\Delta S100\beta$) with corresponding NIHSS, mRs_{30} and mRs_{90} were evaluated ($p < 0.05$).

Results: For analysis, 35 patients were eligible. On univariate analyses, stroke outcomes had significant association with $S100\beta_b$, $S100\beta_{72hrs}$, $NIHSS_b$, $NIHSS_{72hrs}$ and $\Delta S100\beta$. Both $S100\beta_b$ and $S100\beta_{72hrs}$ correlated with corresponding NIHSS values ($\rho_b = 0.51$, $p < 0.001$; $\rho_{72hrs} = 0.74$, $p < 0.001$), mRs_{30} ($\rho_b = 0.58$, $p < 0.001$; $\rho_{72hrs} = 0.72$, $p < 0.001$) and mRs_{90} ($\rho_b = 0.51$, $p = 0.002$; $\rho_{72hrs} = 0.68$, $p < 0.001$). Correlations existed between $\Delta S100\beta$ and mRs_{30} ($\rho = 0.74$, $p < 0.001$) and mRs_{90} ($\rho = 0.71$, $p < 0.001$). Practical cut-off points for unfavourable outcomes (mRs 3–6) were $S100\beta_{72hrs} > 0.288$ μg/L (sensitivity 92.3%; specificity 86.4%) and $\Delta S100\beta > 0.125$ μg/L (sensitivity 100%; specificity 81.8%).

Conclusion: High serum S100β is associated with unfavourable outcome for mixed subtype AIS. Cut-off values of $S100\beta_{72hrs}$ and $\Delta S100\beta$ were optimal for predicting unfavourable stroke outcome.

Keywords: acute ischaemic stroke, serum S100β, outcome

INTRODUCTION

Various neural-specific biomarkers are released into the serum and cerebrospinal fluid during neural tissue injuries. Both direct and indirect cerebral damage (e.g. cerebral trauma, cardiopulmonary arrest, postoperative neurovascular complications and acute ischaemic stroke [AIS]) lead to the release of these biomarkers.[1-5] Thus, assessment of the presence and magnitude of such biomarkers during neurovascular insults may facilitate not only the diagnosis but also prediction of the complications and final outcomes of the neural injury.[1,2,6] A recent study found that each biomarker has a specific cellular origin within the cerebral tissue (e.g. neuron-specific enolase [NSE] is released from neurons; serum S100β is released from astrocytes and Schwann cells; Tau protein is from neurons; metalloproteinase 9 is released from vascular endothelium; and ubiquitin C terminal hydroxylase-L1 is released from neurons).[3] Therefore, several biomarkers associated with specific cerebral cellular damage have been under extensive investigation to identify novel biomarkers that could serve these purposes.[7] Recently, among many stroke-related biomarkers widely evaluated for their suitability for clinical deployment, S100β and NSE were the two most broadly attributed in many clinical studies for their clinical usefulness.[2,3,6,8-12] Because of the greater clinically correlated response of S100β and absence of interference by the body clearance systems, there has been much interest in proving its clinical applicability.[3]

The S100β protein is an acidic, calcium-binding, neural-specific biomarker. It is a ~21-kDa protein with a homodimeric structure (double helix loop) that is encoded on the long arm of chromosome 21 (21q22.3).[2,13] As S100β has been used as a target of immunologically specific staining techniques to demonstrate astrocytes and melanocytes, it is a potentially promising biomarker for damage to astroglial cells as well as melanocyte proliferation.[3,7] Furthermore, a study based on experimental induction of endothelial injury has suggested that S100β could be a biomarker for blood-brain barrier disruption.[14]

Several studies have reported a significant elevation of serial S100β levels following AIS, in particular among patients with large vessel or cortical brain infarction. The elevation of S100β, both initially and subsequently at the appropriate time points, significantly correlated not only with the extent of cerebral infarction as reflected by stroke severity, but also the associated complications and neurological outcomes.[8-12,15,16]

Earlier studies have reported that S100β was first detected in the serum of patients with AIS at 6–12 hours and reached peak levels at 72 hours after the onset of AIS.[12,17,18] It followed first-order kinetics, with a biological half-life of 25.3 ± 5.1 minutes, without effect from a moderately decreased glomerular filtration rate.[5] Nevertheless, due to the delayed kinetics for the first detection in serum (6–12 hours), S100β is not an ideal biomarker for AIS diagnosis.[12,18]

To the best of our knowledge, there has been limited evaluation of the clinical usefulness of S100β in mixed cortical (or, large-vessel occlusive stroke [LVS]) and subcortical (or, small-vessel occlusive stroke [SVS]) AIS. The present study, therefore, aimed to: (a) demonstrate the significance of the correlations between the initial and subsequent (at 72 hours after AIS onset) S100β levels with severity and outcomes of patients with mixed subtype AIS; and (b) determine the optimal cut-off points of S100β levels at each time point for predicting unfavourable outcomes in patients with mixed subtype AIS. We intended to prove the clinical applicability of S100β for predicting the outcomes of patients with mixed cortical and subcortical ischaemic strokes.

METHODS

We prospectively enrolled all patients aged over 18 years who presented to Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand, with newly diagnosed AIS within 24 hours of the onset of symptoms from January 2013 to September

2013. The diagnosis of AIS was based on the patient's clinical presentation and confirmed by either computed tomography or magnetic resonance imaging of the brain. Patients with a previous history of neurological illness, existing neurological disorder or residual neurological disability from any cause (e.g. stroke, cerebral neoplasm, intracranial infection or traumatic cerebral injury) were excluded. To achieve statistically significant power, a sample size of 36 was necessary based on the equation:

$$\therefore n_1 = \frac{\left[Z_{1-\alpha/2}\sqrt{p(1-p)(1+1/r)} + Z_{\beta}\sqrt{p_1(1-p_1)+p_2(1-p_2)/r}\,\right]^2}{\Delta^2}$$

where proportions of positive outcome among the exposed group (p1) = 0.73, proportions of positive outcome among the non-exposed group (p2) = 0.17, $\alpha = 0.05$, power = 0.8, and r = 1.

Patients' demographic data and cardiovascular risk factors were collected during stroke risk screening. Presenting stroke severity was graded using National Institute of Health Stroke Scale (NIHSS) immediately upon the patient's arrival at our centre as the baseline severity scale ($NIHSS_b$). An emergency cranial imaging study, mostly computed tomography of the brain, was performed to confirm the diagnosis and classify the subtype of AIS, in combination with the clinical stroke syndrome. All brain images were subsequently reviewed and confirmed by a clinically blinded neuroradiologist. The first blood sample for the baseline assay of S100β ($S100\beta_b$) was collected prior to starting treatment.

The primary AIS treatment consisted of one or a combination of intravenous thrombolysis, endovascular thrombectomy and antithrombotic agents. The second S100β assay was performed at 72 hours after the onset of stroke symptoms ($S100\beta_{72hrs}$), together with a re-evaluation of stroke severity using NIHSS ($NIHSS_{72hrs}$). Stroke-related complications (e.g. haemorrhagic transformation and malignant cerebral oedema necessitating decompressive craniectomy) were monitored. Stroke outcomes were assessed

using modified Rankin Scale (mRs) at 30 days (mRs_{30}) and 90 days (mRs_{90}) after AIS onset, and mRs ≤ 2 was considered favourable while mRs 3–6 was treated as unfavourable.

Measurement of serum S100β levels was performed using a commercial kit (Elecsys S100; Roche Diagnostics, Indianapolis, IN, USA) that was composed of a two-site monoclonal S100-specific antibody to form a sandwich complex on a fully automated system (Elecsys 2010, Modular Analytics E170; Roche Diagnostics-Hitachi High-Technologies Corporation, Tokyo, Japan). The range of measurement was 0.015–30.0 μg/L. We evaluated within an intra-assay coefficient of variation that varied in the range 1.28%–2.32%.

Descriptive statistics were shown as number (percentage), mean ± standard deviation or median (interquartile range [IQR]). Fisher's exact test and chi-square test were used to analyse categorical variables whereas Student's *t*-test and Wilcoxon rank sum test were used to analyse continuous variables for statistical significance. A p-value < 0.05 was considered to be statistically significant. Continuous variables were assessed using the Shapiro-Wilk test for normality. Correlations between $S100\beta_b$ and $S100\beta_{72hrs}$ and the corresponding $NIHSS_b$ and $NIHSS_{72hrs}$ values, as well as correlations between each S100β level and the difference of the two S100β measurements (ΔS100β) with mRs_{30} and mRs_{90} were evaluated using Spearman's correlation. The optimal cut-off points of $S100\beta_b$, $S100\beta_{72hrs}$ and ΔS100β levels to predict final patient outcomes and mortality were obtained using receiver operating characteristic (ROC) curves. The sensitivity, specificity, positive predictive value and negative predictive value of each S100β and ΔS100β cut-off points obtained were also calculated.

The complete study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand. We strictly followed the regulations of the 1964 Declaration of Helsinki and its later amendments while

performing the study. All identifiable personal information of enrolled patients was made completely anonymous.

RESULTS

A total of 35 of 44 enrolled patients with AIS were eligible for final analysis – six patients met the exclusion criteria and three patients had incomplete follow-up. There were 26 men and nine women, with an overall mean age of 65.3 ± 10.7 (range 43–81) years (Table I). Men were slightly older than women.

Table I. Univariate logistic regression analysis of clinical variables and stroke outcomes at 30 days and 90 days.

Variable	**No. (%)**			**p-value**
	Total (n = 35)	**mRs_{30} and mRs_{90}***		
		0–2 (n = 22)	**3–6 (n = 13)**	
Gender				> 0.999
Men	26 (74.3)	16 (72.7)	10 (76.9)	
Women	9 (25.7)	6 (27.3)	3 (23.1)	
Age (yr)†	65.3 ± 10.7	63.8 ± 10.2	67.8 ± 11.5	0.289
Men	66.5 ± 11.1			
Women	61.6 ± 8.9			
Risk factor				
Smoking	20 (57.1)	12 (54.5)	8 (61.5)	0.960
Hypertension	18 (51.4)	12 (54.5)	6 (46.2)	0.897
Dyslipidaemia	10 (28.6)	8 (36.4)	2 (15.4)	0.259
Diabetes mellitus	7 (20.0)	2 (9.1)	5 (38.5)	0.075
Atrial fibrillation	6 (17.1)	2 (9.1)	4 (30.8)	0.166
Coronary artery disease	4 (11.4)	1 (4.5)	3 (23.1)	0.134
TOAST classification				
Large vessels	13 (37.1)	5 (22.7)	8 (61.5)	
Small vessels	15 (42.9)	14 (63.6)	1 (7.7)	
Cardioembolic	5 (14.3)	1 (4.5)	4 (30.8)	
Others determined	0 (0.0)	0 (0.0)	0 (0.0)	
Others undetermined	2 (5.7)	2 (9.1)	0 (0.0)	
$NIHSS_b$‡	10.0 (6.0–19.0)	7.0 (4.2–9.8)	20.0 (19.0–21.0)	< 0.001§
$NIHSS_{72hrs}$‡	6.0 (2.5–16.0)	3.0 (2.0–4.8)	18.0 (16.0–28.0)	< 0.001§
$S100\beta_b$ (μg/L)‡	0.1 (0.1–0.2)	0.1 (0.1–0.1)	0.2 (0.1–0.2)	< 0.001§
$S100\beta_{72hrs}$ (μg/L)‡	0.2 (0.1–0.7)	0.1 (0.1–0.2)	1.0 (0.5–4.1)	< 0.001§
$\Delta S100\beta$ (μg/L)‡	0.1 (0.0–0.5)	0 (0.0–0.1)	0.9 (0.3–3.8)	< 0.001§
Treatment‡				

Conventional therapy	21 (60.0)	16 (72.7)	5 (38.5)	
Intravenous thrombolysis	10 (28.6)	5 (22.7)	5 (38.5)	
Endovascular thrombectomy	1 (2.9)	0 (0.0)	1 (7.7)	
Haemorrhagic transformation	5 (14.3)	1 (4.5)	4 (30.8)	
Decompression craniotomy	2 (5.7)	0 (0.0)	2 (15.4)	

*mRs at 30 days and 90 days after stroke were identical (mRs 0–2 = favourable outcome, mRs 3–6 = unfavourable outcome). †Data presented as mean ± standard deviation. ‡Data presented as median (interquartile range). §$p < 0.05$ was statistically significant using Mann-Whitney *U* test. Three patients did not receive primary stroke treatment, as two patients had haemorrhagic transformation and one patient had massive middle cerebral artery oedema. ΔS100β: difference between serum S100β at baseline and at 72 hr after stroke onset; mRs: modified Rankin Scale; mRs30: mRs at 30 days after stroke; mRs90: mRs at 90 days after stroke; $NIHSS_{72hrs}$: National Institute of Health Stroke Scale at 72 hr after stroke onset; $NIHSS_b$: National Institute of Health Stroke Scale at baseline; $S100\beta_{72hrs}$: serum S100β at 72 hr after stroke onset; $S100\beta_b$: serum S100β at baseline; TOAST classification: Trial of ORG 10172 in Acute Stroke Treatment classification

Smoking, hypertension and hyperlipidaemia were sequentially the three most common cardiovascular risk factors among our patients. The total number of SVS was 17 (48.6%), and these included 15 SVS and two other undetermined subtypes that were finally classified as SVS. The median $NIHSS_b$ was 10.0 (IQR 6.0–19.0) while the median $NIHSS_{72hrs}$ was 6.0 (IQR 2.5–16.0). The $S100\beta_b$ assessments were available at a mean time of 10.6 ± 7.3 (range 2.0–24.0) hours after stroke onset, while the $S100\beta_{72hrs}$ assessments were performed at 72 hours after stroke onset.

For primary stroke treatment, 21 patients received conventional therapy in the form of antiplatelet or anticoagulant, while ten patients received intravenous thrombolysis and one patient underwent endovascular thrombectomy. Primary stroke treatment was withheld for three patients – two patients had haemorrhagic transformation and one patient had massive cerebral oedema initially. The final stroke outcomes evaluated by mRs_{30} and mRs_{90}, which were categorised as favourable ($mRs \leq 2$) or unfavourable (mRs 3–6), were identical for the categorical outcomes (favourable or unfavourable) at both time points for each patient. Five

patients had complications of haemorrhagic transformation, and two patients developed malignant brain oedema for which decompression craniotomy was indicated. Eventually, 22 patients had a favourable outcome while 13 patients had an unfavourable outcome. Six patients died of direct stroke-related severity and complications.

$S100\beta_b$, $S100\beta_{72hrs}$, $\Delta S100\beta$, $NIHSS_b$ and $NIHSS_{72hrs}$ were significantly associated with categorical stroke outcomes on univariate logistic regression analysis (Table I). Further evaluation of $S100\beta_b$ showed positive correlations with $NIHSS_b$ ($\rho = 0.51$, $p < 0.001$), mRs_{30} ($\rho = 0.58$, $p < 0.001$) and mRs_{90} ($\rho = 0.51$, $p = 0.002$) using Spearman's correlation (Fig. 1). $S100\beta_{72hrs}$ also had positive correlations with $NIHSS_{72hrs}$ ($\rho = 0.74$, $p < 0.001$), mRs_{30} ($\rho = 0.72$, $p < 0.001$) and mRs_{90} ($\rho = 0.68$, $p < 0.001$) (Fig. 2). The difference between $S100\beta_{72hrs}$ and $S100\beta_b$ (i.e. $\Delta S100\beta$) also showed a positive correlation with mRs_{30} ($\rho = 0.74$, $p < 0.001$) and mRs_{90} ($\rho = 0.71$, $p < 0.001$), but no significant correlation with the difference between $NIHSS_{72hrs}$ and $NIHSS_b$ (i.e. $\Delta NIHSS$) [$\rho = 0.07$, $p = 0.700$] (Fig. 3).

The optimal cut-off points for $S100\beta_b$, $S100\beta_{72hrs}$ and $\Delta S100\beta$ for the prediction of unfavourable stroke outcomes and death, as well as sensitivity, specificity, area under the curve (AUC), positive predictive value and negative predictive value identified by the ROC curves are presented in Table II.

Table II. Optimal cut-off points for serum S100β at baseline and at 72 hours after stroke onset for predicting unfavourable stroke outcome and death at 30 days and 90 days after stroke.

Prediction	**S100β level (μg/L)**	**Sensitivity (%)**	**Specificity (%)**	**AUC**	**PPV (%)**	**NPV (%)**
Unfavourable outcome (mRs > 2) (n = 13)						
All stroke (n = 13)						
$S100\beta_b$	0.096	92.3	68.2	0.80	63.0	93.0
$S100\beta_{72hrs}$	0.288	92.3	86.4	0.89	80.0	95.0
$\Delta S100\beta$	0.125	100	81.8	0.91	76.5	100

Large vessels stroke (n = 12)						
$S100\beta_b$	0.158	75.0	100	0.88	100	67.0
$S100\beta_{72hrs}$	0.745	75.0	100	0.88	100	67.0
$\Delta S100\beta$	0.294	83.3	83.3	0.83	90.9	71.4
Small vessels stroke (n = 1)						
$S100\beta_b$	0.098	100	69.0	0.84	16.0	100
$S100\beta_{72hrs}$	0.242	100	87.0	0.94	33.0	100
$\Delta S100\beta$	0.125	100	81.2	0.90	25.0	100
Death (mRs 6) (n = 6)						
At 30 days						
$S100\beta_b$	0.158	100	75.0	0.88	27.3	100
$S100\beta_{72hrs}$	0.375	100	65.6	0.83	21.4	100
At 90 days						
$S100\beta_b$	0.096	100	48.3	0.74	28.6	100
$S100\beta_{72hrs}$	0.242	100	62.1	0.81	35.3	100

ΔS100β: difference between serum S100β at baseline and at 72 hr after stroke onset; AUC: area under the curve; mRs: modified Rankin Scale; NPV: negative predictive value; PPV: positive predictive value; $S100\beta_{72hrs}$: serum S100β at 72 hr after stroke onset; $S100\beta_b$: serum S100β at baseline

DISCUSSION

Unlike most previous studies that have involved large vessel thrombotic and embolic strokes, 17 of 35 (48.6%) patients in our study were classified as SVS. We found that $S100\beta_b$, $S100\beta_{72hrs}$, ΔS100β, $NIHSS_b$ and $NIHSS_{72hrs}$ had significant association with final stroke outcomes upon univariate logistic regression analysis. However, statistical significance was not found following multivariate logistic regression analysis of all NIHSS and S100β values. Therefore, $S100\beta_b$ and $S100\beta_{72hrs}$ may not be superior to $NIHSS_b$ and $NIHSS_{72hrs}$ for predicting the final functional outcome of patients with stroke.

Several widely reported previous clinical studies regarding the usefulness of S100β and other more specific neuronal biomarkers were based on patients with LVS and mostly middle cerebral artery occlusion. Foerch et al[16] reported the correlation between a single

S100β measurement and functional outcome and also the brain infarction volume seven days after stroke. They also found that the S100β level was not influenced by variables, such as age, gender, stroke severity, aetiology, initial lesion size and stroke, upon multivariate logistic regression analysis.[16] Furthermore, a single-measurement study of S100β at 48 hours after stroke onset reported that S100β level ≤ 0.37 μg/L could predict an independent functional outcome, with a sensitivity of 87% and specificity of 78% for patients with middle cerebral artery infarction.[16] Another study confirmed that a S100β cut-off level > 0.2 μg/L at 48 hours after stroke in patients with AIS was a strong predictor for unfavourable functional outcome at three months after stroke onset, with a sensitivity of 85% and specificity of 92%. Moreover, a study demonstrated that elevation of S100β as early as 6 hours after stroke onset marked for a unfavourable functional outcome.[12] Fassbender et al[8] showed a correlation between elevated serum S100β levels at ten hours, 24 hours and 72 hours after stroke onset with an infarction volume > 5 mm^3 and functional outcome. The elevation of S100β, in this study, was found significantly higher for cortical infarctions than for subcortical and brain stem infarctions at 24 hours and 72 hours after stroke onset.[8]

The first blood sample for the S100β assay, in our study, was collected within 12 hours and, significantly, a second sample was collected at 72 hours after stroke onset, which was considered the most optimal time point to assess S100β levels for estimating the extent of cerebral damage after stroke. This time point for the second S100β measurement was selected based on the findings of a previous experimental animal study and a clinical review of the role of S100β in AIS.[17,19] Although the level of S100β in our study was not identical to previous studies, we found a comparable correlation with stroke severity as well as short- and long-term functional outcomes, as evaluated by mRs_{30} and mRs_{90}, among our patients. Similarly, ΔS100β, in our study, showed a correlation with mRs_{30} and mRs_{90}.

The cut-off values of $S100\beta_b$, $S100\beta_{72hrs}$ and ΔS100β were good predictors of unfavourable outcome for all stroke subtypes in our study. However, as only one patient with SVS who experienced unfavourable outcome was included, our findings vis-à-vis the preciseness and generalisation of the cut-off values for S100β to all patients with stroke may be limited. Additionally, the cut-off values found for $S100\beta_{72hrs}$ and ΔS100β were notably more appropriate than $S100\beta_b$ in predicting unfavourable functional outcome. Therefore, similar to previous studies,[8,17,19] we also propose that S100β measurement is appropriate for the prediction of unfavourable stroke outcome among patients with LVS and its usefulness in patients with SVS remains as yet undetermined. Furthermore, a single measurement at 72 hours, or $S100\beta_{72hrs}$, has the highest specificity for predicting unfavourable outcome of AIS.

Most studies have recognised the clinical usefulness of assessments of S100β levels for estimating the extent of cerebral ischaemic damage that is reflected in infarction volume, monitoring patients' response to treatment and their subsequent functional outcome, as assessed by mRs.[6,8,12,15,16,18,20] The S100β level can be detected in the serum as early as 6–12 hours after stroke onset and, in most patients, reaches its peak in 24 hours or more after stroke.[18] However, some other studies have reported the S100β peak at 48–72 hours after stroke onset,[8,9,12,17] suggesting that, as yet, there is no consensus over the optimal time points or number of S100β sample assays to be rationally performed for patients with stroke. On the contrary, certain studies have suggested that cerebrospinal fluid might be a more appropriate source of S100β and NSE assessments for predicting stroke severity since, with cerebrospinal fluid measurements, there is no interference from other potential extracranial sources of S100β, such as adipose tissue, melanocytes, T-lymphocytes, skin or skeletal muscles.[2,11] In view of these earlier findings, physicians should exercise caution when using S100β and NSE

measurements for evaluating patients with stroke unless such potential extracranial sources are carefully excluded.

Other biomarkers for the prediction of stroke outcome have also been investigated. Jauch et al, in the National Institute for Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator (NINDS rt-PA) Stroke Study, demonstrated a positive association between the peak 24-hour level of myelin basic proteins, NSE, S100β and NIHSS at presentation, as well as a worse outcome at three months after stroke among patients with a higher difference of S100β and myelin basic proteins levels between 24 hours and two hours after initiation of intravenous thrombolysis treatment.[6] Although NSE followed the same kinetic pattern as S100β, it showed no correlation with infarction volume and functional outcomes,[8] suggesting that NSE has no clinical efficacy for the prediction of outcome of AIS.

A difference in the elevation of biomarkers among the different AIS subtypes among patients with LVS and SVS has not been clearly elucidated.[2] A study on glial tissue-specific proteins suggested that glial fibrillary acidic protein was more sensitive for estimating brain damage in patients with SVS whereas S100β was more suitable for patients with LVS.[11]

The present study, which was conducted in Thailand, demonstrated that S100β had a high specificity for predicting unfavourable outcomes of LVS in an Asian population. Differences in ethnicity have no influence on the S100β measurements. Further clinical investigations enrolling a larger sample size of various stroke subtypes, with particular emphasis on patients with SVS, are warranted to confirm the true clinical usefulness of S100β as a broad stroke biomarker. The optimal number of assessments required and the appropriate time points at which to perform these S100β assessments also needs to be rationally specified for universal practice and a better understanding of the diagnostic/prognostic value of S100β measurements among patients with stroke.

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REFERENCES

1. Laskowitz DT, Kasner SE, Saver J, Remmel KS, Jauch EC; BRAIN Study Group. Clinical usefulness of a biomarker-based diagnostic test for acute stroke: the Biomarker Rapid Assessment in Ischemic Injury (BRAIN) study. Stroke 2009; 40:77-85.
2. Persson L, Hårdemark HG, Gustafsson J, et al. S-100 protein and neuron-specific enolase in cerebrospinal fluid and serum: markers of cell damage in human central nervous system. Stroke 1987; 18:911-8.
3. Cata JP, Abdelmalak B, Farag E. Neurological biomarkers in the perioperative period. Br J Anaesth 2011; 107:844-58.
4. Jönsson H, Johnsson P, Alling C, et al. S100 beta after coronary artery surgery: release pattern, source of contamination, and relation to neuropsychological outcome. Ann Thorac Surg 1999; 68:2202-8.
5. Jönsson H, Johnsson P, Höglund P, Alling C, Blomquist S. Elimination of S100B and renal function after cardiac surgery. J Cardiothorac Vasc Anesth 2000; 14:698-701.
6. Jauch EC, Lindsell C, Broderick J, et al; NINDS rt-PA Stroke Study Group. Association of serial biochemical markers with acute ischemic stroke: the National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator Stroke Study. Stroke 2006; 37:2508-13.
7. Anderson L. Candidate-based proteomics in the search for biomarkers of cardiovascular disease. J Physiol 2005; 563 (Pt 1):23-60.
8. Fassbender K, Schmidt R, Schreiner A, et al. Leakage of brain-originated proteins in peripheral blood: temporal profile and diagnostic value in early ischemic stroke. J Neurol Sci 1997; 148:101-5.
9. Büttner T, Weyers S, Postert T, Sprengelmeyer R, Kuhn W. S-100 protein: serum marker of focal brain damage after ischemic territorial MCA infarction. Stroke 1997; 28:1961-5.

10. Missler U, Wiesmann M, Friedrich C, Kaps M. S-100 protein and neuron-specific enolase concentrations in blood as indicators of infarction volume and prognosis in acute ischemic stroke. Stroke 1997; 28:1956-60.
11. Herrmann M, Vos P, Wunderlich MT, de Bruijn CH, Lamers KJ. Release of glial tissue-specific proteins after acute stroke: a comparative analysis of serum concentrations of protein S-100B and glial fibrillary acidic protein. Stroke 2000; 31:2670-7.
12. Wunderlich MT, Wallesch CW, Goertler M. Release of neurobiochemical markers of brain damage is related to the neurovascular status on admission and the site of arterial occlusion in acute ischemic stroke. J Neurol Sci 2004; 227:49-53.
13. Moore BW. A soluble protein characteristic of the nervous system. Biochem Biophys Res Commun 1965; 19:739-44.
14. Kapural M, Krizanac-Bengez Lj, BarnettG, et al. Serum S-100beta as a possible marker of blood-brain barrier disruption. Brain Res 2002; 940:102-4.
15. Abraha HD, Butterworth RJ, Bath PM, et al. Serum S-100 protein, relationship to clinical outcome in acute stroke. Ann Clin Biochem 1997; 34 (Pt 5):546-50.
16. Foerch C, Singer OC, Neumann-Haefelin T, et al. Evaluation of serum S100B as a surrogate marker for long-term outcome and infarct volume in acute middle cerebral artery infarction. Arch Neurol 2005; 62:1130-4.
17. Dassan P, Keir G, Brown MM. Criteria for a clinically informative serum biomarker in acute ischaemic stroke: a review of S100B. Cerebrovasc Dis 2009; 27:295-302.
18. Foerch C, Otto B, Singer OC, et al. Serum S100B predicts a malignant course of infarction in patients with acute middle cerebral artery occlusion. Stroke 2004; 35:2160-4.
19. Garcia JH, Liu KF, Yoshida Y, Chen S, Lian J. Brain microvessels: factors altering their patency after the occlusion of a middle cerebral artery (Wistar rat). Am J Pathol 1994; 145:728-40.
20. Foerch C, du Mesnil de Rochemont R, Singer O, et al. S100B as a surrogate marker for successful clot lysis in hyper acute middle cerebral artery occlusion. J Neurol Neurosurg Psychiatry 2003; 74:322-5.

FIGURE

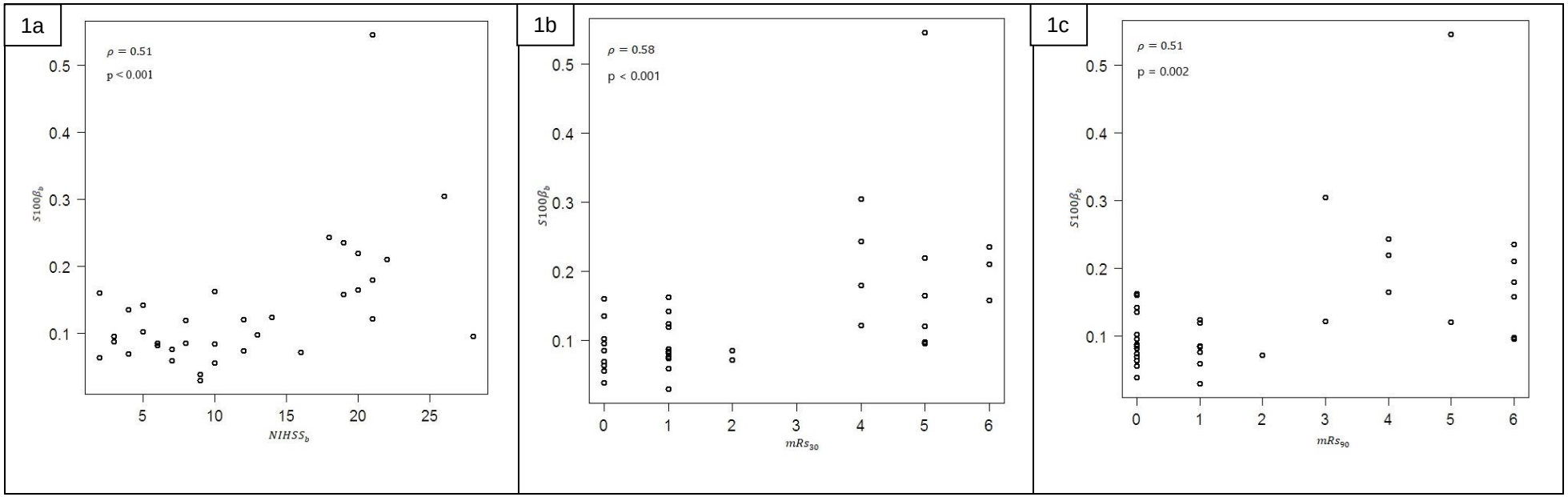

Fig. 1 Charts show correlation of $S100\beta_b$ with (a) $NIHSS_b$, (b) mRs_{30} and (c) mRS_{90}. mRs: modified Rankin Scale; mRs_{30}: mRs at 30 days after stroke; mRs_{90}: mRs at 90 days after stroke; $NIHSS_b$: National Institute of Health and Stroke Scale at baseline; $S100\beta_b$: serum S100β at baseline

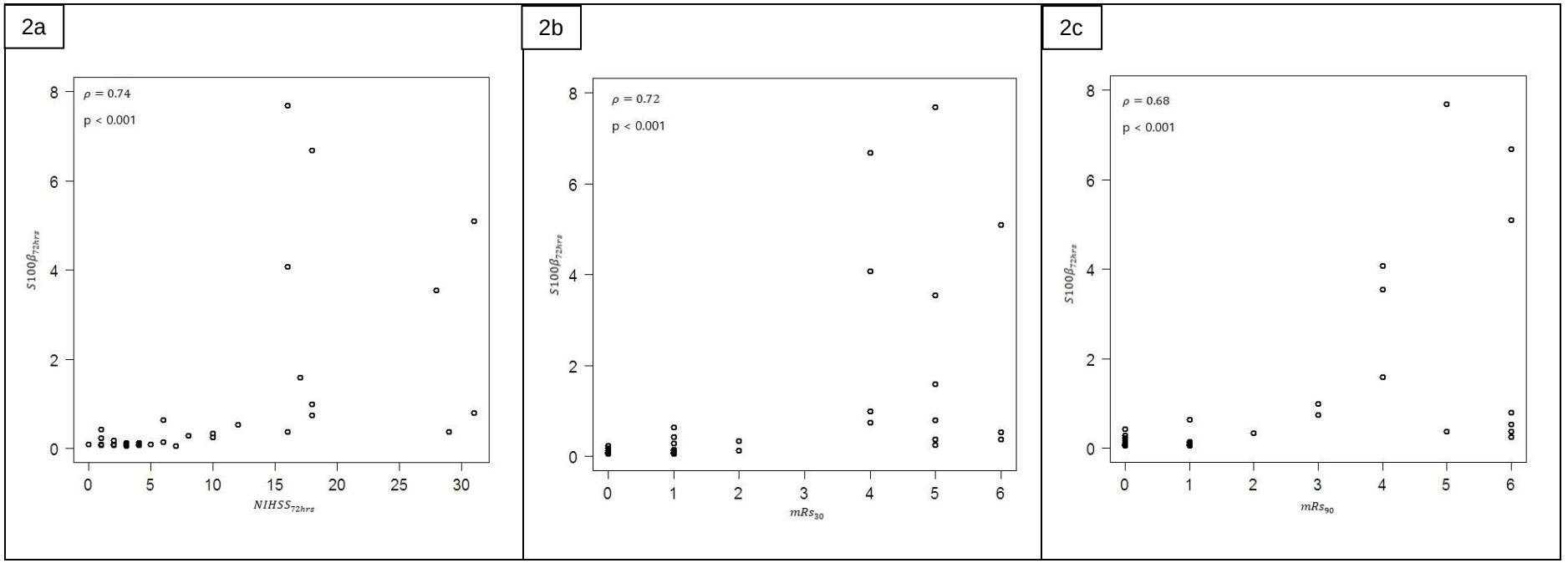

Fig. 2 Charts show correlation of $S100\beta_{72hrs}$ with (a) $NIHSS_{72hrs}$, (b) mRs_{30} and (c) mRS_{90}. mRs: modified Rankin Scale; mRs_{30}: mRs at 30 days after stroke; mRs_{90}: mRs at 90 days after stroke; $NIHSS_{72hrs}$: National Institute of Health Stroke Scale at 72 hr after stroke onset; $S100\beta_{72hrs}$: serum S100β at 72 hr after stroke onset

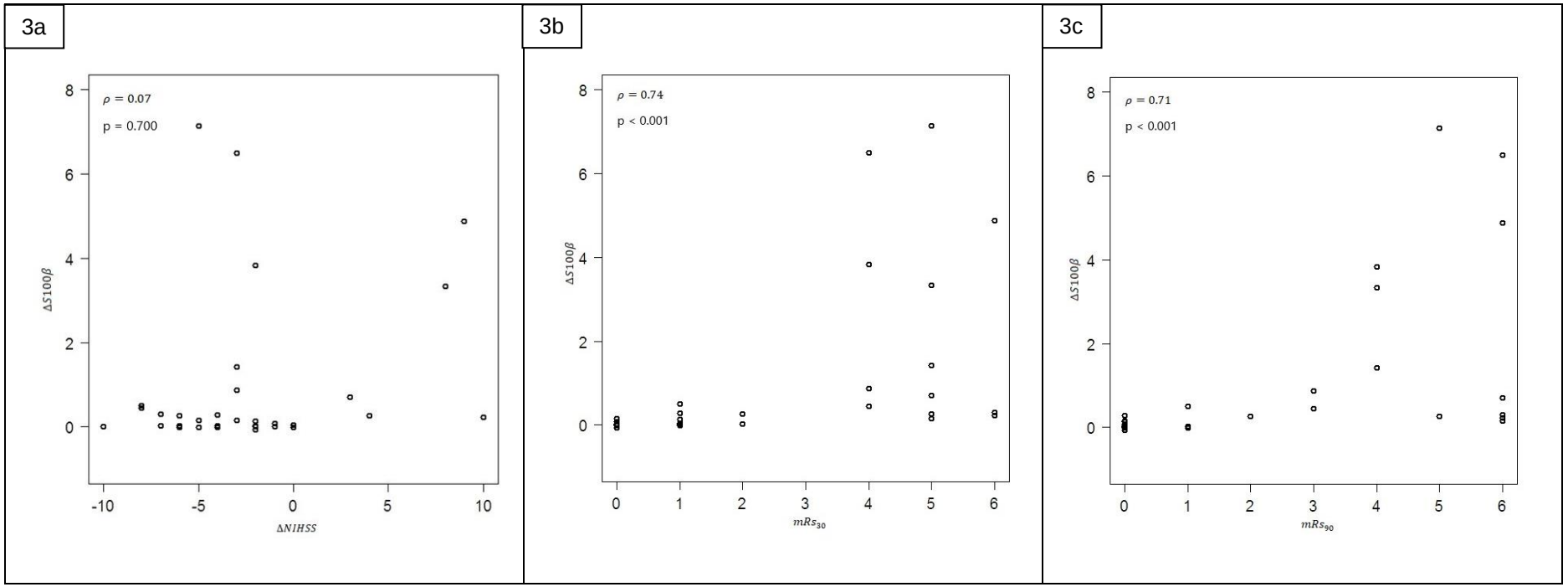

Fig. 3 Charts show correlation of ΔS100β with (a) ΔNIHSS, (b) mRs_{30} and (c) mRS_{90}. ΔNIHSS: difference between National Institute of Health and Stroke Scale at baseline and at 72 hr after stroke onset; ΔS100β: difference between serum S100β at baseline and at 72 hr after stroke onset; mRs: modified Rankin Scale; mRs_{30}: mRs at 30 days after stroke; mRs_{90}: mRs at 90 days after stroke