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The predictive value of serum neopterin for multiple organ dysfunction syndrome in severe burn patients

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Abstract: Objective To investigate the predictive value of serum neopterin for multiple organ dysfunction syndrome (MODS) in severe burn patients.

Methods Seventy-six severe burn patients with burns covering a total body surface area (TBSA) above 70% were included in this study. Of the 76 patients, 29 cases developed MODS (MODS group) and the remaining 47 subjects did not (non-MODS group). From the MODS group, 12 patients died (Death group) and 17 patients survived (Survive group). The serum level of neopterin in the MODS and non-MODS groups were examined by radioimmunoassay on following 1, 3, 7, 14, 21 and 28 post-burn days (PBDs). A receiver operating characteristic (ROC) curve was used to analyse the predictive value of serum neopterin for MODS and death.

Results The serum neopterin level in the MODS group was significantly higher than that of non-MODS group between 3–28 PBDs ($p < 0.001$). However, the serum neopterin levels between the MODS and non-MODS groups following 1 PBD were not statistically significant ($p > 0.05$). The best diagnostic performance of serum neopterin for MODS occurred 14 PBDs with the prediction sensitivity and specificity of 75.86% (56.46%–89.70%) and 85.11% (71.69%–93.80%) respectively. However, serum neopterin levels had no clinical value in predicting the death of

MODS patients. The area under the ROC curve (AUC) was 0.72 (0.58–0.85), 0.81 (0.71–0.92) and 0.83 (0.72–0.94) for serum neopterin as biomarker in the prediction of MODS after 3, 7 and 14 PBDs, respectively. The AUCs were 0.50 (0.27–0.73), 0.53 (0.30–0.76) and 0.56 (0.33–0.79) for serum neopterin as biomarker in prediction of death for MODS patients after 3, 7 and 14 PBDs, respectively.

Conclusion The persistent and significant increase of serum neopterin level is closely related to the development of MODS in patients with severe burns. Serum neopterin is therefore a promising serological marker for MODS early diagnosis, but has little efficacy in the prediction of the likelihood of death in severe burn patients with MODS.

Keywords: MODS; neopterin; death risk; diagnosis; serological marker.

Introduction

Multiple organ dysfunction syndrome (MODS) refers to the clinical syndrome in which two or more organs or systems suffer from simultaneous or sequential dysfunction and thus fail to maintain internal stability in the course of severe trauma, shock, infection and major surgical operations[1]. In patients with severe burns, MODS is one of the most serious complications and main causes of death[2]. The complicated etiology, complicated treatment and poor prognosis of MODS makes it a significant problem for patients with severe burns[3–5]. Early diagnosis of MODS and proper management in severe burn patients can improve their prognosis.

It has been reported that severe burns often trigger an uncontrollable inflammatory response and immune dysfunction, these two factors often lead to the eventual development of MODS[6]. The lymphocyte-macrophage axis *in vivo* is an important response system involved in this pathological process. Therefore, serological markers

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reflecting the activation of this system may provide useful information for early diagnosis of MODS.

Neopterin is synthesised by human macrophages upon stimulation with the cytokine interferon-gamma and is indicative of a pro-inflammatory immune status[7, 8]. It can serve as a marker of cellular immune system activation. Studies have shown that serum and urine neopterin levels are significantly elevated in patients with bacterial or viral infections, immune-related diseases, tumors and organ transplantation[9, 10]. Therefore, a continuous dynamic examination of changes in the levels of neopterin is a helpful method of monitoring cellular immune activation and inflammatory responses.

Material And Methods

Patients

Seventy-six severe burn patients with total body surface area(TBSA) $\geq 70\%$ were included in this study. Of the included 76 patients, 29 cases developed MODS (MODS group) and other 47 subjects did not (non-MODS group). From the MODS group, 12 patients unfortunately died (Death group) while the remaining 17 patients survived (Survive group). The research related to human participation has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration. All the included patients provided written informed consent. The study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Shihezi University.

Serum neopterin examination

The serum level of neopterin in MODS and non-MODS groups were examined by radioimmunoassay on 1, 3, 7, 14, 21 and 28 post burn days (PBDs). Serum neopterin was determined using a radioimmunoassay kit (German Henning, Co. Ltd) and operated strictly according to the manufacturer's instructions. The neopterin standard solution and serum samples with different dilution concentrations were incubated in test tubes with ^{125}I -neopterin and antiserum, respectively.

Statistical methods

Sata11.0 (<http://www.stata.com>; Stata Corporation, College Station, TX) was used to deal with the statistical

Table 1: Main character of the included 68 cases.

Character	
Age(y)	31.2 $\pm$ 14.6
Sex[n,(%)]	
Male	64
Female	12
TBSA(%)	81.2 $\pm$ 8.7
III(%)	41.3 $\pm$ 12.6
Inhalation injury[n,(%)]	
Positive	30
Negative	46

analyses. Measurement data was expressed as $\bar{x} \pm s$ and the comparison between groups was made based on the student-test of the sample mean. The enumeration data were expressed as a relative number, and the comparison between groups was made based on the χ^2 test. A receiver operating characteristic (ROC) curve was used to analyse the predictive value of serum neopterin for (MODS) and death. Two tails $p < 0.05$ was considered as statistical difference.

Results

General characteristics of the included cases

The general characteristic of the included 76 cases are listed in **Table 1**. There were 64 males and 12 females with a mean age of 31.2 ± 14.6 . The median TBSA were 81.2 ± 8.7 with 30 cases of inhalation injury.

MODS and death occurrence time

Of the included 76 patients, 29 cases developed MODS (MODS group) and other 47 subjects did not (non-MODS group). The mean MODS occurrence time was 8.97 ± 3.88 PBDs (**Figure 1**). Of the 29 MODS cases, 12 patients died with a mean post burn survival time of 14.08 ± 5.98 days.

Serum neopterin comparison

The serum neopterin level in the MODS group was significantly higher than that of the non-MODS group between 3~28 PBDs ($p < 0.001$) (**Figure 2**). However, the serum neopterin level was not statistically different

Figure 1: MODS risk in severe burn patients between PBDs 1 to 28.

Figure 2: Bar plot of serum neopterin comparison between MODS and non-MODS groups in PBDs 1 to 28.

Table 2: The serum neopterin comparison between MODS and non-MODS groups in PBDs 1 to 28 ($\bar{x} \pm s$).

Group	MODS(n=29)	Non-MODS(n=47)	t	P
1	11.81±5.62	11.25±6.12	0.399	0.671
3	23.40±11.05	14.03±5.48	4.927	<0.001
7	60.54±27.18	30.33±17.93	5.843	<0.001
14	54.99±25.14	25.70±13.72	6.573	<0.001
21	48.53±17.74	23.48±15.82	6.401	<0.001
28	37.86±14.23	24.13±14.21	4.09	<0.001

between MODS and non-MODS groups following 1 PBD ($p > 0.05$) (Table 2).

Predictive value of serum neopterin for (MODS) and death

The best diagnostic performance of serum neopterin for MODS occurred after 14 PBDs with the prediction

sensitivity and specificity being 75.86% (56.46%~89.70%) and 85.11% (71.69%~93.80%), respectively. However, serum neopterin for death prediction was limited without clinical usage (Table 3). The AUC were 0.72 (0.58~0.85), 0.81 (0.71~0.92) and 0.83 (0.72~0.94) for serum neopterin as biomarker in diagnosis of MODS on PBDs 3, 7 and 14, respectively. The AUC were 0.50 (0.27~0.73), 0.53 (0.30~0.76) and 0.56 (0.33~0.79) for serum neopterin as biomarker in the prediction of death for MODS patients on PBDs 3, 7 and 14, respectively Figure 3.

Discussion

Patients with severe burns require immediate specialised care in order to minimise morbidity and mortality[11, 12]. Despite the continuous improvement of modern medical technology and intensive care in the treatment of severe burns, the mortality rate of severely burned patients is still high especially in patients with sepsis and MODS. Furthermore, it has been reported that MODS is one of the leading causes of death in patients with severe burns[5].

At present, there are no sensitive, specific and practical markers for predicting the occurrence of MODS in extensive burn patients. Although some cytokines and inflammatory mediators can reflect the pathophysiological process of organ damage to a certain extent, there are many associated disadvantages including poor stability, poor specificity and poor susceptibility[13]. Neopterin is stable in blood, urine, ascites and other body fluids of healthy subjects. However, the serum neopterin level is usually elevated in patients with viral infections (such as the human immunodeficiency virus[14, 15], hepatitis B and hepatitis C[16, 17]), bacterial infections, autoimmune disease (such as rheumatoid arthritis[18, 19], systemic lupus erythematosus[20, 21]) and malignant carcinomas. Studies[22] have also demonstrated that neopterin levels in serum also increased in severe infection subjects. Balogh et al[22] investigated the influence of burn trauma on neopterin levels and evaluated whether serum neopterin had a prognostic or diagnostic value. They found that extensive burn injuries can cause a constant increase of serum neopterin concentrations which can be used as a promising parameter for the diagnosis of sepsis. Yao and his colleges[23] performed a prospective study to evaluate the predictive value of serum neopterin for MODS in extensively burned patients and they found that the presence of constant high neopterin serum levels appears to be associated with the development of post-burn MODS. Serum levels of neopterin might be a useful marker for the

Table 3: The diagnostic performance of serum neopterin for (MODS) and death.

Diagnostic efficacy	Sensitivity(95%CI)	Specificity(95%CI)	AUC(95%CI)	Cut off(nmol/L)
MODS				
Day 3	68.97%(49.17%~84.72%)	72.34(57.36%~84.38%)	0.72(0.58~0.85)	17.85
Day 7	79.31(60.28%~92.01%)	74.47(59.65%~86.06%)	0.81(0.71~0.92)	37.64
Day 14	75.86(56.46%~89.70%)	85.11(71.69%~93.80%)	0.83(0.72~0.94)	37.14
Death				
Day 3	50.00(21.09%~78.91%)	64.71(38.33%~85.79%)	0.50(0.27~0.73)	25.64
Day 7	58.33(27.67%~84.83%)	64.71(38.33%~85.79%)	0.53(0.30~0.76)	67.44
Day 14	66.67(34.89%~90.08%)	47.06(22.98%~72.19%)	0.56(0.33~0.79)	53.48

Figure 3: ROC curve of serum neopterin for (MODS) and death [(roc curve for diagnosis of MODS by serum neopterin on PBDs 3(a), PBDs 7 (b), and PBDs 14(c); roc curve for prediction death by serum neopterin on PBDs 3(d), PBDs 7 (e), and PBDs 14(f)].

early identification of extensive burned patients who are at risk for developing MODS.

In our present work, 76 extensive burn patients were included and 29 cases developed MODS (MODS group) with the mean MODS occurrence time was 8.97 ± 3.88 PBDs. We evaluated the prediction efficacy of MODS by the serum neopterin concentration on PBDs 3, 7 and 14. The results demonstrated that the best diagnostic performance of serum neopterin for MODS was on PBDs 14 with the prediction sensitivity and specificity of 75.86% (56.46%~89.70%) and 85.11% (71.69%~93.80%) respectively. Neopterin is therefore a promising serological marker for MODS early diagnosis. However, serum neopterin had little efficacy in the prediction of the risk of death in burn MODS patients. Our results are in accordance with Yao's study[23].

In conclusion, extensive burn injuries usually cause serum neopterin elevation by tissue injury, uncontrollable inflammatory responses and endotoxemia. Dynamic observation of serum neopterin can provide useful information for early diagnosis of MODS in extensive burn patients. However, the sample size of our present study is small and has limited statistical power. Multiple center prospective studies relevant to neopterin level and MODS are needed to further evaluate its clinical efficacy.

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