PREDICTIVE VALUE OF PLASMA FIBRINOGEN LEVELS FOR OUTCOME OF ANEURYSMAL SUBARACHNOID HAEMORRHAGE DURING THE FIRST WEEK OF ILLNESS

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ABSTRACT

Objectives: Aneurysmal subarachnoid haemorrhage (SAH) is an acute cerebrovascular event characterised by the rupture of an aneurysm within the subarachnoid space. Secondary injuries increase both mortality and morbidity in patients who survive the primary haemorrhage. Inflammation and coagulation play critical roles in the pathophysiology of SAH. Fibrinogen is involved in both, yet despite wide availability, its prognostic value in aneurysmal SAH is not clear.

Material and methods: A prospectively collected database of 97 aneurysmal SAH patients was reviewed for plasma fibrinogen level results. All patients admitted within 24 hours of aneurysm rupture and treated endovascularly within 48 hours were included. The outcome was assessed at three months according to the Glasgow Outcome Scale (GOS). Correlation with the outcome and analysis for patients' death and unfavourable outcome were performed.

Results: Fibrinogen level on day 2 significantly correlates with GOS at 3 months. The analysis for mortality revealed that high levels of fibrinogen on days 1, 2 and 3-4 were significant, but not independent predictors for mortality. Univariate analysis for unfavourable outcome indicated no significant prognostic value of fibrinogen levels. Statistically significant elevation of fibrinogen level was found on day 2 in patients with an intraventricular haematoma ($p < 0.01$). We also noted that fibrinogen level was elevated in patients with a Glasgow Coma Scale score less than 13 ($p = 0.013$).

Conclusions: Fibrinogen level might serve as an accessory prognostic tool for patients' death. Fibrinogen level was significantly elevated in patients with intraventricular haematoma and in patients with a poor clinical condition on admission.

Key words: subarachnoid haemorrhage, early brain injury, outcome.

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INTRODUCTION

The annual incidence of cerebral aneurysm rupture is 1 in 10,000 for the general population. This devastating condition kills or severely disables 70% of victims [1-3]. Those who survive aneurysmal haemorrhage often suffer delayed ischaemic neurological deficits (DINDs). Unfortunately, despite the significant consequences of DINDs, prompt diagnosis can be elusive, and may result in delay of administering effective treatment and compromise patient outcome. Despite the improvement of treatment options, the outlook remains serious. Therefore, all available data should be used to characterise adverse factors and indicate pathophysiological mechanisms leading to deterioration [4]. Currently, the most widely used markers of aneurysmal subarachnoid haemorrhage (SAH) prognosis are age, neurological state, volume of subarachnoid blood measured by computed tomography (CT) at admission, pre-existing hypertension, and complications such as aneurysmal rebleeding or angiographic vasospasm [5, 6]. Several scales, including the Glasgow Outcome Scale (GOS) [7], Hunt and Hess scale (HH) [8], World Federation of Neurological Societies scale (WFNS) [9], and Fisher scale [10], are known to be associated with SAH clinical outcomes [11]. It has been suggested that factors other than SAH

alone may play a role in the development of vasospasm. The possibility of exploring genetic links to vasospasm was raised by Rabb *et al.* in 1994 [12]. Early brain injury (EBI), defined as damage sustained within 72 hours of the ictus, has been attributed to an interplay between alterations in cerebral blood flow (CBF) autoregulation, disrupted cerebral metabolism, altered permeability of the blood-brain barrier (BBB), as well as inflammatory cytokines, leukocytes and pro-thrombotic pathways [13, 14]. Results from CONSCIOUS trials have suggested that early brain injury immediately follows SAH and precedes the onset of delayed vasospasm [15-17]. EBI is a result of increased intracranial pressure and decreased CBF, causing cerebral ischaemia. These early events are followed by neuroinflammation, BBB breakdown, and neuronal apoptosis [18, 19]. After SAH, brain injuries from the initial haemorrhage occurring within 72 hours and cerebral vasospasm developing 3-7 days after rupture are the most important causes of mortality and morbidity [20]. Numerous studies suggest that inflammation and coagulation play key roles in the pathophysiology of SAH and contribute to the functional and cognitive outcomes [21-23]. Identifying a plasma biomarker with early prognostic value for SAH outcome is attracting increased attention [24, 25] and could aid in identifying high-risk patients, guide treatment and improve outcome. Unfortunately, clinically reliable blood biomarkers are still not available. In this study, changes in plasma fibrinogen levels were measured in patients diagnosed with SAH in an attempt to correlate levels of this biomarker with clinical outcomes.

MATERIAL AND METHODS

Patient population

This prospective observational study was conducted at a single academic tertiary care centre over a one-year period. All patients were admitted within 24 hours of confirmed aneurysmal SAH. The diagnosis was based on computed tomography and catheter angiography. None of the enrolled patients had a history of any chronic neurological disorder or chronic inflammatory disease; there was no history of surgical procedures or nosocomial infection within four weeks of SAH onset. All patients underwent cerebral angiography with arterial catheterisation or multislice CT angiography within 48 hours of onset.

Ethics and consent

This prospective observational study was conducted in accordance with the Declaration of Helsinki. The Poznan University of Medical Sciences Bioethics Committee approved the study protocol, consenting protocol and consent forms. Patients were assessed by two specialists (a neurosurgeon and an anaesthesiologist) as to their ability to give informed consent for inclusion in the study, and permission to use blinded medical data for analysis and publication.

Population: inclusion and exclusion criteria

Ninety-seven patients with SAH (confirmed by non-contrast CT) were referred to our department during the study recruitment period from October 2015 to October 2016. Data were collected prospectively and analysed retrospectively. All patients had an aneurysmal SAH treated endovascularly within 48 hours of rupture. Exclusion criteria were: 1) history of central nervous system (CNS) disease, 2) active CNS infection, 3) active systemic disease (diabetes mellitus, rheumatoid arthritis, malignancy, cirrhosis, renal failure), 4) age under 18, 5) pregnancy.

Management, definitions, endpoints

On admission the clinical status was assessed using the GCS and specific SAH-grading scales (HH [26], WFNS [27]). Patients received a continuous infusion of nimodipine for at least ten days, hypotension was avoided using vasopressors and euvolaemia was maintained. Induced hypertension (20-30% above baseline levels) was used to treat patients diagnosed with delayed cerebral ischaemia (DCI), based on the appearance of a new focal deficit, or a drop of at least two points on the GCS lasting at least two hours after the exclusion of systematic causes. The primary end point was the treatment outcome assessed at three months using GOS [28]. Patients were divided into two groups according to the GOS. The good outcome group consisted of those with no disability, moderate disability or severe disability (GOS grades 5, 4 and 3); the poor outcome group consisted of those with a persistent vegetative state or death (GOS grades 2 and 1). DCI-related infarction was defined as a new cerebral infarction identified on a head CT scan within six weeks of rupture and not present on the immediate post-treatment scan (as proposed by Vergouwen *et al.* [17]).

Fibrinogen assay

During hospitalisation, decisions regarding type and timing of laboratory tests (including fibrinogen levels) were left solely to the judgement of the physician. Consequently, the number of subjects available for analysis at each time point varied. The fibrinogen level was assessed using the automatic analyser ACL TOP 500 (Instrumentation Laboratory, Italy).

Statistical analysis

Statistica 12 software (Stat Soft Inc., Tulsa, OK, USA) was used to perform all analyses. The Shapiro-Wilk test was used to test the normality of the data distribu-

Table 1. Patient characteristics

Variables	Descriptive statistics
	n = 97 (%)
Male	47 (48)
Age (years)	56.0 ±14.2
Aneurysm location	
Middle cerebral artery	22 (22.7)
Anterior communicating artery	27 (27.8)
Internal carotid artery	22 (22.7)
Anterior cerebral artery	7 (7.2)
Basilar artery	10 (10.3)
Posterior cerebral artery	1 (1)
Vertebral artery	3 (3.1)
Posterior inferior cerebellar artery	5 (5.2)
Aneurysmal size (mm)	5.5 ±2.8
Fisher CT scale	4 (4; 4)
Modified Fisher CT scale	3 (2; 4)
HH grade on admission	4 (2; 5)
WFNS grade on admission	4 (2; 5)
GCS on admission	7 (4; 13)
Treatment outcome according to GOS at 3 months	
5 (no/low disability)	19 (19.6)
4 (moderate disability)	10 (10.3)
3 (severe disability)	25 (25.8)
2 (persistent vegetative state)	13 (13.4)
1 (death)	30 (30.9)

Values are presented as: 1) mean ±standard deviation for numerical data, 2) median (lower quartile, upper quartile) for ordinal data, 3) count (percentage) for categorical/ordinal data. WFNS – World Federation of Neurosurgical Societies scale; HH – Hunt and Hess scale; GCS – Glasgow Coma Scale; GOS – Glasgow Outcome Scale.

tion. Student's t-test, Cochran-Cox correction, and the Mann-Whitney test were used for pairwise comparisons, i.e. favourable vs. unfavourable outcome, and survivors vs. non-survivors. Spearman's test was used to assess correlation: a correlation coefficient (cc) of > 0.4 or < –0.4 was considered significant. To identify independent prognostic factors for unfavourable outcome and mortality, univariate and multivariate logistic regression analysis adjusted for HH and age was performed as appropriate.

RESULTS

Ninety-seven subjects (45% males; mean 56 years) were included in the study based on the availability of fibrinogen assay data. On admission, 57% of patients were classified as poor grade (HH grades 4 and 5). At three months, 69% of patients had an unfavourable outcome (GOS scores 1-3), including 31% who died (Table 1). Pairwise comparison of favourable and unfavourable treatment outcome groups is presented in Table 2. Both age ($p = 0.0226$) and clinical status on admission ($p < 0.0001$ on all three scales) differed significantly between the two groups. The fibrinogen level was unable to differentiate between the favourable and unfavourable groups (Fig. 1). Table 3 and Figure 2 present a pairwise comparison of survivors and non-survivors. Analysis showed that clinical status on admission was significantly different between the groups ($p \leq 0.0001$ on all three scales), but the age rating did not reach significance ($p = 0.0642$). Significantly higher fibrinogen levels on day 2 ($p = 0.0302$) and day 3-4 ($p = 0.0459$) were found in non-survivors (Fig. 2). Correlation analysis for this cohort (Table 4) showed the closest correlation with admission status; the coefficient was –0.679, –0.699 and –0.630 for the GCS, HH and WFNS scores, respectively. There was a significant association between outcome and

Table 2. Comparison between favourable and unfavourable outcome in subarachnoid haemorrhage patients

Variables	Favourable outcome		Unfavourable outcome		*p*-value
	n	mean ±SD/median (Q1; Q3)	*n*	mean ±SD/median (Q1; Q3)	
Age	29	51.0 ±14.9	68	58.1 ±13.4	0.0226*
HH on admission	29	2 (2; 3)	68	5 (4; 5)	< 0.0001*
WFNS on admission	29	1 (1; 3)	68	5 (4; 5)	< 0.0001*
GCS on admission	29	15 (12; 15)	68	6 (3; 9)	< 0.0001*
Fibrinogen (mg/dl), day 0	16	282.3 ±73.5	30	306.2 ±98.5	0.3993
Fibrinogen (mg/dl), day 1	9	274.7 ±83.4	29	348.1 ±130.1	0.1591
Fibrinogen (mg/dl), day 2	9	391.4 ±116.8	20	472.5 ±141.6	0.1454
Fibrinogen (mg/dl), days 3-4	11	447.5 ±177.0	36	603.6 ±251.4	0.0875
Fibrinogen (mg/dl), days 5-7	6	703.8 ±243.7	40	726.4 ±225.4	0.8218
Fibrinogen (mg/dl), days 9-11	6	703.3 ±231.7	37	673.7 ±247.7	0.7855

*Statistical significance for pairwise comparisons between the groups of death/survivor was tested by Student's t-test, Cochran-Cox correction or the Mann-Whitney test as appropriate. Values are presented as: 1) mean ±standard deviation for numerical data, 2) median (lower quartile, upper quartile) for ordinal data. *significant p-value. GCS – Glasgow Coma Scale; HH – Hunt and Hess scale; Q – quartile; SD – standard deviation; WFNS – World Federation of Neurosurgical Societies scale*

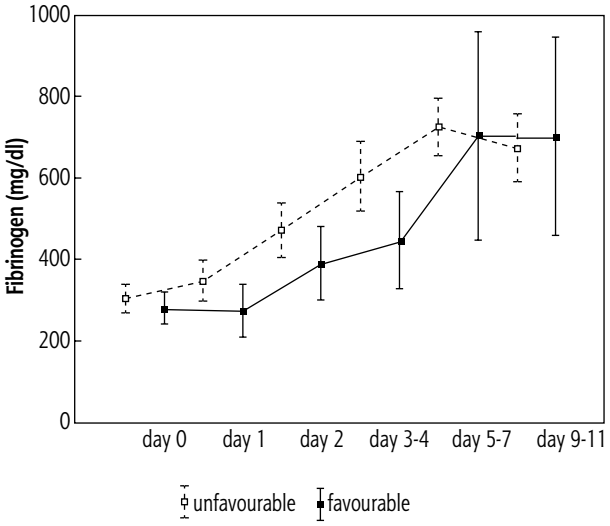

Fig. 1. Changes in plasma fibrinogen level in time in patients with favourable and unfavourable treatment outcome

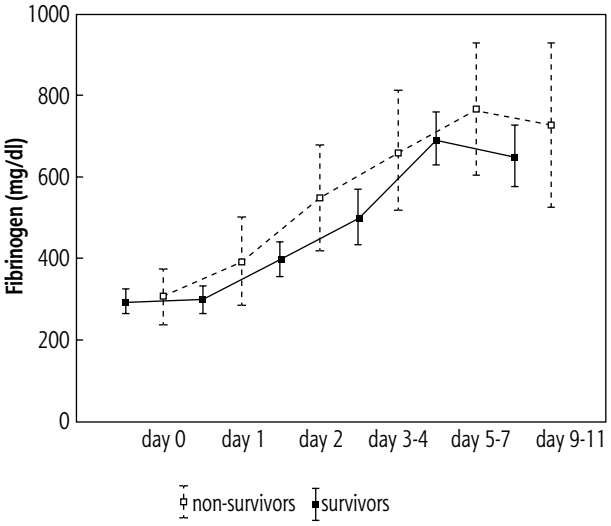

Fig. 2. Changes in plasma fibrinogen level in time in survivors and non-survivors of subarachnoid haemorrhage

Table 3. Comparison between survivors and non-survivors of subarachnoid haemorrhage

Variables	Survivors		Non-survivors		*p*-value
	n	mean ±SD/median (Q1; Q3)	*n*	mean ±SD/median (Q1; Q3)	
Age	67	54.5 ±14.0	30	59.3 ±14.3	0.0642
HH on admission	67	3 (2; 4)	30	5 (5; 5)	< 0.0001*
WFNS on admission	67	4 (1; 5)	30	5 (4; 5)	0.0001*
GCS on admission	67	12 (6; 15)	30	4 (3; 6)	< 0.0001*
Fibrinogen (mg/dl), day 0	34	294.5 ±85.0	12	307.6 ±108.1	0.6718
Fibrinogen (mg/dl), day 1	26	301.1 ±84.9	12	394.8 ±169.1	0.0921
Fibrinogen (mg/dl), day 2	20	400.5 ±92.1	9	551.6 ±168.7	0.0302*
Fibrinogen (mg/dl), days 3-4	29	504.0 ±178.7	18	668.6 ±300.5	0.0459*
Fibrinogen (mg/dl), days 5-7	31	700.2 ±182.7	15	771.5 ±296.1	0.4025
Fibrinogen (mg/dl), days 9-11	31	656.5 ±207.9	12	732.9 ±321.1	0.3615

*Statistical significance for pairwise comparisons between the groups of death/survivor was tested by Student's t-test, Cochran-Cox correction or the Mann-Whitney test as appropriate. Values are presented as: 1) mean ±standard deviation for numerical data, 2) median (lower quartile, upper quartile) for ordinal data. *significant p-value. Q – quartile; SD – standard deviation; HH – Hunt and Hess scale; WFNS – World Federation of Neurosurgical Societies scale; GCS – Glasgow Coma Scale*

fibrinogen level on day 2 (cc = –0.476), independent of age (cc = –0.229). Univariate analysis of the unfavourable outcomes confirmed that fibrinogen levels failed to differentiate between the two groups (Table 5). However, univariate analysis for mortality indicated that the fibrinogen level on day 1 (OR = 1.90 [1.02; 3.57], $p = 0.0444$), day 2 (OR = 2.87 [1.15; 7.15], $p = 0.0239$) and day 3-4 (OR = 1.37 [1.02; 1.85], $p = 0.0379$) were predictors for mortality. Despite this, multivariate analysis adjusted for age and HH scores showed that the fibrinogen level was not an independent predictor (Table 6). We also analysed the relationship between fibrinogen level on day 2 post-SAH, clinical condition on admission and the extent of haemorrhage in imaging studies (Table 7). We found a statistically significant elevation of fibrinogen level on day 2 (correlating with treatment outcome) in patients with an intraventricular haematoma ($p < 0.01$). We also noted that fibrinogen level was elevated in patients with a GCS score less than 13 ($p = 0.013$).

DISCUSSION

Changes of coagulation and fibrinolytic mechanisms in relation to SAH have been analyzed since 1970 [29]. Elevated fibrinogen level is associated with the severity of the ischaemic event [30], and a sustained increase in

the fibrinogen level during a stroke reduces the prospect of a favourable outcome [31]. Patients with DINDs have been reported to have higher levels of fibrinogen on days 3, 6 and 14 [32]. Our study demonstrated a significant difference in fibrinogen levels between survivors and non-survivors on days 1, 2 and 3-4. There was a constant increase in fibrinogen level on consecutive days following SAH with a significant negative correlation between GOS and fibrinogen on day 2. Univariate analysis confirmed that the fibrinogen level on day 2 was a predictor for mortality; however, multivariate analysis showed it was not independent of the HH score. Patient's age and clinical status at admission were correlated with outcome. Increased fibrinogen levels at baseline and post-SAH days 1 to 4 were observed but were not significantly correlated with outcome. Multivariate analysis adjusted for age and HH scores showed that the fibrinogen level was not an independent predictor. Fibrinogen levels were significantly elevated in patients with intraventricular haematoma. On day 2 fibrinogen level was also significantly elevated in patients with a GCS score less than 13. It is therefore difficult to predict whether fibrinogen level changes represent activation of the coagulation system as the response to the severity of brain tissue damage. Coagulation and inflammation are intricately related processes. A combination of ischaemia and hypoxia precipitates platelet accumulation and fibrinogen deposition almost immediately [33]. Fibrinogen is an acute-phase coagulation factor produced by hepatocytes and is activated by thrombin to form fibrin monomers and polymers [34]. The early blood flow reduction is postulated to be due to microcirculatory constriction and microthrombosis. Platelet aggregates are found in the major cerebral arteries within two hours of experimental SAH [35]. The elevation of fibrinogen might represent microclot formation within 24 h after SAH [36]. This might be one reason for the beneficial effect of nimodipine [37], which may improve recovery from ischaemia by increasing fibrinolytic activity [38]. On the other hand, previous studies

Table 4. Correlation between patient age, clinical status on admission, fibrinogen level and outcome

Variables	*n*	Correlation coefficient	*p*-value
Age	97	–0.229	0.0240
HH on admission	**97**	**–0.669**	**< 0.0001**
WFNS on admission	**97**	**–0.630**	**< 0.0001**
GCS score on admission	**97**	**0.679**	**< 0.0001**
Fibrinogen day 0	46	–0.123	0.4136
Fibrinogen day 1	38	–0.309	0.0588
Fibrinogen day 2	**29**	**–0.476**	**0.0090**
Fibrinogen days 3-4	47	–0.358	0.0135
Fibrinogen days 5-7	46	–0.100	0.5075
Fibrinogen days 9-11	43	–0.052	0.7411

Outcome assessed using Glasgow Outcome Scale at 3 months. Statistical significance was tested by Spearman's rank correlation test. Correlation coefficient > 0.4 or < –0.4 was considered significant and shown in bold. HH – Hunt and Hess scale; WFNS – World Federation of Neurosurgical Societies scale; GCS – Glasgow Coma Scale

Table 5. Univariate and multivariate logistic regression analysis for unfavourable outcome

Variables	Univariate analysis		Multivariate analysis*	
	OR (95% CI)†	*p*-value	OR (95% CI)†	*p*-value
Age	**1.04 (1.00; 1.07)**	**0.0262**	–	–
HH on admission	**3.52 (2.13; 5.81)**	**< 0.0001**	–	–
WFNS on admission	**2.73 (1.86; 4.01)**	**< 0.0001**	–	–
GCS on admission	**0.71 (0.61; 0.82)**	**< 0.0001**	–	–
Fibrinogen (mg/dl), day 0	1.36 (0.67; 2.78)	0.3917	1.18 (0.34; 4.08)	0.7949
Fibrinogen (mg/dl), day 1	1.99 (0.81; 4.86)	0.1325	2.63 (0.58; 12.00)	0.2105
Fibrinogen (mg/dl), day 2	1.72 (0.82; 3.63)	0.1517	1.46 (0.45; 4.73)	0.5292
Fibrinogen (mg/dl), days 3-4	1.48 (0.97; 2.25)	0.0681	1.36 (0.78; 2.38)	0.2798
Fibrinogen (mg/dl), days 5-7	1.05 (0.71; 1.54)	0.8170	1.07 (0.66; 1.74)	0.7921
Fibrinogen (mg/dl), days 9-11	0.95 (0.67; 1.35)	0.7795	1.01 (0.67; 1.52)	0.9541

**Model adjusted for age and HH scale; †odds ratio corresponds to increase of 100 mg/dl in fibrinogen level and a unit increase in the rest of variables. Significant results are bolded. OR – odds ratio; CI – confidence interval; HH – Hunt and Hess scale; WFNS – World Federation of Neurosurgical Societies scale; GCS – Glasgow Coma Scale*

Table 6. Univariate and multivariate logistic regression analysis for mortality

Variables	Univariate analysis		Multivariate analysis*	
	OR (95% CI)†	*p*-value	OR (95% CI)†	*p*-value
Age	1.03 (0.99; 1.06)	0.1315	–	–
HH on admission	**3.10 (1.71; 5.61)**	**0.0002**	–	–
WFNS on admission	**2.29 (1.39; 3.78)**	**0.0011**	–	–
GCS on admission	**0.75 (0.65; 0.87)**	**0.0001**	–	–
Fibrinogen (mg/dl), day 0	1.17 (0.57; 2.42)	0.6641	0.93 (0.31; 2.77)	0.8946
Fibrinogen (mg/dl), day 1	**1.90 (1.02; 3.57)**	**0.0444**	1.90 (0.89; 4.07)	0.0968
Fibrinogen (mg/dl), day 2	**2.87 (1.15; 7.15)**	**0.0239**	2.26 (0.84; 6.06)	0.1055
Fibrinogen (mg/dl), days 3-4	**1.37 (1.02; 1.85)**	**0.0379**	1.33 (0.93; 1.92)	0.1228
Fibrinogen (mg/dl), days 5-7	1.16 (0.87; 1.53)	0.3139	1.30 (0.95; 1.78)	0.1055
Fibrinogen (mg/dl), days 9-11	1.14 (0.86; 1.50)	0.3541	1.21 (0.89; 1.64)	0.2156

**Model adjusted for HH scale; †odds ratio corresponds to increase of 100 mg/dl in fibrinogen level and a unit increase in the rest of variables. Significant results are bolded. OR – odds ratio; CI – confidence interval; HH – Hunt and Hess scale; WFNS – World Federation of Neurosurgical Societies scale; GCS – Glasgow Coma Scale*

Table 7. Relationship of fibrinogen level on post-subarachnoid haemorrhage day 2 to clinical condition on admission and extent of haemorrhage on imaging studies

Variables	Yes		No		*p*-value
	n	mean ±SD	*n*	mean ±SD	
Intraventricular haematoma	21	492.4 ±133.2	8	329.1 ±55.3	< 0.01*
Intracerebral haematoma	15	458.7 ±119.8	14	435.2 ±158.3	0.655
Intraventricular and intracerebral haematoma	13	483.2 ±105.7	16	418.1 ±156.2	0.100
Good clinical condition on admission (GCS 15-13)	9	355.8 ±87.6	20	488.6 ±137.6	0.013*

**Significant results; GCS – Glasgow Coma Scale; SD – standard deviation*

have also shown that nimodipine is an effective cerebral vasodilator, making it useful in the treatment of cerebral vasospasm [39]. Fibrinogen and its degradation products have a prominent role in the regulation of the inflammatory response in several target tissues [40]. Pathological conditions such as injury, or disease associated with vascular disruption, infection or inflammation, increase the blood concentration of fibrinogen several fold [40]. Fibrinogen has been shown to activate the proinflammatory NF-κβ pathway, which results in the local production of inflammatory cytokines TNF-α and IL-1β [41-43]. Fibrinogen signals either directly or indirectly through a number of other receptors, adhesion molecules and cell-surface proteins that are involved in the inflammatory processes. For example, the toll-like receptor 4 (TLR-4) related to SAH [44] has been implicated in the induction of macrophage activation and the release of several chemokines and cytokines [45, 46]. Some authors have reported increased levels of TAT, thrombin/antithrombin complex (a marker for activation of the coagulation cascade), and D-dimer (marker for plasmatic fibrinolysis) and their association with poor outcome. Additionally, the correlation between fibrinogen and outcome varied and therefore was inconclusive [47-49].

CONCLUSIONS

This study was designed to investigate the association between plasma fibrinogen levels and patient outcome following SAH. There were three limitations: firstly, data were collected prospectively and analysed retrospectively; secondly, the number of readings available was limited; thirdly, plasma levels may not precisely reflect local changes at the site of SAH. For the patient population in this study, we found a significant negative correlation between GOS and plasma fibrinogen level on day two after SAH. We also found that elevation of fibrinogen levels on day 2 and days 3-4 after SAH was associated with increased mortality. Larger prospective studies will be required to reassess fibrinogen levels following SAH and establish whether they have a role in the development of DINDs. Fibrinogen level on the second day after SAH was significantly elevated in patients with intraventricular haematoma. This significance was not present

in patients with intracerebral haematoma. Patients with a poor clinical condition on admission also had elevated fibrinogen levels on day two.

The authors declare no conflict of interest.

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