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VEGF, TNF-α, and PCT efficiency for traumatic brain injury prognosis evaluation in the first 72 h

Diya Hasan[1], Ola M. Al-Sanabra[2], Mutaz Jamal Al-Khreisat[3], Ghaith H Mansour[1], Tareq Nayef AlRamadneh[3], Moath Alqaraleh[2], Alqassem H. Abuarqoub[3], Ahmad Al Tibi[4], Mu'ad Al-zu'abe[1], Sara Abaza[1]

[1]Department of Allied Medical Sciences, Zarqa College, Al-Balqa Applied University, Zarqa - Jordan
[2]Department of Medical Laboratory Sciences, Faculty of Allied Medical Sciences, Al-Balqa Applied University, Al-Salt - Jordan
[3]Department of Medical Laboratory Sciences, Faculty of Allied Medical Sciences, Al-Ahliyya Amman University, Amman - Jordan
[4]Biolab Diagnostic Laboratories, Amman - Jordan

ABSTRACT

Introduction: Traumatic brain injury (TBI) is linked to poor progression and a high mortality rate. It is classified and evaluated using the standard Glasgow Coma Scale (GCS). In addition, serum biomarkers, such as vascular endothelial growth factor (VEGF), procalcitonin (PCT), and tumor necrosis factor-alpha (TNF-α), may facilitate accurate TBI severity evaluation, thereby assisting in its prognosis and clinical outcome.

Methods: This study included 20 patients with TBI aged ≥18 years who were admitted within 12 h of injury to the intensive care unit (ICU). Serum samples for assessing VEGF, TNF-α, and PCT concentrations were acquired at admission 0 h, 24 h, and 72 h and analyzed by ELISA.

Results: Serum concentrations of VEGF, TNF-α, and PCT ($p < 0.0001$) were significantly elevated at all time intervals in patients with TBI than in the control group (healthy individuals). Compared to the admission (0 h) time point, VEGF concentrations exhibited no significant differences among different time points, whereas TNF-α concentrations had increased significantly ($p < 0.001$) at 24 h. PCT concentrations exhibited a continuous elevation through time points, peaking at 72 h ($p < 0.01$). The highest diagnostic performance for PCT was noted at 72 h, with an AUC of 0.834 ($p < 0.004$). In addition, PCT and VEGF showed a significant negative correlation at 24 h, indicating potential opposing roles in trauma response.

Conclusion: Serum PCT concentrations can be utilized to track the progression of TBI because of a continuous increase in its concentration with time.

Keywords: Prognosis, Procalcitonin, Traumatic brain injury, Tumor necrosis factor-alpha, Vascular endothelial growth factor

Introduction

Traumatic brain injury (TBI) is caused by damage inflicted on the brain due to an external force. Almost 61 million individuals are estimated to experience TBI worldwide annually (1). The intensive care unit (ICU) physicians need to crucially assess the prognosis of patients with potentially fatal illnesses and recognize the possible positive or negative outcome (2). The most widely used classification for patients with TBI upon admission is the Glasgow Coma Scale (GCS) score, which indicates the trauma severity and is also used for predicting the outcome following TBI (3).

GCS categorizes TBI into three distinct groups: patients with mild TBI who typically recover fully neurologically, those with moderate TBI who are drowsy or unconscious, and those with severe TBI who are in a coma state, incapable of opening their eyes or communicating (4). However, the use of GCS is limited by the precision gaps between experienced and well-trained users and those who lack experience (5). The agreement rate for the precise total GCS among physicians has been reported to be 32% (6).

TBI can be characterized as a disorder that pathologically progresses in a time-dependent manner. Thus, biomarker-based prognostic and diagnostic techniques can efficiently assess its progression. In other words, the rate at which biomarkers are expressed and transported through the blood–brain barrier (BBB) into the blood is referred to as TBI pathology (7).

A variety of immune mediators are released immediately after the initial injury, marking the onset of the acute post-traumatic phase of TBI. This response enhances the vascular permeability of the BBB, facilitating the infiltration and accumulation of leukocytes in the affected tissue.

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Corresponding author:
Diya Hasan
email: diyahasan@bau.edu.jo

This consequently elevates the production of growth factors, inflammatory biomarkers, and pro- and anti-inflammatory cytokines, such as vascular endothelial growth factor (VEGF), procalcitonin (PCT), and tumor necrosis factor-α (TNF-α) (8).

Vascular repair following TBI involves VEGF family members, including VEGF-A, B, C, and D, that significantly regulate vasculogenesis and angiogenesis by their interaction with VEGF receptors (VEGFR1, VEGFR2, and VEGFR3)—an essential step for the brain tissue healing following injury (9). Increased concentrations of VEGF-A in the plasma have been observed following TBI (10). The elevated concentrations of VEGF have been associated with the interruption of the BBB, thereby facilitating brain edema (11). Although VEGF is not an inflammatory protein, it can potentially influence immune responses within the central nervous system (CNS) by facilitating the permeability of the BBB and modifying the brain's immune-favored condition (12).

PCT is commonly used as a diagnostic marker of sepsis and infection and has been linked to mortality in several clinical situations, including cancer, sepsis, and trauma (13). Furthermore, the predictive significance of PCT in individuals suffering from neurological disorders, such as ischemic stroke and intracerebral hemorrhage, has been investigated (14).

The concentrations of PCT could serve as an effective marker for the early identification of septic complications in individuals with multiple trauma (15). Absolute values and serial variations in PCT concentrations following the treatment hold prognostic importance across different clinical stages (16).

Elevated TNF-α concentrations have been observed immediately after TBI and possibly contribute to subsequent neuronal damage (17). TNF-α has been implicated in TBI outcomes; it is involved in the permeability of endothelial cell layers, which may promote the impaired action of the BBB (18). Despite the potential negative effects of elevated tumor necrosis factor-alpha (TNF-α) concentrations in the initial hours following TBI, cytokine balance is crucial for sustained recovery (19).

We assessed the relevance of serum biomarker concentrations of TNF-α, VEGF, and PCT in patients with TBI. In addition, we studied the predictive sensitivity of these biomarkers in relation to injury severity and mortality within the first 72 h to gain insights into patient outcomes alongside the GCS score.

Materials and methods

This study is an extension of our previously published work in which the serum concentrations of PCT, TNF-α, and VEGF were investigated at 12 and 48 h in patients with TBI (20). Samples from the same group of patients were used in the present study to quantify the concentrations of the targeted biomarkers and explore their possible prognostic value in correlation with the 72 h time point. Therefore, patients, sample grouping, and enzyme-linked immunosorbent assay (ELISA) concentrations of PCT, TNF-α, and VEGF are reproductions of earlier published work (20).

After approval from the institutional ethics committee of the Jordanian Royal Medical Services (JRMS) (ref: 2011-281), 20 male patients aged 18-53 years with TBI and admitted to the hospital ICU were included in the study on a prospective basis. The data collected during admission included the nature of the injury (such as accident or assault), any chronic medical history, GCS score indicating the severity of the trauma, and the patient's age and gender. The inclusion criteria consisted of patients over 18 years old with head injury, and who survived for a minimum of 12 h post-injury. Exclusion criteria included patients who were not admitted within 72 h following their injury, as well as those who had been on inflammatory or immune therapy for more than 3 days prior to admission.

Intravenous (IV) blood samples were obtained from patients upon admission at 0, 24, and 72 h for the diagnosis of PCT, TNF-α, and VEGF. These samples were processed at the Department of Biochemistry, Biolab Diagnostic Laboratories in Amman, Jordan. Marker assays were conducted using commercially available ELISA kits. PCT (human procalcitonin ELISA Kit, ABclonal), TNF-α (human TNF-α ELISA Kit, ABclonal), VEGF (human VEGF ELISA Kit, ABclonal). The concentrations exceeding 0.05 ng/mL for PCT, 0.0028 ng/mL for TNF-α, and 0.0962 ng/mL for VEGF were considered positive according to the kit's instructions.

Statistical analysis

Statistical analysis was conducted using GraphPad Prism 10.3.0 (GraphPad Software, Inc., CA, USA). The data are presented as means ± standard error of the mean (mean ± SEM). The statistical differences in marker concentrations across specified time points were assessed using a one-way analysis of variance accompanied by Dunnett's test. The receiver operating characteristic (ROC) curve analysis was used to assess the truncated diagnostic performance of selected markers. Spearman's rank correlation coefficient was used to assess the relationship between variables.

Results

We have included some of our previously published data for convenience in understanding the present results (20). The serum concentrations of VEGF, TNF-α, and PCT were measured in all 20 patient samples using ELISA. Initially, the biomarker concentrations were compared at different time points (0, 24, and 72 h). Healthy individuals were included in the control group.

The VEGF concentration was significantly elevated ($p < 0.0001$) at 0, 24 and 72 h compared to that in the control group (Fig. 1A). The 95% confidence intervals for all comparisons with the control group excluded zero (−0.2078 to −0.1726 at 0 h; −0.2117 to −0.1755 at 24 h; −0.2202 to −0.1811 at 72 h; all $p < 0.0001$), indicating robust and precise VEGF elevation at all time points. In contrast, VEGF concentration at 24 h (0.20 ng/mL) and 72 h (0.21 ng/mL) revealed no significant changes to the baseline concentration at 0 h (0.21 ng/mL), unlike the observed variations in TNF-α and PCT concentrations.

As shown in Figure 1B, serum concentrations of TNF-α were significantly increased ($p < 0.0001$) at all measured time points (0, 24, and 72 h) compared with the control group. The control concentration was 0.001 ng/mL, whereas

concentrations were 0.15 ng/mL at 0 h, 0.19 ng/mL at 24 h, and 0.17 ng/mL at 72 h. The 95% confidence intervals for comparisons with control also excluded zero (−0.1719 to −0.1331 at 0 h; −0.2094 to −0.1686 at 24 h; −0.1865 to −0.1457 at 72 h; all $p < 0.0001$), demonstrating strong and consistent inflammatory responses across all time points. The highest TNF-α concentration was observed at 24 h, suggesting a peak inflammatory phase following trauma.

The serum concentrations of PCT exhibited distinct patterns compared to those of TNF-α and VEGF at different time points. As shown in Figure 1C, the control concentration was 0.012 ng/mL, whereas PCT concentrations were 0.09 ng/mL at 0 h, 0.12 ng/mL at 24 h, and 0.23 ng/mL at 72 h. Significant elevations were observed at 0 h ($p = 0.009$), 24 h ($P = 0.0006$), and 72 h ($p < 0.0001$) compared with the control. The 95% confidence intervals for these comparisons were −0.1356 to −0.0157 at 0 h, −0.1631 to −0.0382 at 24 h, and −0.2812 to −0.1501 at 72 h, confirming a progressive widening from control values and indicating increasing effect magnitude over time. Notably, the increase in PCT concentrations correlated with the duration of hospitalization, reaching the highest level at 72 h.

The ROC curve analysis was performed to reveal the potential of using these three serum variables—PTC, TNF-α, and VEGF as prognostic biomarkers post 72 h of a TBI incident. A highly significant ($p = 0.004$) PCT concentration demonstrated it to be a clinically meaningful effect size and

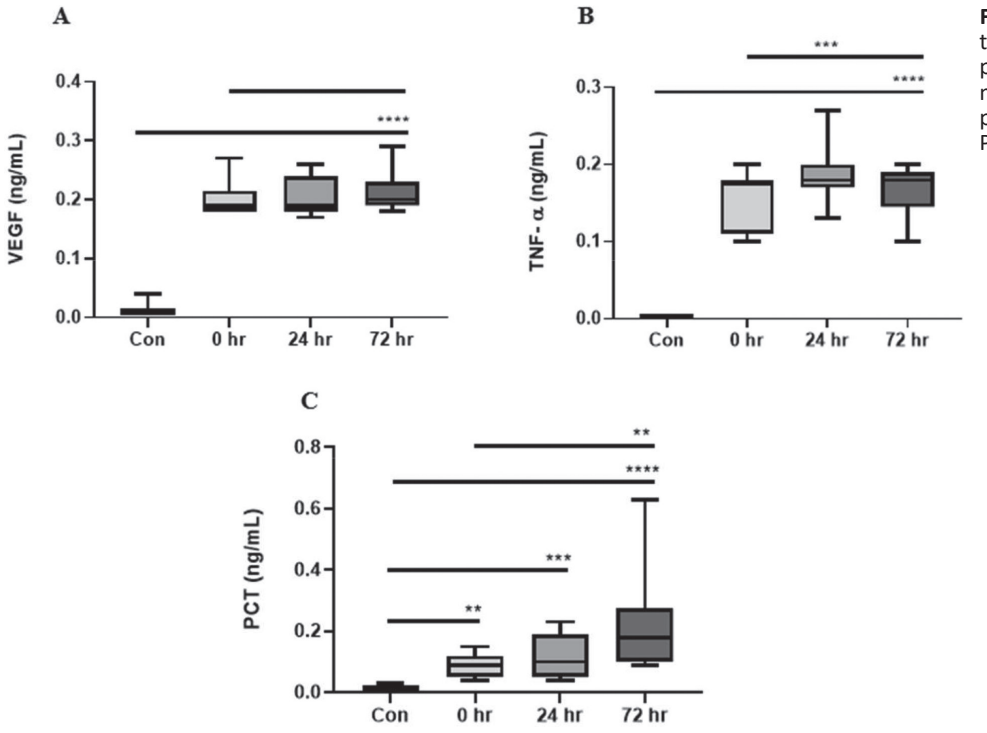

FIGURE 1 - Biomarkers serum concentration variations among targeted time points in comparison to the non-traumatic group and admission: (0 h) time point of (A) VEGF, (B) TNF-α, and (C) PCT.

a reliable biomarker in discriminating the progression of TBI post 72 h, with an AUC of 0.834 at 72 h and 0.607 at 24 h from the admission time. The optimal cut-off values of 0.095 ng/mL and 0.07 ng/mL for each time point yielded sensitivities of 84.6% and 61.5%, and specificities of 38.5% and 53.8%, respectively (Figs 2A and B).

The analysis results for TNF-α demonstrated it to be a poor biomarker at 24 h with an AUC of 0.676 at a cut-off of 0.175 ng/mL with a sensitivity of 70.6% and specificity of 58.8%. In addition, no discrimination was observed in TBI at 72 h with an AUC of 0.578, and sensitivity and specificity of 70.6% at a cut-off of 0.16 ng/mL, reflecting small effect magnitudes despite statistical elevation compared with controls (Figs 2C and D).

The ROC analysis for VEGF concentration showed no discrimination at 24 h and 72 h from the admission time, with an AUC of 0.491 (cut-off = 0.21) and 0.484 (cut-off = 0.195) and sensitivity and specificity of 53.3% and 66.7%, respectively (Figs 2E and F), suggesting VEGF to be an unreliable prognostic biomarker for TBI in early or later time point of TBI.

The correlation analysis between the three serum variables (PCT, TNF-α, and VEGF) and time points revealed that the control group demonstrated no statistically significant associations between the measured variables. The correlation between PCT and TNF-α was very weak and positive ($r = 0.092$, $p = 0.7$), indicating no meaningful relationship. A moderate negative correlation was observed between PCT and VEGF ($r = −0.413$, $p = 0.07$); however, this did not reach statistical significance. Similarly, TNF-α and VEGF exhibited a very weak positive correlation ($r = 0.058$, $p = 0.807$), also lacking significance. Overall, these results suggest that no significant correlations between PCT, TNF-α, and VEGF concentrations existed in healthy controls (Table 1 and Fig. 3A).

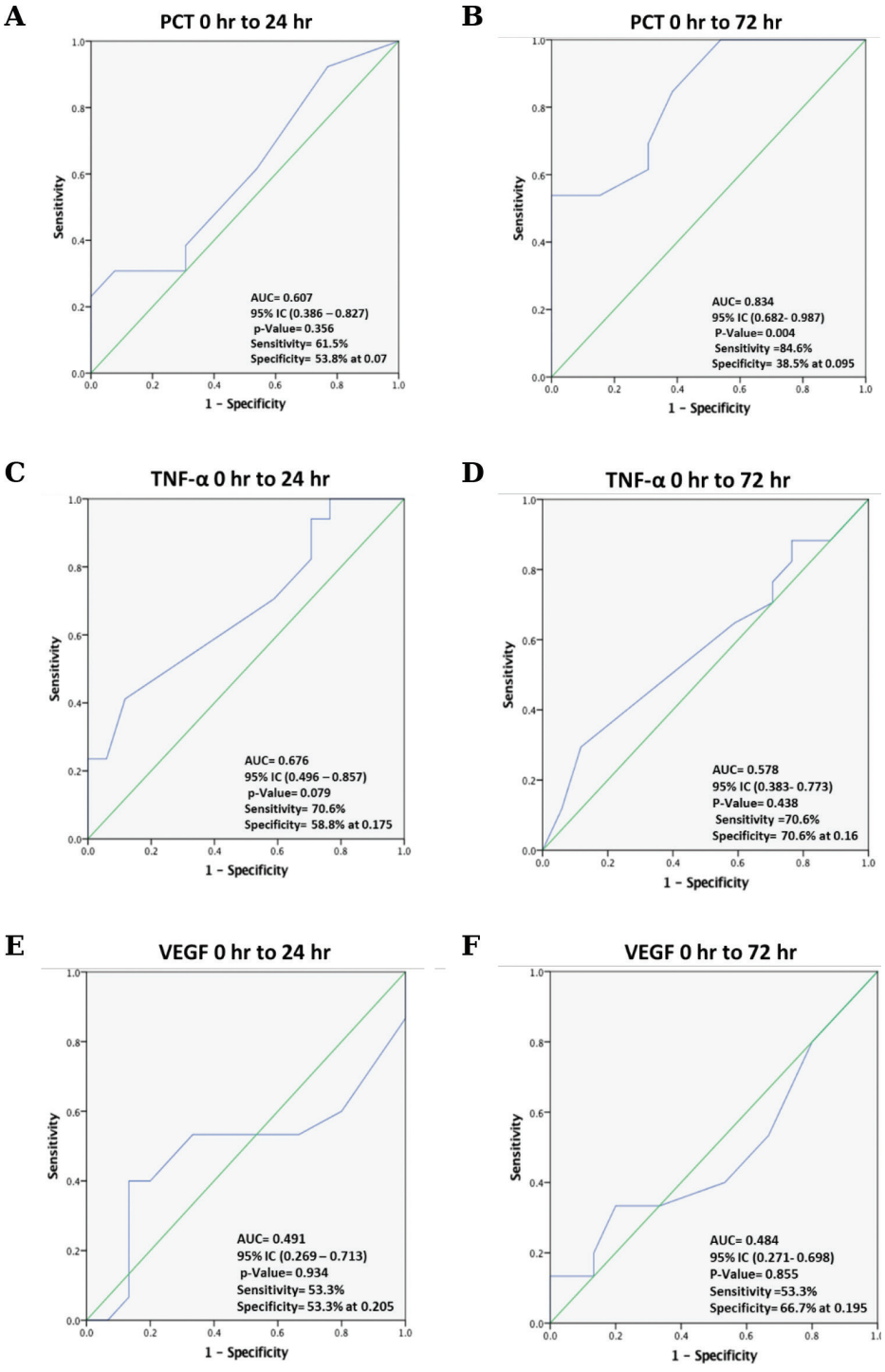

FIGURE 2 - Receiver operating characteristic curve (ROC) for serum biomarkers measured at two time points post-trauma. The ROC curves in each panel demonstrate the diagnostic performance of each biomarker in distinguishing between control (without trauma) and trauma patients. (**A**) PCT at 24 h, (**B**) PCT at 72 h, (**C**) TNF-α at 24 h, (**D**) TNF-α at 72 h, (**E**) VEGF at 24 h, and (**F**) VEGF at 72 h. Areas under the curve (AUC) reflect the accuracy of each biomarker in differentiating between the two groups.

The correlation analysis demonstrated no statistically significant associations between the variables at 0 h. The correlation between PCT and TNF-α was very weak and positive (r = 0.09, p = 0.700), indicating no meaningful relationship. Although a weak negative correlation was observed between PCT and VEGF (r = −0.35, p = 0.130), it was not statistically significant. Similarly, TNF-α and VEGF exhibited a very weak negative correlation (r = −0.15, p = 0.540), also lacking significance. Overall, no significant correlations were observed between PCT, TNF-α, and VEGF at the initial time point (Table 1 and Fig. 3B).

The correlation between PCT and TNF-α was very weak and not statistically significant at 24 h (r = −0.01, p = 0.980), indicating no meaningful association at this time point.

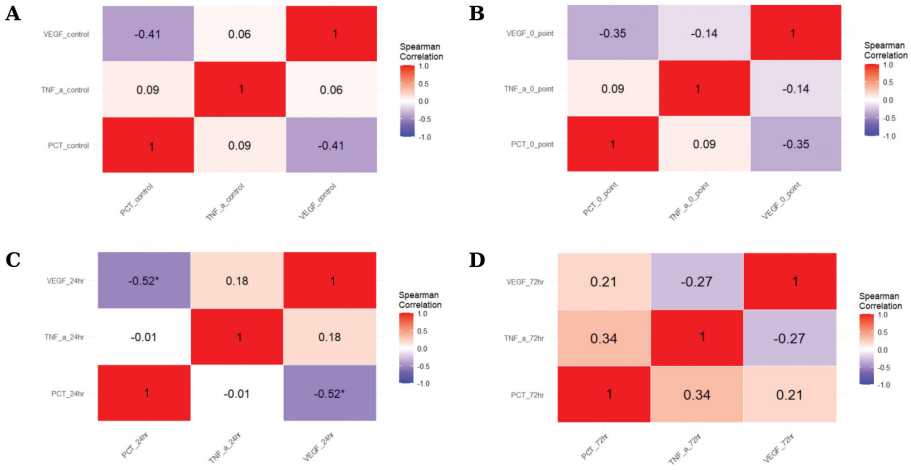

FIGURE 3 - Heat maps showing the correlation of PCT, TNF-α, and VEGF in the control and trauma patient groups over time. Panel **A** represents the control group, whereas panels **B**, **C**, and **D** illustrate the correlations in trauma patients at baseline (0 h), 24 h, and 72 h, respectively.

TABLE 1 - Spearman's rank correlation coefficients and *p*-values for PCT, TNF-α, and VEGF in control and trauma patients over time

		Variables		
		PCT and TNF-α	**PCT and VEGF**	**TNF-α and VEGF**
Control	**Correlation (*r*)**	0.092	−0.413	0.058
	***p*-value**	0.700	0.070	0.807
Time				
0 h	**Correlation (*r*)**	0.09	−0.35	−0.14
	***p*-value**	0.7	0.13	0.54
24 h	**Correlation (*r*)**	-0.01	−0.52	0.18
	***p*-value**	0.980	**0.045**	0.520
72 h	**Correlation (*r*)**	0.341	0.206	−0.273
	***p*-value**	0.250	0.450	0.370

Spearman's rank correlation coefficient

However, a moderate negative correlation between PCT and VEGF ($r = -0.52$) was noted, which was statistically significant ($p = 0.045$). This suggests that higher concentrations of PCT are associated with lower concentrations of VEGF in trauma patients after 24 h. The correlation between TNF-α and VEGF was weak and positive ($r = 0.18$) but not statistically significant ($p = 0.520$), indicating no relationship between these markers at 24 h post-trauma. Altogether, no significant correlations were observed between PCT, TNF-α, and VEGF at the initial time point (Table 1 and Fig. 3C).

The correlation between PCT and TNF-α showed a positive but weak association at 72 h ($r = 0.34$), which was not statistically significant ($p = 0.250$). Similarly, PCT and VEGF had a weak positive correlation ($r = 0.21$) with no statistical significance ($p = 0.500$). Lastly, TNF-α and VEGF exhibited a weak negative correlation ($r = -0.27$), also not statistically significant ($p = 0.370$). Overall, no strong or significant correlation was observed between PCT, TNF-α, and VEGF concentrations at 72 h in trauma patients, indicating that these biomarkers may vary independently at this time point (Table 1 and Fig. 3D).

Discussion

Because serum biomarkers are linked to TBI, they constitute a crucial parameter to monitor patients with TBI. These biomarkers can identify individuals at high risk within the initial 72 h, as well as during subsequent follow-up assessments. In this study, the concentration of TNF-α was significantly increased following admission and remained elevated at subsequent time points, with the most significant elevation noted at 24 h compared to the admission concentrations. Its concentration was lower than that of VEGF and PCT at 72 h.

Our findings align with those of previous studies, which identified a persistent and significant increase in TNF-α concentrations 4 h post-trauma (21). Highest concentrations of TNF-α were observed 24 h post-injury (20). Furthermore, significantly elevated concentrations of TNF-α were found to persist for up to 3 days following the traumatic event (22). Elevated concentrations of TNF-α following trauma have been reported to have detrimental effects on the body (23). Certain studies have reported that TNF-α is released more rapidly than other inflammatory cytokines (24, 25). TNF-α plays a neuroprotective role by facilitating neuroanatomical plasticity (26) following a TBI. Multiple investigations regarding TBI models have indicated an elevation in TNF-α concentrations in the brain shortly after the injury occurs (27).

The concentration of VEGF was markedly increased upon admission and continued to be elevated at later time intervals compared to that in healthy controls. However, no discernible change in its concentration was noted from admission to different time points. Studies have demonstrated an increase in VEGF concentration in chronic stages of TBI (20), indicating that VEGF concentrations are increased in the vicinity of the injury site (10). In addition, increased VEGF concentration has been reported after TBI. The findings indicated that both mRNA expression and protein concentration of VEGF were

increased following TBI, peaking at 24 h post-injury (28). It has been demonstrated that excessive inflammatory signaling can negatively affect endothelial function and modify VEGF pathways (29). As a result, increased inflammatory activation may be associated with a relative suppression of early angiogenic responses. VEGF is a crucial growth factor that stimulates angiogenesis and enhances vascular permeability, thereby potentially facilitating the onset of brain edema and meticulously regulating angiogenesis (30) (31). The expression of VEGF was found to be at its peak 72 h post-injury (32).

Our results demonstrate that PCT concentration was notably elevated at admission as compared to that in healthy controls, and this elevation increased gradually over the subsequent time intervals, peaking 72 h after admission. The concentration of PCT was less than that of both VEGF and TNF-α at each time interval, except at 72 h, when its concentration was higher than that of both VEGF and TNF-α.

PCT has been utilized to assess the progression of inflammation and sepsis in patients with trauma and operating conditions (33). PCT concentrations might be a more accurate predictor of septic complications in the early stages in patients who have experienced multiple trauma (34). Increased concentrations of PCT possibly suggest a traumatic cause rather than the presence of active sepsis in the initial 48 h following trauma (35). Persistent elevation of PCT concentrations is associated with prolonged ICU stay and increased mortality rates (36). Increased levels of PCT suggest the presence of persistent inflammatory stress, which has been associated with endothelial dysfunction and disrupted angiogenic signaling (37). Serial PCT measurements obtained at 72 h of admission have been reported to assess mortality and bacterial functions in cirrhotic patients with systemic inflammatory response syndrome (38). PCT is used as a prognostic indicator in patients with several traumatic injuries; however, its relative effectiveness as a predictive marker concerning outcomes in different forms of TBI has yet to be evaluated (39).

The findings of this study underscore the clinical relevance of TNF-α, VEGF, and PCT in the context of TBI. We aim to conduct further investigation into the correlation between biomarker concentrations and the outcomes of patients with severe TBI.

Limitations

The small sample size (n = 20) poses a notable limitation for this study, likely impairing statistical power and limiting the applicability of the outcomes. In addition, despite the observation of alterations in biomarker levels, a formal assessment of their relationship with clinical outcomes, including mortality, neurological recovery, and progression on the Glasgow Coma Scale, was not viable. As a result, the prognostic importance of these biomarkers should be viewed as exploratory and must be corroborated in larger, independent cohorts and longitudinal outcome data.

Conclusion

The findings of the present study are clinically significant as they overcome one of the primary challenges in the follow-up care of Jordanian patients with TBI, that is, the dependence on the GCS score for case assessment and observation. The study demonstrated that PCT correlates with time and exhibits greater sensitivity compared to TNF-α and VEGF. Consequently, a precise and dependable serum biomarker system for observation within the initial 72 h could efficiently determine the outcomes for patients with TBI, supplement the GCS score, reduce mortality rates, and improve the quality of treatment.

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Disclosures

Conflict of interest: The authors declare that they have no conflict of interest.

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Data availability: The data that underpins the conclusions of this research can be obtained from the corresponding author upon a reasonable request.

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