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ORIGINAL ARTICLE

Impact of body temperature and serum procalcitonin on the outcomes of critically ill neurological patients

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KEYWORDS

Serum procalcitonin;
PCT;
Hyperthermia;
Head trauma;
Stroke

Abstract *Introduction:* Fever is common in patients with acute stroke, and mostly it is due to infectious complications. The neurologic effects of fever are significant, increased temperature in the post-injury period has been associated with increased cytokine activity and increased infarct size.

Aim: To test the hypothesis that fever and increased serum procalcitonin are associated with poor outcomes after neurological injury.

Methodology: Fifty patients (30 males (60%) and 20 females (40%) mean 43.8 ± 11.7 years) were divided into two groups: Group I: 25 traumatic patients (i.e., head injury) and Group II: 25 non-traumatic patients (i.e., stroke). Temperature was measured from admission until the patients were discharged or died, and PCT was measured on day 1 of admission and after 48 h of admission.

Results: Fever has been associated with poor outcome, as fever is linked to worse GCS scores (12.6 ± 1.2 vs. 7.7 ± 2.6 in patients with fever, *P* 0.001), longer MV durations (3.6 ± 1.0 vs. 22.4 ± 9.1 days, in patients with fever, *P* 0.001), longer ICU length of stay (8.1 ± 4.7 vs. 23.0 ± 8.0 days in patients with fever, *P* 0.001) and increased mortality (*P* = 0.001). There were significantly higher PCT levels in the mortality group versus the survived group at day 1 (4.15 ± 0.82 vs. 2.47 ± 0.059 ng/ml, respectively, *P* 0.0001) and after 48 h of admission (5.20 ± 1.14 vs. 3.19 ± 0.092 ng/ml, respectively, *P* 0.0001).

Conclusion: Fever had a strong link to worse GCS, longer MV durations, increased length of ICU stay, higher mortality rates and worse overall outcomes in neurocritical patients. High PCT levels can predict mortality in those patients.

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1. Introduction

Fever is a common condition in patients with stroke and other brain injuries. Hyperthermia appears to correlate with poor outcome in these patients, although a direct causative link has not been established yet. After controlling for illness

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severity, diagnosis, age, and complications, fever has been found to be strongly associated with increased lengths of intensive care unit (ICU) and hospital stays, a higher mortality rate and worse overall outcomes [1,2].

Sometimes fever in stroke patients is due to infectious complications. In some patients with acute stroke and fever, the infection source cannot be identified. In some of these cases where fever exists without an obvious infection source, fever does not respond to empirical antibiotic treatment and is thought to be due to a central nervous system lesion. The presence of fever, in general, in patients with acute stroke has been associated with poor outcomes [3].

The neurologic effects of fever are significant as increased temperature in the post-injury period has been associated with increased local cytokine activity, increased infarct size, and poorer outcomes in the acute phase of injury. This is, in part, related to the fact that patients at risk of intracranial hypertension may be significantly affected by an increase in temperature because the intracranial blood volume increases with fever. This reduces compliance and puts the brain at risk for further injury. Hyperthermia, when high enough (>43 °C), has been reported to cause neuronal injury in normal brain, and lengthy periods of moderate (40 °C) hyperthermia have been reported to alter brain structure and function [4].

Additionally, traumatic brain injury (TBI) patients are at risk for secondary injury from fever because for every 1 °C increase in core temperature, there is a 5–7% increase in the metabolic rate. This taxes the stressed energy reserves of these severely brain injured catabolic patients. The higher metabolic demand of fever exacerbates this problem and can lead to additional muscle and fat store losses [5].

In TBI patients procalcitonin (PCT) increased only moderately in most patients and peaked at days 1, 2 after trauma, and the concentrations rapidly decline thereafter. Complications, such as sepsis, infection, blood transfusion, prolonged intensive care unit treatment, and poor outcomes were more frequent in patients with initially high PCT levels (>1 ng/ml) [6].

Traumatic brain injury patients are especially prone to develop complications such as infections and sepsis. Because clinical symptoms and conventional markers are not always reliable signs for sepsis and infection diagnoses; therefore, biomarkers such as PCT are often used as a diagnostic tool in these patients. However, similar to patients undergoing elective surgery, an increase of PCT during the early postoperative or post-traumatic period may occur independent of the sepsis or infection diagnoses [6].

Inflammatory response is also a principal early component in the pathophysiology of stroke. Serum PCT, a marker of septicaemia and infection severity, has also been proposed as an indicator of systemic inflammatory response in noninfectious situations in these patients [7].

2. Aim of the work

The purpose of this study was to test the hypothesis that fever and increased serum PCT are associated with poor outcomes after neurological injury.

3. Patients and methods

3.1. Patients

Study was conducted on 50 acute neurological insult patients (30 males and 20 females) that were admitted to the neurocritical unit at Cairo University between January 2012 and September 2012.

3.1.1. Patients were divided into two equally large groups

- Group I: 25 patients (traumatic patients, e.g., head injury).
  - 3 pts with diffuse axonal injury.
  - 5 pts with concussion.
  - 4 pts with cerebral contusion.
  - 2 pts with cerebral haemorrhage.
  - 2 pts with fracture base of skull.
  - 4 pts with subdural haemorrhage.
  - 3 pts subarachnoid haemorrhage.
  - 2 pts intracerebral haemorrhage.

- Group II: 25 patients (non-traumatic patients, e.g., stroke).
  - 14 pts with thrombotic stroke.
  - 4 pts with embolic stroke.
  - 7 pts with haemorrhagic stroke.

3.1.2. Exclusion criteria

- Sepsis patients.
- Septic shock patients.
- Chronically ill patients.
- Patients with known hyper-bilirubinemia (>0.4 mg/ml) or hypertriglyceridemia (>10 g/l). We excluded pts with hyper-bilirubinemia and hypertriglyceridemia due to possible interference with PCT measurement.

3.1.3. All patients were subjected to the following

1. History evaluation.
2. Clinical examination.
3. Glasgow coma scale assessment.
4. Body temperature measurement.
5. PCT level measurement.
6. Intensive care unit duration (in days) assessment.
7. Mechanical ventilation (MV) duration (in days) assessment.

3.2. Methods

Body temperature was measured in the axillary region with a medical thermometer. We defined ICU fever as body temperature above 38 °C. Body temperature was measured daily from day 1 of admission until patient discharge or death.

3.3. Procalcitonin measurements

We measured PCT on day 1 of admission (PCT1) and 48 h after admission (PCT2).

Table 1 Ages for both groups.

Group	No. of pts	Mean ± SD	*P*
Group I	25	39.93 ± 8.82	Non-significant
Group II	25	45.45 ± 12.55	

Table 2 GCS values for both group.

	Group	Mean ± SD	*P* value
GCS	Group I	12.33 ± 1.17	0.0001
	Group II	7.31 ± 2.45	

Table 3 Need for MV in both groups.

	Group	No. of pts	*P* value
MV	Group I	5	0.0001
	Group II	23	

3.4. Sample collection

Two to three millilitres of whole blood was collected from the patients and transported to the laboratory in an icebox. These samples are known to be stable regarding PCT for one week in a 2–8 °C refrigerator. The serum PCT levels were evaluated with an enzyme-linked immunosorbent assay (ELISA). A serum separator tube (SST) was used to allow the samples to clot for two hours at room temperature or overnight at 4 °C before centrifugation for 15 min at 1000*g*. The serum samples were then removed and assayed immediately or were aliquoted and stored at −20 °C or −80 °C. Repeated freeze–thaw cycles were avoided.

3.5. The statistical methods

Data were statistically described in terms of mean ± standard deviation (SD), frequencies (case numbers) and percentages when appropriate. Numerical variable comparisons between the study groups were conducted using a Student's *t* test for independent samples. For comparing categorical data, a Chi square (χ^2) test was performed. Correlation between various variables was determined using a Spearman rank correlation equation for normal variables. *P* values less than 0.05 were considered statistically significant. All statistical calculations were performed using Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

4. Results

Our study was conducted on 30 males (60%) and 20 females (40%) with a mean age of 43.8 ± 11.7 years, a minimum age of 17 and maximum age of 76 years.

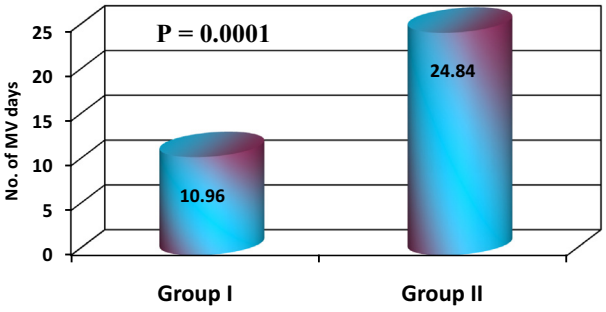

Figure 2 Mechanical ventilation durations for both groups.

4.1. Demographic data

4.1.1. Age distribution

There was no statistically significant difference between the two groups with regard to age, as shown in Table 1.

4.1.2. Gender distribution

There was no statistically significant difference between the two patient groups regarding gender ($P = 0.15$), as shown in Fig. 1.

4.1.3. Glasgow coma scale (GCS)

There was a statistically significant difference between the two patient groups regarding the GCS values ($P = 0.0001$), as shown in Table 2.

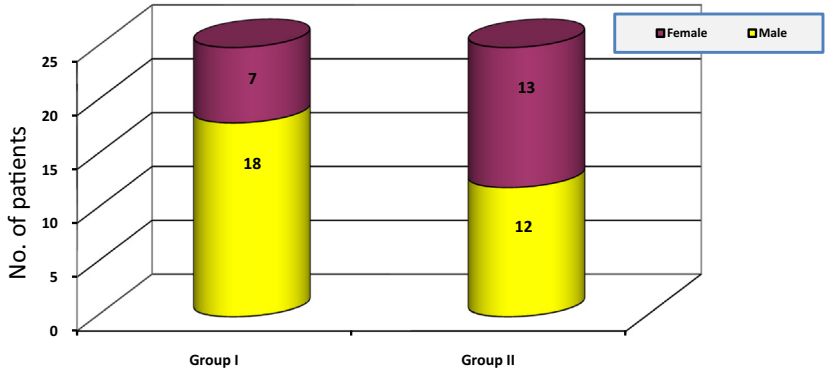

Figure 1 Gender distribution for both groups.

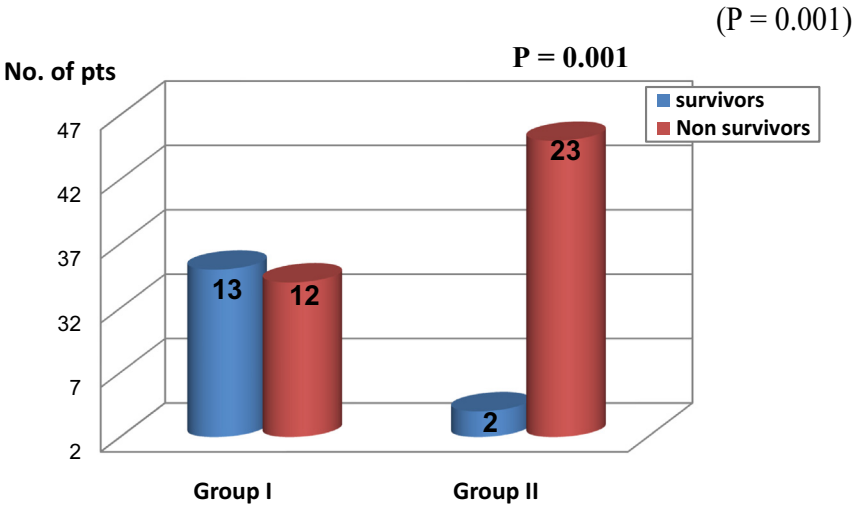

Figure 3 Mortality in both groups.

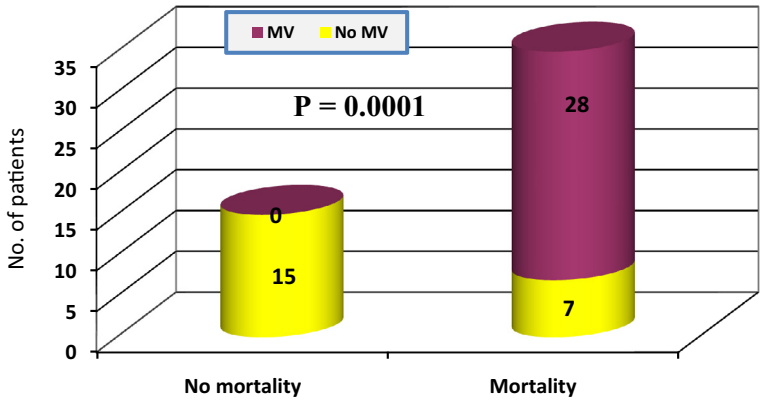

Figure 4 Mortality in patients who needed MV assistance.

Table 4 Body temperature for both groups.

High temperature (>38 °C)	Group	No. of pts	*P* value
	Group I	15	0.0001
	Group II	23	

5. Outcome

5.1. Need for mechanical ventilation

Twenty-eight of our patients needed MV assistance throughout their ICU stay. There was a statistically significant difference between the two patient groups regarding the need for MV ($P = 0.0001$), as shown in Table 3.

5.2. Duration of mechanical ventilation

A statistically significant shorter MV day period in group I compared with group II patients was found (10.96 + 10.47 vs. 24.84 + 6.96 days, respectively, $P = 0.0001$), as shown in Fig. 2.

5.3. Mortality

Thirty-five patients died. There was a significantly higher mortality rate among the group II patients compared with group I ($P = 0.001$), as shown in Fig. 3.

5.4. The relation between MV and mortality

Twenty-eight patients of the 35 patients who died had needed MV assistance while none of the patients that survived needed MV assistance ($P = 0.0001$), as shown in Fig. 4.

6. Body temperature

There was a statistically significant difference between groups I and II with regard to body temperature ($P = 0.0001$), as shown in Table 4.

6.1. Fever in relation to GCS, MV and length of ICU stay

Fever has been associated with poor outcomes, and fever was linked to more worse GCS values (12.6 ± 1.2 vs. 7.7 ± 2.6 in

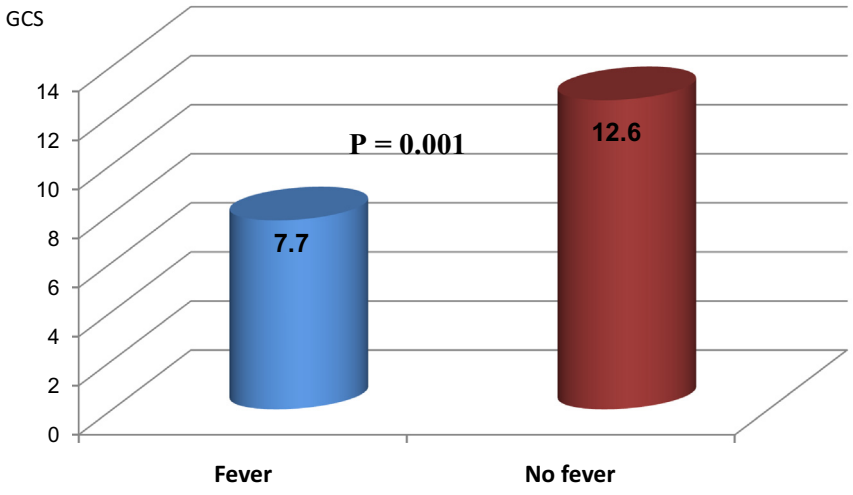

Figure 5 Fever in relation to GCS.

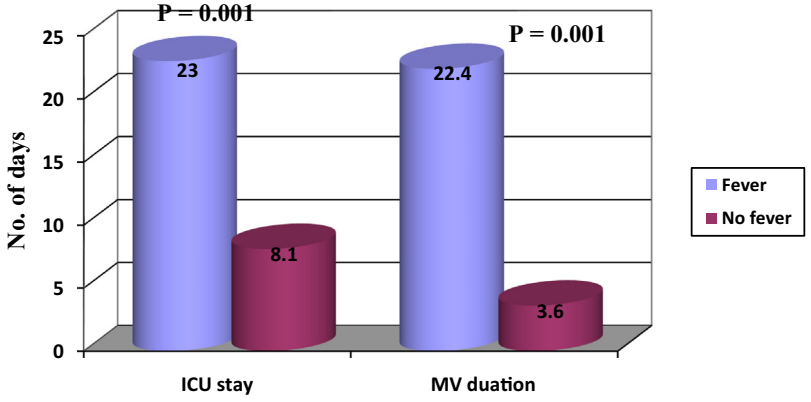

Figure 6 Fever in relation to MV and length of ICU stay.

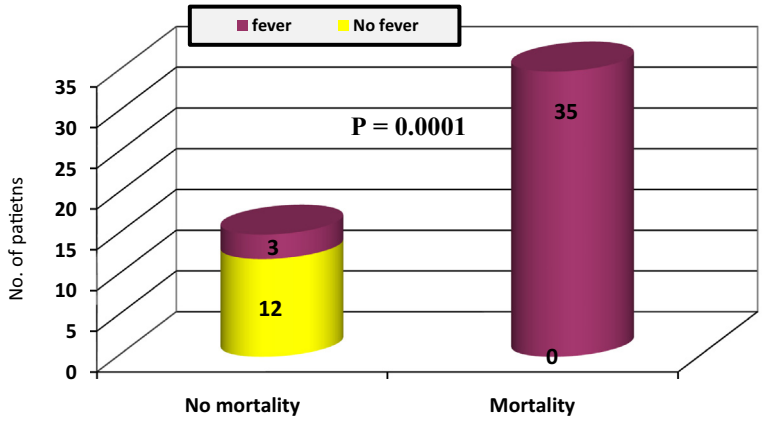

Figure 7 Fever in relation to mortality.

patients with fever, $P = 0.001$), longer MV durations (3.6 ± 1.0 vs. 22.4 ± 9.1 days, in patients with fever, $P = 0.001$), and longer ICU stays (8.1 ± 4.7 vs. 23.0 ± 8.0 days, in patients with fever, $P = 0.001$), as shown in Fig. 5 (see Fig. 6).

6.2. Fever in relation to mortality

All mortality patients had elevated body temperatures compared with three out of the 15 patients who survived ($P = 0.0001$), as shown in Fig. 7.

7. Procalcitonin levels (PCT1, PCT2)

There were significantly higher PCT levels in group II compared with group I at PCT1 and PCT2 ($P = 0.0001$), as shown in Table 5.

There were significantly higher PCT levels in the mortality versus the survived group at PCT1 and PCT2 ($P = 0.0001$), as shown in Table 6.

7.1. PCT1 and PCT2 cut-off point analyses for mortality predictions

PCT1 at cut off to 3.32 ng/ml was found to be 79.4% sensitive and 100% specific for mortality prediction with a 100% positive predictive value, a 68.2% negative predictive value and an AUC of 95.7%.

Conversely, PCT2 at a 3.54 ng/ml cutoff point was found to have a sensitivity of 91.4% and a specificity of 73.3% for mortality predictions with a 88.6% positive predictive value, a 78.6% negative predictive value and an AUC of 0.91, as shown in Fig. 8.

7.2. Correlation between body temperature and PCT

Body temperature was correlated with PCT1 (R value 0.685 and P value <0.001) and PCT2 (R value 0.683 and P value <0.001).

7.3. Discussion

Fever is a common condition in stroke and other types of brain injury, and previous research has shown a strong link to increased length of ICU and hospital stay, higher mortality rates, and worse overall outcome [8].

Traumatic brain injury (TBI) patients frequently experience febrile episodes that may be of infectious or non-infectious origins. Neurogenic fever (NF) is a non-infectious source of fever in TBI patients. Until recently, NF was thought to be a relatively rare consequence of TBI, but other studies have reported that 4–37% of TBI survivors experience this sequelae [9].

Table 5 Procalcitonin levels in both groups.

Group	PCT	Mean ± SD	P value
Group I	PCT 1 (ng/ml)	2.8 ± 0.7	0.0001
	PCT 2 (ng/ml)	3.4 ± 0.7	
Group II	PCT 1 (ng/ml)	4.4 ± 0.7	
	PCT 2 (ng/ml)	5.8 ± 0.7	

Table 6 PCT levels in the mortality versus survived groups.

		Mean + SD	P value
PCT1 (ng/ml)	No mortality	2.47 ± 0.59	0.0001
	Mortality	4.15 ± 0.82	
PCT2 (ng/ml)	No mortality	3.19 ± 0.92	0.0001
	Mortality	5.20 ± 1.14	

Neurogenic fever results from a disruption in the hypothalamic thermostat, which results in an abnormal increase in body temperature [10].

The neurologic effects of fever are significant, as increased temperature in the post-injury period has been associated with increased local cytokine activity, increased infarct size, and worse outcomes in the acute phase of injury. This is, in part, related to the fact that patients at risk of intracranial hypertension may be significantly affected by rises in temperature because the intracranial blood volume increases with temperature. This reduces compliance and puts the brain at risk for further injury. Hyperthermia, when high enough (>43 °C), has been reported to cause neuronal injury in normal brain, and lengthy periods of moderate (40 °C) hyperthermia have been reported to alter brain structure and functioning. Neurogenic fever may be associated with the presence of prolonged unawareness or a coma state [4].

In our studied patients, group I (traumatic patients) had better GCS values than group II (stroke patients) and this translated to a higher need for MV assistance in group II (twenty-three out of twenty-eight patients needed MV).

Thirty-five of our patients died, and there was a higher mortality rate among the group II patients (23 out of 25 patients vs. 12 out of 25 patients in group I, $P = 0.001$).

In our attempt to separate patients with fever due to infection from those with fever and no infection (fever of a central origin), we found that the only factor that was predictive of a central origin fever was earlier fever onset because an incubation period for an infection to develop would not be needed. However, some overlap between the two groups was expected.

In our study, we found that fever onsets that happened in the first 2 days of hospitalization occurred in 64% of the febrile patients. These rates are similar to those described by Hindfelt in 1976, while Przelomski et al. in 1986 and Terent and Anderson in 1981 described a lower fever incidence. Comparisons among various studies are difficult, however, because of the differences in the fever definitions and measurements. Considering death within 30 days after hospital admission as the main measure of outcome, we found that fever was confirmed to be significantly related to a poorer outcome; however, it was not possible to estimate a threshold above which fever seemed detrimental [11–13].

Similar to our study, several studies measured fever over the entire ICU stay duration so that patients with a longer stay had a greater chance of fever being identified. However, several studies found a significant association between outcomes in patients with stroke and body temperature measured on admission, suggesting that the relationship between longer ICU stays and fever cannot be attributed solely to treatment effects [14–18].

In our study, fever occurred in 76% of patients and the mortality rate in these patients was more than 90%. This result is higher than the result obtained in a study by Kilpatrick and colleagues in 2000 [19] who found that fever occurred in 47% of their observed patients. Additionally, other studies [11–13] showed that fever occurred in up to 20–30% of patients. Moreover, after haemorrhagic stroke, fever has been reported in 40–50% of patients. And the high mortality rate in our study can be explained by a higher infection rate in our patients (64%) compared with this study, which had a 50% infection rate.

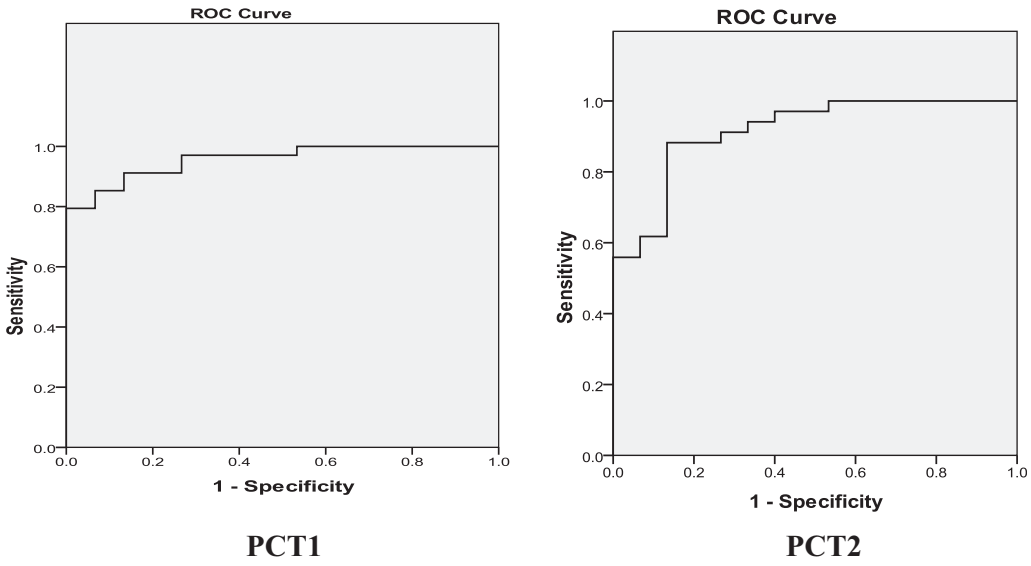

Figure 8 ROC curve.

Only two studies have investigated the prognostic significance of fever in stroke. In one study, Hindfelt found that a mean body temperature above 37.5 °C from any cause in the first 7 days was associated with a poor prognosis at 2 months after the stroke. However, his study was retrospective, the sample excluded patients who died within 2 months, and the outcome measurement was not validated; therefore, his conclusions are not easily generalized to the whole stroke patient population [11].

In a prospective study of 281 patients with stroke, Terent and Andersson found that in patients with a mean body temperature of 38 °C or more during the first week, chest X-ray films revealed bronchopneumonia in half. Fever indicated a significantly worse prognosis [13].

Przelomski et al. [12] prospectively investigated the frequency and causes of fever in a sample of 104 consecutive stroke patients. In particular, these authors studied the possible association between fever and it was almost always secondary to infections and the lesion size. A comparison with our study is difficult because the authors excluded brain stem infarcts and intraventricular haemorrhage, conditions in which ''neurogenic fever'' is most likely, and they did not evaluate the prognostic value of fever.

High fever thus seemed to be associated with a higher probability of early death, whereby it was shown that fever of at least 37.9 °C indicated poor early prognosis even without a consideration of its causes. Because the majority of the experimental studies documented the direct effects of temperature on neurological damage, our data suggest that fever could worsen prognosis through direct neurological damage.

In patients with multiple traumas, the PCT level provides information because only moderate amounts of PCT are induced, and higher concentrations correlate with a more severe trauma and a higher frequency of various complications, including sepsis and infection. Most importantly, the moderate trauma-related increase of PCT and the rapidly declining concentrations provide a baseline value near to the normal range [6].

The effects of haemorrhagic stroke on PCT are not yet known. Determining the natural history of PCT in a haemorrhagic stroke patient would provide beneficial information as to whether PCT can be used as a biomarker in this population to help differentiate a bacterial from a non-bacterial hyperthermia cause [7].

We measured PCT levels (ng/ml) on day one and after 48 h of admission in order to evaluate the early PCT levels that occur before the development of an infection. There were significantly higher PCT levels in the mortality versus survived groups at day 1 ($P = 0.0001$) and after 48 h of admission ($P = 0.0001$).

Our results are in agreement with a study by O'Connor E et al. in 2004 [20] that evaluated PCT and CRP as mortality markers in 62 patients with TBI and subarachnoid haemorrhage and they found that serum PCT appeared to correlate with TBI severity and mortality.

Our study is also in agreement with a study by Linda et al. [6]. This was a prospective study that included all admissions <12 h after TBI where serum PCT and S100B were measured immunoluminometrically for 5 days. They concluded that PCT and S100B are useful for mortality predictions in TBI patients.

Our study is not in agreement with the study by Miyakis et al. in 2004 [7]. They studied the prognostic value of PCT measured on days 2, 3 and 4 of admission in 30 patients who were admitted with acute stroke. They found that serial serum PCT levels did not correlate with stroke mortality or neurologic outcomes at discharge and this could be explained by the fact that studies that have correlated laboratory parameters with prognoses for acute stroke sometime had conflicting results [21–23].

In general, head trauma patients had good prognoses compared with stroke patients because they had significantly fewer fever instances and lower PCT levels, and this translated into less mortality in this group.

8. Conclusion

Fever has a strong link to worse GCS values, longer MV durations, increased length of ICU stay, higher mortality and worse overall outcomes in neurocritical patients. High PCT levels can

predict mortality in those patients. Head trauma patients had a good prognosis compared with stroke patients.

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