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脓毒症患者发生凝血功能紊乱的临床特征及预后影响因素分析*

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摘要 目的:探究脓毒症患者发生凝血功能紊乱的临床特征及预后影响因素。**方法:**选择2019年9月~2023年1月本院收治的80例脓毒症患者为本次研究对象,对所有患者开展凝血功能检验,并依据检验结果,将患者分为凝血功能异常组($n=60$)及正常组($n=20$),分析凝血功能障碍异常及正常患者临床特征、凝血功能障碍异常及正常患者病情严重程度,并依据脓毒症患者预后,将其分为存活组($n=64$)及死亡组($n=16$)脓毒症患者预后的单因素与多因素 Logistic 回归分析。**结果:**凝血功能正常组及异常组平均动脉压、体温、白细胞计数(WBC)、纤维蛋白原(FIB)、凝血酶时间(TT)指标水平无较大差异($P>0.05$),与凝血功能正常组比较,凝血功能异常组患者呼吸、脉率、降钙素原(PCT)、C反应蛋白(CRP)指标水平相对较高,部分凝血活酶时间(APTT)、凝血酶原时间(PT)指标水平相对较长,PLT 指标水平相对较高($P<0.05$);与凝血功能正常的脓毒症患者相比较,凝血功能异常患者急性肾损伤(AKI)及急性呼吸窘迫综合征(ARDS)发生率、急性生理与慢性健康评分(APACHE II)及急性生理功能评分(SOFA)评分更高,住ICU时间均相对较长($P<0.05$),机械通气及住院时间比较($P>0.05$);脓毒症患者预后影响因素分析中,结果显示,年龄、体质指数(BMI)、性别、糖尿病史、高血压病史均未对脓毒症患者预后产生较大影响($P>0.05$),PT、PCT、APTT、CRP、SOFA 评分及 APACHE II 评分对脓毒症预后产生严重影响,死亡组患者各指标水平平均高于存活组($P<0.05$);将影响脓毒症患者预后的单因素予以赋值,纳入 Logistic 回归分析,以 PCT、PT、APTT、CRP、SOFA、APACHE II 评分为自变量,结果显示,PCT、PT、CRP、SOFA、APACHE II 评分是影响脓毒症患者预后的独立危险因素($P<0.05$)。**结论:**脓毒症患者发生凝血功能紊乱会对临床相关指标产生影响,从而增加疾病严重程度,依据脓毒症患者预后,研究结果显示,PT、PCT、CRP、SOFA 及 APACHE II 评分均会对脓毒症患者预后产生不良影响,检验上述指标水平,可为临床评估脓毒症预后提供一定参考价值。

关键词:脓毒症;凝血功能异常;临床特征;预后

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To Analyze the Clinical Characteristics and Prognostic Factors of Coagulation Disorders in Patients with Sepsis*

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ABSTRACT Objective: To explore the sepsis patients of blood coagulation dysfunction clinical characteristics and prognosis influencing factors. **Methods:** A total of 80 patients with sepsis admitted to our hospital from September 2019 to January 2023 were selected as the subjects of this study. Coagulation function tests were carried out on all patients. According to the test results, patients were divided into abnormal coagulation function group ($n=60$) and normal coagulation function group ($n=20$). Analysis of abnormal blood coagulation dysfunction and clinical features in patients with normal and abnormal blood coagulation dysfunction and disease severity in patients with normal, and on the basis of the prognosis of patients with sepsis, it can be divided into survival group ($n=64$) and death group ($n=16$) the prognosis of patients with sepsis of single factor and multi-factor Logistic regression analysis. **Results:** There were no significant differences in the mean arterial pressure, body temperature, white blood cell count (WBC), fibrinogen (FIB) and thrombin time (TT) indexes between normal and abnormal groups ($P>0.05$). The levels of respiration, pulse rate, procalcitonin (PCT), C-reactive protein (CRP), partial thromboplastin time (APTT), prothrombin time (PT) and PLT index were relatively high in patients with abnormal coagulation function group ($P<0.05$). Compared with sepsis patients with normal coagulation function, patients with abnormal coagulation function had higher incidence of acute kidney injury (AKI) and acute respiratory distress syndrome (ARDS), acute physiology and chronic health evaluation II (APACHE II) and acute physiological function assessment (SOFA) scores, and longer ICU stay ($P<0.05$). Mechanical ventilation and hospital stay were compared ($P>0.05$); In the analysis of prognostic factors in patients with sepsis, the results showed that age, body mass index (BMI), gender, history of diabetes and history of hypertension did not have a great impact on the prognosis of patients with sepsis ($P>0.05$), while PT, PCT, APTT, CRP, SOFA score and APACHE II score had a serious

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impact on the prognosis of patients with sepsis. All indexes in death group were higher than those in survival group ($P<0.05$). The single factors affecting the prognosis of patients with sepsis were assigned values and included in the Logistic regression analysis. With PCT, PT, APTT, CRP, SOFA and APACHE II scores as independent variables, the results showed that PCT, PT, CRP, SOFA, APACHE II score is the independent risk factors affecting the prognosis of patients with sepsis ($P<0.05$). **Conclusion:** The occurrence of coagulation disorders in patients with sepsis will affect the clinical related indicators, thus increasing the severity of the disease. According to the prognosis of patients with sepsis, the study results show that PT, PCT, CRP, SOFA and APACHE II scores will have adverse effects on the prognosis of patients with sepsis. Can provide certain reference for clinical evaluation of prognosis of sepsis.

Key words: Sepsis; Abnormal coagulation function; Clinical features; Prognosis

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前言

脓毒症是一种以细菌、病毒及真菌感染等为主要发生机制的功能障碍综合征,疾病发生后,机体内炎症因子会大量释放,诱发机体免疫功能紊乱、失调,诱导器官功能障碍,且随疾病进展,会逐渐发生多器官衰竭或休克,严重甚至致人死亡,威胁患者生命健康^[1,2]。随临床对脓毒症的深入性研究发现,脓毒症病发后,破坏宿主的内皮细胞,可在一定程度上对内皮病变产生激活作用,而激活微血栓及炎症通路,使其发生凝血功能障碍,进而导致患者出现凝血因子消耗及持续性血栓,表现出一种低凝血样功能紊乱状态,且轻重程度不一^[3,4]。近年,多项研究表明,脓毒症患者机体内炎症反应,与凝血功能紊乱二者可发生相互促进、相互作用,从而放大级联反应,此外,脓毒症凝血功能紊乱是加速疾病进展,影响患者预后的关键因素^[5,6]。因此,了解脓毒症患者凝血功能紊乱的相关症状及影响患者预后的相关因素具有极大意义。而随着对脓毒症患者凝血功能紊乱的相关认识,加之国内外大量的临床研究在逐渐的深化及修正,临床意在寻找影响脓毒症患者预后的独立风险因素,以为治疗提供理论依据,但由于凝血功能紊乱发生机制复杂及其对脓毒症的预后尚存在不确定因素^[7,8]。鉴于此,本研究拟讨论脓毒症患者发生凝血功能紊乱的临床特征及预后影响因素,现报道如下。

1 资料与方法

1.1 一般资料

选择2019年9月~2023年1月本院收治的80例脓毒症患者为本次研究对象,对所有患者开展凝血功能检验,并依据检验结果,将患者分为凝血功能异常组($n=60$)及正常组($n=20$),并依据脓毒症患者预后,将其分为存活组($n=64$)及死

亡组($n=16$)。所有患者中,男患者47例、女患者33例;患者年龄38-76岁,平均 (63.25 ± 3.25) 岁;BMI:18-26kg/m²,平均 (21.20 ± 2.15) kg/m²。本研究经本院伦理委员会批准。

纳入标准:(1)符合脓毒症相关临床标准^[9];(2)年龄 ≥ 18 岁;(3)患者知情,自主签署同意书;(4)血培养结果呈阳性者;排除标准:(1)年龄 <18 岁及 >80 岁;(2)先天性凝血功能紊乱;(3)肝肾功能障碍;(4)合并恶性肿瘤;(5)免疫抑制类疾病;(6)长期予以抗血小板及抗凝干预者。

1.2 方法

1.2.1 血清水平检验 入院后,利用抗凝试管对所有患者开展8 mL空腹静脉血采集,并以3000 r/min的离心速率、15 min的离心时间对其开展常规离心处理,离心处理结束后,利用无菌试管采集上层血清,置于-20℃环境待检。并针对PCT、CRP开展酶联免疫吸附试验(生产厂家:上海泽叶生物科技有限公司)检验,对WBC予以血细胞全自动分析仪(生产厂家:世联博研(北京)科技有限公司)实施检验,对PLT予以血常规分析仪(生产厂家:深圳市尚道医疗技术有限公司)进行计数,检测过程严格按照试剂盒说明进行。

1.2.2 凝血功能检验 血样本采集及处理方式同上,采集血样本后,针对PT、APTT、TT、FIB等指标予以C3510全自动凝血功能分析仪(生产厂家:北京普利生仪器有限公司)分析,分析过程严格按照仪器说明进行。

1.2.3 APACHE II、SOFA调查 所有患者入院后,均在2h内完成动脉血气分析、血常规及生化检验等相关检查,并依据患者的检查结果及实际情况,确定并记录患者APACHE II及SOFA评分。

1.2.4 凝血功能异常判定标准 依据相关标准^[10],凝血功能障碍诊断标准(SIC) ≥ 4 分即表示凝血功能异常,其中,PT-INR及PLT总分 >2 分,具体见表1。

表1 SIC评价标准(分)

Table 1 SIC Evaluation Criteria (score)

SIC scoring item	0	1	2
PT-INR	≤ 1.2	>1.2	>1.4
PLT($\times 10^9/L$)	≥ 150	<150	<100
SOFA score and (score) of cardiovascular/Kidney/Respiratory/liver 4 items	0	1	≥ 2

1.3 资料收集

对所有患者开展一般资料问卷调查,并结合患者临床相关

指标检查结果采集患者信息,其中主要包括平均动脉压、体温、WBC、FIB、TT、PCT、CRP、APTT、PT、PLT、AKI、ARDS发生率、

APACHE II、SOFA 评分、住 ICU 时间、机械通气、住院时间、年龄、BMI、性别、糖尿病史、高血压病史等。

1.4 统计学方法

应用 SPSS20.0 软件分析数据,以 $\bar{x} \pm s$ 表示计量资料,组间比较采用独立样本 t 检验,组内比较采用配对样本 t 检验;计数资料用百分比表示,组间比较采用 χ^2 检验,多因素予以 Logistic 回归方程予以分析, $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 凝血功能障碍异常及正常患者临床特征

凝血功能正常组及异常组平均动脉压、体温、WBC、FIB、TT 指标水平无较大差异($P > 0.05$),与凝血功能正常组比较,凝血功能异常组患者呼吸、脉率、PCT、CRP 指标水平相对较高,APTT、PT 指标水平相对较长,PLT 指标水平相对较高($P < 0.05$),见表 2。

表 2 凝血功能障碍异常及正常患者临床特征($\bar{x} \pm s$)

Table 2 Blood coagulation dysfunction in patients with abnormal and normal clinical features($\bar{x} \pm s$)

Clinical features	The group with normal coagulation function($n=20$)	The group with abnormal coagulation function($n=60$)	t	P
Pulse rate (times/min)	109.51±13.20	121.23±14.10	3.269	0.002
Body temperature (°C)	37.2±1.10	37.3±1.20	0.329	0.743
Breaths (times/min)	24.10±5.20	27.55±5.10	2.607	0.011
Mean arterial pressure (mmHg)	73.21±11.20	68.98±12.10	1.378	0.172
PCT(ng/mL)	35.58±5.32	55.17±5.25	14.405	<0.001
WBC($\times 10^9/L$)	17.21±2.32	18.15±2.15	1.660	1.101
CRP(mg/L)	177.35±26.21	197.25±31.10	2.571	0.012
TT(s)	16.58±2.11	17.11±2.13	0.966	0.337
PT(s)	15.36±2.17	17.75±2.12	4.341	<0.001
APTT(s)	43.25±6.56	53.14±6.78	5.694	<0.001
FIB(g/L)	5.15±0.85	4.86±0.80	1.382	0.171
PLT($\times 10^9/L$)	211.23±31.25	92.36±12.26	24.553	<0.001

2.2 凝血功能障碍异常及正常患者病情严重程度

与凝血功能正常的脓毒症患者相比较,凝血功能异常患者 AKI 及 ARDS 发生率、APACHE II 及 SOFA 评分更高,住 ICU

时间均相对较长($P < 0.05$),机械通气及住院时间比较($P > 0.05$),见表 3。

表 3 凝血功能障碍异常及正常患者病情严重程度($\bar{x} \pm s$)

Table 3 Patients with abnormal blood coagulation dysfunction and normal illness severity($\bar{x} \pm s$)

Evaluation index	Normal coagulation function group ($n=20$)	Group with abnormal coagulation function ($n=60$)	t	P
APACHE II score (points)	13.21±2.01	19.75±2.32	11.265	<0.001
SOFA score (score)	6.36±1.01	11.12±1.52	13.049	<0.001
Length of stay in ICU (d)	6.01±0.92	8.65±1.21	8.921	<0.001
Length of hospital stay (d)	16.89±2.10	17.78±2.16	1.607	0.112
Mechanical ventilation duration (d)	2.89±0.42	3.12±0.51	1.819	0.073
ARDS[n(%)]	7(35.00)	38(63.33)	4.893	0.027
AKI[n(%)]	9(45.00)	45(75.00)	6.154	0.013

2.3 脓毒症患者预后的单因素分析

脓毒症患者预后影响因素分析中,结果显示,年龄、BMI、性别、糖尿病史、高血压病史均未对脓毒症患者预后产生较大影响($P > 0.05$),PT、PCT、APTT、CRP、SOFA 评分及 APACHE II 评分对脓毒症患者预后产生严重影响,死亡组患者各指标水平均

高于存活组($P < 0.05$),见表 4。

2.4 脓毒症患者预后多因素 Logistic 回归分析

将影响脓毒症患者预后的单因素予以赋值,纳入 Logistic 回归分析,以 PCT、PT、APTT、CRP、SOFA、APACHE II 评分为自变量,结果显示,PCT、PT、CRP、SOFA、APACHE II 评分是

表 4 脓毒症患者预后的单因素分析

Table 4 Univariate analysis of the prognosis of sepsis patients

Clinical data	Survival group (n=64)	Group of Death (n=16)	Statistical value	P
Age (year)	63.25±3.21	64.14±3.25	0.990	0.325
BMI(kg/m ²)	21.15±2.10	21.35±2.32	0.334	0.740
Gender				
Male	38(59.38)	9(56.25)	0.052	0.820
Female	26(40.62)	7(43.75)		
Diabetes history				
Yes	14(21.87)	4(25.00)	0.005	0.947
No	50(78.13)	12(75.00)		
History of hypertension				
Yes	17(26.56)	6(37.50)	0.309	0.578
No	47(73.44)	10(62.50)		
PCT(ng/mL)	3.26±0.51	25.10±4.11	42.016	<0.001
PT(s)	15.13±2.01	22.32±3.21	11.232	<0.001
APTT(s)	33.25±5.06	37.63±5.25	3.074	0.003
CRP(mg/L)	63.65±10.01	176.89±20.14	32.136	<0.001
SOFA (part)	5.69±0.78	9.65±1.17	16.309	<0.001
APACHE II score (points)	11.23±1.25	33.69±5.04	32.411	<0.001

表 5 脓毒症患者预后因素赋值

Table 5 Multiple prognosis values for patients with sepsis

Independent variable	The assignment
PCT(ng/mL)	≤7.32ng/mL=0, >7.32ng/mL=1
PT(s)	≤15.48s=0, >15.48s=1
APTT(s)	≤36.74s=0, >36.74s=1
CRP(mg/L)	≤86.73ng/mL=0, >86.73ng/mL=1
SOFA (part)	≤6.48 score=0, >6.48score=1
APACHE II score (points)	≤15.88 score=0, >15.88 score=1

表 6 脓毒症患者预后多因素 Logistic 回归分析

Table 6 The prognosis of patients with sepsis multivariable Logistic regression analysis

Independent variable	β	SE	Waldχ ²	OR(95%CI)	P
PCT(ng/mL)	0.693	0.121	21.263	2.121(0.569-5.625)	<0.001
PT(s)	0.862	0.141	15.893	2.421(1.140-6.698)	<0.001
APTT(s)	0.354	0.103	0.958	1.162(0.728-7.892)	0.352
CRP(mg/L)	0.786	0.023	25.156	1.817(1.021-8.779)	<0.001
SOFA (part)	0.889	0.087	16.145	2.315(0.695-7.267)	<0.001
APACHE II score (points)	0.911	0.059	11.326	1.968(1.012-8.521)	0.001

影响脓毒症患者预后的独立危险因素($P<0.05$),见表 6。

3 讨论

脓毒症主要是由于机体在真菌、细菌、病毒等病原体的感染过程中,机体反应失调导致,是一种以组织器官功能衰竭为临床特征的炎症反应综合征^[11,12]。近年,随着对脓毒症疾病的深

入性研究,临床已证实,脓毒症发生过程中,会进一步激活凝血系统,从而对机体内炎症反应的发展产生促进作用,而大量炎症因子的释放,又会对凝血系统产生二次激活,二者相互作用,相互促进,导致病情加重,而有研究表明,重症脓毒症患者,常伴随凝血功能障碍^[13,14],当患者出现凝血功能异常时,会对整个治疗过程产生影响,且凝血功能异常可在治疗过程中的任意一个阶段发生,并随着疾病进展而发生不同的变化,因此,有限检测患者机体凝血功能相关指标水平,有利于实时掌握患者病情进展,且在改善患者预后中占据重要地位^[15,16]。鉴于此,积极了解脓毒症凝血功能异常发生后的临床特征,了解影响其预后的危险因素,并予以早期控制,对于改善凝血功能异常及预后具有极大意义。

研究结果显示,凝血功能正常组及异常组平均动脉压、体温、WBC、FIB、TT 指标水平无较大差异,与凝血功能正常组比较,凝血功能异常组患者呼吸、脉率、PCT、CRP 指标水平相对较高,APTT、PT 指标水平相对较长,PLT 指标水平相对较低。分析原因在于,PT、TT、APTT、FIB 是临床用于检测凝血功能最常见的检测因子,可评估凝血功能是否异常,脓毒症发生后,内毒素及单核细胞可对机体产生影响,并对外源性凝血功能产生刺激、激活作用,以至于凝血因子被大量消耗,以此降低凝血因子合成量,刺激纤溶亢进,延长 PT、TT 及 APTT 时长,导致 FIB 水平降低,但本研究中,TT 及 FIB 水平并未呈现显著变化,原因与本研究与既往研究相比,在凝血功能紊乱分组的截点可能存在一定差异性相关^[17,18]。脓毒症发生后,机体炎症反应会进一步损伤内皮细胞,激活单核细胞,增加机体内组织细胞因子的表达,从而刺激外源性凝血途径的有效启动,机体内的炎症反应与内皮细胞的损伤,可活化血小板、聚集 PLT,当内皮细胞与 PLT 相互作用增加时,会使机体内血小板呈现高凝状态,从而降低 PLT 指标水平^[19,21]。研究结果显示,与凝血功能正常的脓毒症患者相比较,凝血功能异常患者 AKI 及 ARDS 发生率、APACHE II 及 SOFA 评分、住 ICU 时间均相对较高,机械通气及住院时间比较无较大意义。分析原因在于,APACHE II 可针对危重疾病患者的病情严重程度进行有效的评估,SOFA 可有效评估机体器官功能的衰竭程度,针对脓毒症患者,当其凝血功能紊乱时,疾病越严重,且预后越差,因此 APACHE II 及 SOFA 评分越高,研究结果与 Iba T 等^[22]既往研究结果类似,凝血功能异常的脓毒症患者,其病情更加严重,进而导致 AKI 及 ARDS 发生风险更高^[23],而由于脓毒症患者不管是否存在凝血功能障碍,其总体治疗效果及预后均效果不佳,对患者的机体健康均会产生较大影响,因此住院时间与机械通气时间上,凝血功能正常及异常组患者无较大差异^[24,25]。研究结果显示,将影响脓毒症患者预后的单因素予以赋值,纳入 Logistic 回归分析,结果显示,PCT、PT、APTT、CRP、SOFA、APACHE II 评分是影响脓毒症患者预后的独立危险因素。分析原因在于,经内源性多肽酶切割的 PCT,可在一定条件下产生活性降钙素,在此基础上,作用于降钙素受体,刺激钙离子使其紊乱,而紊乱的钙离子可与器官衰竭发生产生一定相关性,因此,PCT 可对细胞吸收钙离子产生极大的促进作用,从而导致细胞代谢紊乱,增加器官衰竭速度,最终增加死亡风险,结果与秦苏徽等^[26]相关

研究结果类似;PT 指标水平可有效评估外源性凝血功能,当机体内凝血因子水平低于正常值的 1/2 时,会导致 PT 明显延长,因此,临床可通过 PT 指标水平的延长时间,评估患者的病情严重程度,本研究中,死亡组患者的 PT 水平明显长于存活组患者,PT 水平可有效评估脓毒症患者预后,Delabranche X 等^[27]相关研究中,针对 265 例脓毒症患者前瞻性研究,结果表明 PT 为影响脓毒症患者预后的独立因素,与本研究结果一致;APACHE II 评分可针对患者机体内的异常生理参数予以反映,而 SOFA 可有效评估患者机体内器官功能的衰竭情况,二者均可对脓毒症患者预后进行有效评估,结果与 Huang X 等^[28]相关研究结果类似;脓毒症发病会对机体的免疫细胞产生刺激作用,使其释放 CRP,原因与脓毒症患者机体内存在大量的炎症因子,而免疫细胞受炎症因子作用后,会产生大量 CRP,并将其释放至血液中,而据有关报道表示^[29],CRP 的主要作用靶点为脂肪酸合成酶相关死亡结构蛋白,当 CRP 作用于结构域蛋白后,会刺激组织细胞凋亡,并加速进程,诱发多器官衰竭,影响脓毒症患者预后,结果与 Shim BS 等^[30]相关研究结果类似。

综上所述,脓毒症患者发生凝血功能紊乱会对临床相关指标产生影响,从而增加疾病严重程度,依据脓毒症患者预后,PT、PCT、CRP、SOFA 及 APACHE II 评分均会对脓毒症患者预后产生不良影响,检验上述指标水平,可为临床评估脓毒症预后提供一定参考价值。

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