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ORIGINAL ARTICLE

Early Systemic Procalcitonin Levels in Patients with Aneurysmal Subarachnoid Hemorrhage

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Abstract
Background Early (≤24 h) systemic procalcitonin (PCT) levels are predictive for unfavorable neurological outcome in patients after out-of-hospital cardiac arrest (OHCA). Subarachnoid hemorrhage (SAH) due to aneurysm rupture might lead to a cerebral perfusion stop similar to OHCA. The current study analyzed the association of early PCT levels and outcome in patients after SAH.
Methods Data from 109 consecutive patients, admitted within 24 h after SAH, were analyzed. PCT levels were measured within 24 h after ictus. Clinical severity was determined using the World Federation of Neurological Societies (WFNS) scale and dichotomized into severe (grade 4–5) and non-severe (1–3). Neurological outcome after 3 months was assessed by the Glasgow outcome scale and dichotomized into unfavorable (1–3) and favorable (4–5). The predictive value was assessed using receiver operating curve (ROC) analysis.
Results Systemic PCT levels were significantly higher in patients with severe SAH compared to those with non-severe SAH: 0.06 ± 0.04 versus 0.11 ± 0.11 μg/l (median ± interquartile range; $p < 0.01$). Patients with unfavorable outcome had significantly higher PCT levels compared to those with favorable outcome 0.09 ± 0.13 versus 0.07 ± 0.15 ng/ml ($p < 0.01$). ROC analysis showed an area under the curve of 0.66 ($p < 0.01$) for PCT, which was significantly lower than that of WFNS with 0.83 ($p < 0.01$).
Conclusions Early PCT levels in patients with SAH might reflect the severity of the overall initial stress response. However, the predictive value is poor, especially compared to the reported predictive values in patients with OHCA. Early PCT levels might be of little use in predicting neurological outcome after SAH.

Keywords Early brain injury · Outcome · Procalcitonin · Subarachnoid hemorrhage

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Introduction

Current evidence suggests that treatment of cerebral vasospasm (CVS) alone does not avoid the occurrence of neuronal injury, i.e., delayed cerebral ischemia (DCI), with consequent poor outcome in patients with aneurysmal subarachnoid hemorrhage (aSAH) [1, 2]. More recently, mechanisms of early brain injury have moved center stage in the research focus. It has been suggested that these mechanisms evolve with time and contribute to the pathogenesis of DCI [3, 4]. The rupture of an aneurysm and consequent release of blood into the subarachnoid space leads to an abrupt increase of the intracranial pressure (ICP), which is suggested to cause a brief cerebral perfusion arrest [4].

Out-of-hospital cardiac arrest (OHCA) is associated with brief cerebral perfusion stop as well. More recently, early elevated systemic procalcitonin (PCT) levels have

been described to accurately predict unfavorable neurological outcome after OHCA [5–7]. Increased PCT levels have been sparsely described with regard to the course of illness after aSAH [8, 9]. However, the prognostic value of early PCT levels in patients with aSAH is unknown. The current study intended to evaluate the prognostic value of early PCT levels on the neurological outcome after aSAH.

Materials and Methods

The database consisted of prospectively collected data of 231 patients with confirmed aSAH, admitted at the Neurocritical Care Unit, University Hospital Zurich (an academic tertiary care center), during a 3-year period, from 2007 to 2009. In brief, the diagnosis was based on either CT or catheter angiography. The clinical severity at time of admission was assessed according to the World Federation of Neurological Surgeons (WFNS) grading [10]. The radiological severity was assessed based on the Fisher grading [11]. All patients were treated according to a standardized treatment protocol as previously described [12, 13]. Neurological outcome was assessed 3 months after aSAH in the outpatient clinic according to the Glasgow outcome scale (GOS). For the current study only patients with admission and PCT level measured within 24 h after ictus were included. Patients with rebleeding after admission were also excluded. The study was approved by the local ethics committee.

PCT measurements were performed by the Institute of Clinical Chemistry, University Hospital Zurich, using an electrochemiluminescence immunoassay. Blood sampling and measurements were performed in terms of clinical routine, i.e., no additional blood sampling was performed. Having a potential influence on the PCT levels, we assessed the presence of a systemic inflammatory response syndrome (SIRS) and pneumonia at time of admission [14]. As the assessment and interpretation of classic SIRS symptoms was hampered in the current study population [15, 16], the presence of SIRS was assumed when ≥ 2 of the following conditions were present: Body temperature >38.5 °C, leukocyte count $<4{,}000/\mu l$ or $>12{,}000/\mu l$, and volume-resistant shock syndrome with the need of epinephrine >30 µg/min. Pneumonia was assumed to be present if specific signs of alveolar infiltrate on chest X-ray and microorganisms from tracheobronchial secretion cultures were present.

Categorical variables were described using frequency and percentage. Patients' ages were given as mean ± standard deviation (SD). PCT levels were given as median ± interquartile range (IQR) due to its variance. For statistical analysis, WFNS grade was dichotomized into clinically severe (WFNS 4–5) and non-severe (WFNS 1–3) and GOS in unfavorable (GOS 1–3) and favorable (GOS 4–5). Binominal variables were compared between the groups by the Fisher's exact test, and continuous variables by the independent *t* test. PCT values were compared using the Mann–Whitney U or Kruskal–Wallis test, as normal distribution was not present. Receiver operating characteristics (ROC) analysis was performed to assess and compare the predictive value of early PCT values with known predictors. Sensitivity and specificity were calculated using the cut-off value of 0.50 ng/ml for PCT, which has been described as optimal in patients with OHCA [5, 6]. A p value <0.05 was regarded as statistically significant. IBM SPSS Statistics 20.0 Software was used.

Results

Out of 231 patients, a total of 109 (47 %) fulfilled the inclusion criteria. The patients' characteristics are summarized in Table 1. Unfavorable neurological outcome after 3 months was observed in 32 patients (29 %). Two of them underwent cardio-pulmonary resuscitation prior to admission. As expected, patients with unfavorable outcome presented with clinically and radiologically severe aSAH (both $p < 0.01$) and tended to be more elderly ($p = 0.05$). The presence of SIRS was higher in patients with unfavorable outcome, however, without any statistical significance. Ruptured aneurysm location and the assumed presence of pneumonia at time of admission were statistically not different. The results are summarized in Table 1. Systemic PCT levels were significantly higher in patients with severe than in patients with non-severe aSAH: 0.06 ± 0.04 versus 0.11 ± 0.11 µg/l ($p < 0.01$) (Fig. 1a). Patients with radiologically severe aSAH also had higher PCT levels; however, there was no statistical significance between patients presenting with Fisher 1–2 and 3 (Fig. 1b). Furthermore, systemic PCT levels within 24 h after ictus were significantly higher in patients with unfavorable compared to patients with favorable outcome: 0.09 ± 0.13 versus 0.07 ± 0.15 ng/ml ($p < 0.01$) (Fig. 1c). Two patients underwent cardio-pulmonary resuscitation prior to admission. Both of them also had a clinically and radiologically severe bleeding. PCT levels at admission were 0.29 and 0.68 ng/ml, respectively. Both patients survived. However, functional outcome was unfavorable.

The ROC curve analysis showed an area under the curve (AUC) of 0.66 ($p < 0.01$; 95 % CI: 0.55–0.77) for PCT, 0.64 ($p = 0.02$; 95 % CI: 0.53–0.75) for age, 0.83 ($p < 0.01$; 95 % CI: 0.74–0.91) for WFNS, and 0.68 ($p < 0.05$; 95 % CI: 0.57–0.79) for Fisher grade (Fig. 2). Analysis of the combined predictive probability (age, WFNS, and Fisher grade) with and without PCT revealed

Table 1 Patients characteristics

	All patients ($n = 109$)	GOS 1–3 ($n = 32$)	GOS 4–5 ($n = 77$)	Sig.
Sex				
Female	67 (62 %)	23 (72 %)	44 (57 %)	$p = 0.196$
Male	42 (38 %)	9 (28 %)	33 (43 %)	
Age	54.0 ± 13.8	58 ± 13.8	52.3 ± 13.5	$p = 0.050$
WFNS Grade				
1–3	65 (60 %)	7 (22 %)	58 (75 %)	$p < 0.001$
4–5	44 (40 %)	25 (76 %)	19 (25 %)	
Aneurysm location				
Anterior circulation	82 (75 %)	24 (75 %)	58 (75 %)	$p > 0.999$
Posterior circulation	27 (25 %)	8 (25 %)	24 (25 %)	
SIRS	7 (6 %)	4 (13 %)	3 (4 %)	$p = 0.191$
Pneumonia	4 (4 %)	2 (6 %)	2 (3 %)	$p = 0.579$

GOS Glasgow outcome scale, *Sig* significance, *SIRS* systemic inflammatory response syndrome, *WFNS* world federation of neurological surgeons

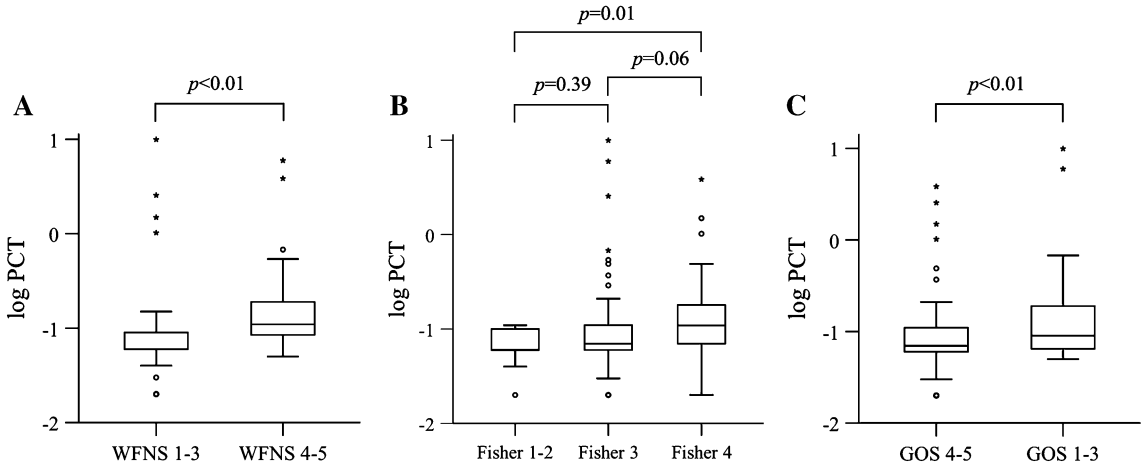

Fig. 1 PCT levels (≤24 h) shown as box-plots. **a** Patients with clinically severe aSAH (WFNS 4–5) had significantly higher PCT levels. **b** Patients with radiologically severe aSAH had significantly higher PCT levels. There was no statistical significance between patients presenting with Fisher grade 1–2 and 3. **c** Patients with unfavorable outcome (GOS 1–3) had significantly higher PCT levels compared to patients with favorable outcome (GOS 4–5). PCT levels are logarithmically transformed for illustrative purposes

an AUC of 0.88 ($p < 0.01$; 95 % CI: 0.81–0.91) and 0.87 ($p < 0.01$; 95 % CI: 0.80–0.94), respectively (Fig. 2). Using the PCT cut-off value of 0.50 ng/ml, the sensitivity was poor (12 %), while the specificity was high (94 %). The ROC curves are shown in Fig. 2.

Discussion

In the current study we intended to assess the predictive value of early PCT values (≤24 h after ictus) with regard to the neurological outcome after aSAH. The results showed increased PCT levels in patients with initially severe hemorrhage and in patients with clinically unfavorable outcome. Based on the ROC curve analysis, the predictive value of PCT on the neurological outcome was poor to moderate and by that showed to be far less predictive than WFNS grade. Comparing the combined predictive probabilities of well-known risk factors (WFNS, Fisher grade, and age) with and without PCT, the inclusion of PCT showed virtually no advantage.

Little is known about the origin, liberation kinetics, or pathophysiology of PCT. The acute-phase protein has been reported to be a useful biomarker to determine bacterial infection or sepsis [14]. In particular, it has been reported to allow discrimination between sepsis and SIRS. However, more recent evidence suggests that PCT can also be elevated under various other "acute stress conditions," such as polytrauma, heat stroke, cardiac arrest, burns, traumatic brain injury, and aSAH [8, 9, 14, 17]. Post-cardiac-arrest status has been designated as a "sepsis-like" syndrome [18, 19]. Moreover, transient myocardial dysfunction can occur after resuscitation, mainly as a result of "myocardial stunning" [19], which might further aggravate ischemic–hypoxic brain injury. It is of particular interest that high specificity and sensitivity of early PCT values in

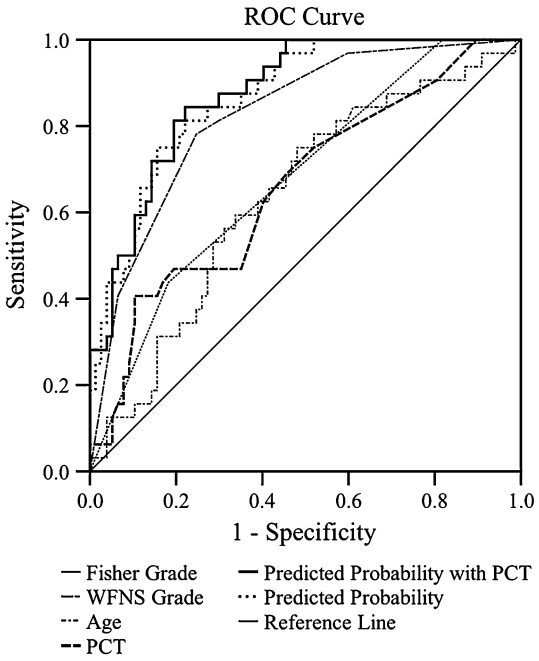

Fig. 2 ROC curves of PCT beside WFNS grade, Fisher grade, and age. The combined predictive probability with PCT showed virtually no advantage in comparison to that without PCT

predicting neurological outcome have been reported [5–7, 20]. In particular, PCT levels >0.50 ng/ml at day one after OHCA showed a sensitivity of 91.7 % and specificity of 100 % in one study [5]. In another study a sensitivity of 100 % and specificity of 81.3 % was reported [6]. ROC curve analysis of the two studies revealed an AUC of 0.98 and 0.94, respectively [5, 6].

The rupture of an intracranial aneurysm is associated with a sudden ICP increase and may reach values as high as 162 mmHg [3, 21, 22]. The sharp increase of ICP leads to a decrease of the cerebral perfusion pressure (CPP) with a consequent critical decrease of the cerebral blood flow (CBF) [22–24]. In severe hemorrhage, intracranial circulatory arrest lasting for several minutes might occur [22, 25], which might be comparable with intracranial circulatory arrest after OHCA. Furthermore, a "neurogenic stunned myocardium" with consecutive cardiac dysfunction might occur, with similar effects as the "myocardial stunning" after OHCA [26]. However, with only 2 patients, the number of patients with documented cardio-pulmonary resuscitation in the current study population was low. The current results show increased PCT levels in patients with clinically and radiologically severe aSAH. It can be assumed that these patients suffered more seriously from cerebral circulatory compromise at the time of hemorrhage. The PCT levels probably reflect an acute systemic stress response to the hemorrhage. Although patients with unfavorable outcome showed significantly higher PCT levels within 24 h after ictus, the predictive value for unfavorable neurological outcome was rather poor compared to previous reports on patients after OHCA. This might be explained as follows: Early brain injury after aSAH cannot be (over-) simplified to transient global cerebral hypoxia due to CBF decrease or arrest. There are several pathophysiological mechanisms that activate within minutes after the initial bleeding such as mechanical and biochemical trauma caused by the hematoma itself [3]. Furthermore, it is well known that patients with aSAH are specifically at risk of secondary neurological injury, which may be caused by 1) CVS-dependent or -independent delayed ischemic events, aka DCI, 2) "collateral damage" in conjunction with the aneurysm securement, and/or 3) rebleeding [1, 27].

With respect to the current results, following limitations have to be considered. The crucial disadvantage of the current study is its anecdotal nature. Furthermore, the database was derived from a single tertiary care center and, therefore, might carry the risk of being biased as well as of over representing severe cases.

Conclusion

Early elevated systemic PCT levels in patients with severe aSAH might reflect the overall initial stress response. In the current study, patients with unfavorable neurological outcome had higher PCT levels within 24 h after ictus. However, their predictive value appeared to be poor, especially compared to the reported predictive values in patients with OHCA. Therefore, early PCT levels might be of little practical use in predicting neurological outcome after aSAH. Furthermore, the results underline once more the pathophysiological complexity of neuronal injury after aSAH.

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