

doi: 10.13241/j.cnki.pmb.2021.12.011

中性粒细胞绝对值对脓毒血症并发肾损伤的早期诊断*

董锦秀 方玉明 周红娟 张志飞 夏正新[△]

(上海交通大学医学院附属第九人民医院急诊科 上海 200011)

摘要 目的:探讨中性粒细胞绝对值对脓毒血症并发肾损伤的早期诊断价值。**方法:**2016年1月-2020年6月选择在本院重点监护病房(Intensive care unit, ICU)和急诊科进行诊治的脓毒血症患者145例,测定与计算患者的中性粒细胞绝对值,调查患者的临床资料并进行早期诊断分析。**结果:**在145例患者中,发生肾损伤69例(肾损伤组),发生率为47.6%。肾损伤组的年龄、性别、白细胞计数(white blood cell, WBC)计数、C反应蛋白(C reactive protein, CRP)、降钙素原(procalcitonin, PCT)、体重指数等与非肾损伤组对比差异无统计学意义($P>0.05$)。肾损伤组的肌酐(Serum creatinine, Scr)和尿素氮(Blood urea nitrogen, BUN)、急性生理和慢性健康评分II (acute physiology and chronic health evaluation II, APACHE II)评分、序贯多器官功能障碍评分(sequential organ failure assessment, SOFA)都显著高于非肾损伤组($P<0.05$)。肾损伤组的中性粒细胞绝对值都显著高于非损伤组($P<0.05$)。logistic回归分析显示中性粒细胞绝对值、BUN、Scr、APACHE II评分、SOFA评分都为影响肾损伤发生的主要独立因素($P<0.05$)。**结论:**脓毒血症患者多伴有肾损伤,可导致中性粒细胞绝对值升高,中性粒细胞绝对值也是导致脓毒血症并发肾损伤的主要因素,也具有的诊断价值。

关键词:中性粒细胞绝对值;脓毒血症;肾损伤;诊断;急性生理和慢性健康评分II;序贯多器官功能障碍评分

中图分类号:R631.2;R692;R459.7 **文献标识码:**A **文章编号:**1673-6273(2021)12-2249-04

Application of Absolute Value of Neutrophils in Early Diagnosis of Sepsis Combined with Renal Injury*

DONG Jin-xiu, FANG Yu-ming, ZHOU Hong-juan, ZHANG Zhi-fei, XIA Zheng-xin[△]

(Emergency Department, The Ninth People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, 200011, China)

ABSTRACT Objective: To investigate the values of absolute neutrophils in the early diagnosis of sepsis with renal injury. **Methods:** A total of 145 patients with sepsis, who were diagnosed and treated in the Intensive Care Unit (ICU) and Emergency departments of our hospital from January 2016 to June 2020, were selected. The absolute values of neutrophils of the patients were detected and calculated, and clinical data and early diagnosis were recorded. **Results:** There were 69 cases of renal injury (kidney injury group) in 145 cases, the incidence was 47.6%. There were not statistical significance in the age, gender, WBC count, CRP, PCT, body mass index, etc. between the kidney injury group and the non-kidney injury group ($P>0.05$). The Scr and BUN, APACHE II scores, SOFA scores in the kidney injury group were significantly higher than those in the non-kidney injury group ($P<0.05$). The absolute values of neutrophils in the kidney injury group were significantly higher than those in the non-injury group ($P<0.05$). Logistic regression analysis showed that the absolute value of neutrophils, BUN, Scr, APACHE II score, and SOFA score were the main independent factors affecting the occurrence of kidney injury ($P<0.05$). **Conclusion:** Patients with sepsis are mostly accompanied by renal injury, which can lead to increase of the absolute value of neutrophils. The absolute value of neutrophils is also the main factor leading to sepsis with renal injury, with good diagnostic value.

Key words: Neutrophil absolute value; Sepsis; Kidney injury; Diagnosis; Acute physiology and chronic health score II; Sequential multiple organ dysfunction score

Chinese Library Classification (CLC): R631.2; R692; R459.7 **Document code:** A

Article ID: 1673-6273(2021)12-2249-04

前言

脓毒血症(sepsis)患者具有比较高的病死率,是临床上危重患者死亡的重要原因之一,是由内外在多种因素作用的结果,多需要在ICU诊治^[1,2]。随着病情的进展,脓毒血症可进一步发

展,甚至可导致休克和多器官功能衰竭,给个人、家庭、社会带来了巨大的负担,为此需要进行早期病情诊断与预后预测。肾功能损伤是脓毒血症最常导致的器官功能障碍,脓毒血症并发肾损伤除了影响患者的肾功能外,也会延长患者的住院时间,提高患者的死亡率^[3,4]。肾损伤的病情判断对改善预后具有重要

* 基金项目:国家自然科学基金面上项目(31170828, 31370884)

作者简介:董锦秀(1989-),女,硕士,住院医师,研究方向:脓毒症,电话:15216695235, E-mail: Dong152166@163.com

△ 通讯作者:夏正新(1978-),男,本科,副主任医师,研究方向:脓毒症,电话:18321171781, E-mail: 18321171781@139.com

(收稿日期:2020-11-03 接受日期:2020-11-26)

意义,早期采用正确的干预措施可逆转肾功能损害^[5,6]。常规的监测指标如白细胞(White blood cells, WBC)、心率、体温等在脓毒血症的诊断方面缺乏特异性,更不能反映预后。传统的炎症指标是经典的估计感染严重程度的实验室指标,能区分细菌感染所致的特异性炎症及非特异性炎症,但是在肾损伤中的判断效应还不明确。脓毒血症并发肾损伤的发病机制涉及免疫系统、氧化应激、内皮细胞微脉管等系统导致的肾小管细胞损伤的过程,也是一个多步骤、多基因参与的过程^[7,8]。中性粒细胞(Neutrophils)是免疫应答中免疫防御的主要防线,也是机体重要的免疫细胞。其作为专职的吞噬细胞,吞噬对象不仅以细菌为主,也能吞噬异物,也具有趋化作用,具有无抗原提呈、对抗胞外寄生菌感染、髓过氧化物酶杀菌等多种特点^[9,10]。CD64 是 IgG Fc 段受体之一,也是中性粒细胞膜表面发现的 CD 分子,能被 CD64 的抗体识别,对 IgG 和 IgG3 具有较高的亲和性^[11]。其主要分布于树突细胞、单核细胞等抗原递呈细胞表面^[12]。在机体发生感染或创伤性疾病时,可诱导中性粒细胞表面大量表达 CD64,导致 CD64 表达水平升高^[13,14]。本文具体探讨了中性粒细胞绝对值对脓毒血症并发肾损伤的早期诊断价值,以明确中性粒细胞的作用机制。现总结报道如下。

1 对象与方法

1.1 研究对象

2016 年 1 月 -2020 年 6 月选择在本院重点监护病房(Intensive care unit, ICU) 和急诊科进行诊治的脓毒血症患者 145 例,纳入标准:首次入住 ICU,发病到入院时间 ≤ 48 h;符合脓毒血症的诊断标准(血培养结果或存在一个明确的细菌感染部位(革兰氏阴性菌感染);所有入组者均经过授权委托人知情同意签字;临床与调查资料完整;本院伦理委员批准了此次研究;年龄 20~80 岁。排除标准:入院后 24 h 内死亡者;颅脑损伤、胸腹腔脏器的损伤以及骨折等合并伤患者;妊娠或哺乳期妇女;入院前 1 个月内使用大剂量激素者;恶性肿瘤、血液系统疾病

者;传染性疾病者。

1.2 中性粒细胞绝对值计算

采集患者静脉血样本 2~3 mL, 抗凝后 4℃ 静置 30 min, 3000 rpm 离心 15 min。取下层全血细胞, CD64/CD163 混合抗体 50 μ L 于测定管中, 然后取抗凝全血 100 μ L 加入测定管中, 振荡后室温避光反应 20 min, 在 FACSCantow II 流式细胞仪上检测中性粒细胞绝对值, 以 CD64/CD163 指数进行表示。试剂及仪器均由意大利生物梅里埃公司提供, 检验时间 ≤ 30 min, 检测灵敏度为 0.005 ng/mL, 严格按照仪器与试剂说明书操作。

1.3 数据收集

记录患者入 ICU 的一般资料(年龄、性别、BMI、WBC、CRP、PCT);同时记录反映患者肾功能的指标, 包括 Scr、BUN 等;也记录反映患者病情状态的指标, 包括 SOFA、APACHE II 评分等指标。

1.4 肾损伤判断标准

记录所有患者在 ICU 期间发生的肾损伤情况, 肾损伤判断标准:48 h 内肾功能急剧下降, 表现为尿量减少 ≥ 6 h 或 SCr 上升 $>50\%$ 。

1.5 统计方法

应用 SPSS 19.00, 计量资料以 $\bar{x} \pm s$ 表示, 对比用 t 检验, 计数资料采用%表示, 对比 χ^2 检验, 影响因素分析采用 logistic 回归分析, $P < 0.05$ 有统计学意义。

2 结果

2.1 肾损伤发生情况

在 145 例患者中, 发生肾损伤 69 例(肾损伤组), 未发生肾损伤 76 例(非肾损伤组), 发生率为 47.6%。

2.2 一般资料对比

肾损伤组的年龄、PCT、体重指数、性别、WBC 计数、CRP 等与非肾损伤组对比差异无统计学意义($P > 0.05$), 见表 1。

表 1 两组一般资料对比

Table 1 Comparison of general data between two groups

Groups	n	Age (years)	Gender (M/F)	WBC count($\times 10^9/L$)	CRP(mg/dl)	PCT(ng/mL)	BMI(kg/m ²)
Renal injury group	69	56.22 $\pm$ 4.29	39/30	15.79 $\pm$ 3.29	54.29 $\pm$ 2.57	8.24 $\pm$ 1.30	22.17 $\pm$ 2.75
Non-renal Injury group	76	56.14 $\pm$ 3.89	43/33	16.01 $\pm$ 4.11	54.20 $\pm$ 3.11	8.45 $\pm$ 2.11	22.08 $\pm$ 3.17

2.3 肾功能与病情评分对比

肾损伤组的 BUN、Scr、APACHE II 评分与 SOFA 评分都显著高于非肾损伤组($P < 0.05$), 见表 2。

2.4 中性粒细胞绝对值对比

肾损伤组的中性粒细胞绝对值都显著高于非损伤组($P < 0.05$), 见表 3。

表 2 两组肾功能与病情评分对比($\bar{x} \pm s$)

Table 2 Comparison of renal function and disease score between two groups ($\bar{x} \pm s$)

Groups	n	BUN(mmol/L)	Scr(μ mol/L)	APACHE II score (score)	SOFA score (score)
Renal injury group	69	12.31 $\pm$ 1.33*	137.20 $\pm$ 10.44*	18.53 $\pm$ 2.14*	9.51 $\pm$ 0.44*
Non-renal injury group	76	6.18 $\pm$ 0.49	73.65 $\pm$ 11.62	15.00 $\pm$ 1.47	7.87 $\pm$ 0.81

Note: compared with the non-renal injury group, * $P < 0.05$.

表 3 两组中性粒细胞绝对值对比($\bar{x} \pm s$)Table 3 Comparison of absolute values of neutrophils between two groups ($\bar{x} \pm s$)

Groups	n	Absolute value of neutrophils
Renal injury group	69	7832.88± 139.39*
Non-renal injury group	76	2366.98± 176.28

2.5 影响因素分析

在 145 例患者中,以发生肾损伤作为因变量,以年龄、PCT、体重指数、性别、WBC 计数、CRP、BUN、Scr、APACHE II 评分与 SOFA 评分、中性粒细胞绝对值等作为自变量,logistic

回归分析显示中性粒细胞绝对值、BUN、Scr、APACHE II 评分、SOFA 评分都为影响肾损伤发生的主要独立因素 ($P<0.05$),见表 4。

表 4 脓毒血症患者发生肾损伤的多因素分析(n=145)

Table 4 Multi-factor analysis of renal injury in patients with sepsis (n=145)

Indicators	AUC	S	P	95%CI	
				Lower limit	Upper limit
Absolute value of neutrophils	0.671	0.064	0.025	1.489	4.823
BUN	0.562	0.193	0.000	1.942	3.933
Scr	0.513	0.089	1.009	1.003	3.913
APACHE II score	0.781	0.133	0.000	2.984	9.111
SOFA score	0.722	0.182	0.000	1.738	5.844

3 讨论

脓毒血症是一种可危及生命的临床综合征,也已成为 ICU 患者死亡的主要原因之一,且近年来发病人数逐年增加^[15]。脓毒血症并发肾损伤的确切机制和临床特定尚未探明,早期诊断肾损伤对改善预后具有重要意义。本研究显示肾损伤组的 APACHE II 评分与 SOFA 评分都显著高于非肾损伤组,王海波^[16]等学者的研究探讨 APACHE II 和 SOFA 评分对脓毒症急性肾损伤患者的预后评估价值,结果显示脓毒症肾损伤患者的 APACHE II 及 SOFA 评分均高于非急性肾损伤患者,说明 APACHE II、SOFA 评分对脓毒症肾损伤患者整体预后都有较好的预测价值,提示肾功能损伤是脓毒症最常导致的器官功能障碍,也是导致脓毒症患者的主要死亡原因之一^[17]。现代研究表明肾脏血流量不足会促使蛋白沉积于管腔,使得肾脏血流量减少,小球基底膜通透性降低,导致肾功能损伤^[18,19]。也有研究发现年龄增加、氧自由基的过量释放等是脓毒血症患者肾脏损害的高危险因素,导致患者病情恶化^[20]。脓毒血症病情进展快,目前临床上用于评判感染的指标有 WBC、ALT,但不是感染的独立预测指标,诊断的效果一直不佳。理想化的生物标志物应具备的特征:(1)不需连续监测,一次检测的效果比较好;(2)检测时间短,有较高的灵敏性和特异性;(3)可预测患者的病情变化与预后;(4)检测方法应当便捷可靠,不需要涉及大量的仪器设备,也不需要大量的人力投入^[21]。本研究显示肾损伤组的 BUN、Scr 都显著高于非肾损伤组,孙志刚^[22]等学者的探究血清 Scr 水平对脓毒血症患儿继发急性肾损伤的早期预测价值,结果显示急性肾损伤入组 24 h 时血清 Scr 水平较入组 0 h 时明显升高,非急性肾损伤组血清 Scr 水平各时点均未见明显

变化,急性肾损伤入组 24 h 时 Scr 水平显著高于非急性肾损伤组,与本研究类似。不过 BUN、Scr 不能确切地反映年龄、性别、体重、肝功能等多重因素影响^[22,23]。

中性粒细胞来源于骨髓的髓样干细胞,是白细胞中数量最多的一种细胞,主要存在于人体外周血中,具有更新快、寿命短的特点^[24]。中性粒细胞作为专职的吞噬细胞,可通过抗体依赖性细胞毒作用、细胞吞噬实现对介导炎症介质释放的作用^[26]。中性粒细胞 CD64 属于和免疫球蛋白具有很高的亲和性,对免疫球蛋白 IgG 段、Fc 段的识别能力比较强,主要是集中分布在白细胞表面,在先天性与后天性免疫应答过程中都有参与^[27,28]。CD64 的相对分子量是在 70000 左右,在树突状细胞、巨噬细胞、单核细胞中表面高表达^[29,30]。一旦中性粒细胞被内外在因素刺激下,CD64 可呈现高表达情况,且刺激强度与表达量成正相关。也有学者研究认为,当机体受到炎症细胞因子的刺激后可导致 CD64 水平增加,且上升程度与炎症细胞因子的表达水平显著相关^[31-33]。本研究显示肾损伤组的中性粒细胞绝对值都显著高于非损伤组,与邓龙天^[34]的研究类似,探索脓毒症患者发生急性肾损伤的危险因素,结果显示脓毒症患者发生急性肾损伤的发生率为 56.5%,脓毒症急性肾损伤组患者中性粒细胞绝对值显著高于脓毒症非急性肾损伤组。logistic 回归分析显示中性粒细胞绝对值、BUN、Scr、APACHE II 评分、SOFA 评分都为影响肾损伤发生的主要独立因素。当前有研究显示外周血中性粒细胞 CD64 上调表达可表明整个细胞群体发生的变化,其表达程度与组织损伤、临床感染密切相关,可作为机体对感染所产生的系统反应的指标^[35-37]。本研究也存在一定不足,没有对患者中性粒细胞绝对值进行动态检测与计算,纳入患者的数量比较少,且影响并发肾损伤的影响因素比较多,将在下一步深入

分析。

综上所述,脓毒血症患者多伴有肾损伤,可导致中性粒细胞绝对值升高,中性粒细胞绝对值也是导致脓毒血症并发肾损伤的主要因素,且具有很好的诊断价值。

参考文献(References)

- [1] Zheng R, Pan H, Wang JF, et al. The association of coagulation indicators with in-hospital mortality and 1-year mortality of patients with sepsis at ICU admissions: A retrospective cohort study [J]. *Clinica Chimica Acta*, 2020, 504: 109-118
- [2] Ding MC. Sepsis: recognition, diagnosis and early management[J]. *Bju International*, 2018, 121(4): 497-514
- [3] Sae-Khow K, Tachaboon S, Wright H L, et al. Defective Neutrophil Function in Patients with Sepsis Is Mostly Restored by ex vivo Ascorbate Incubation[J]. *J Inflamm Res*, 2020, 13(8): 263-274
- [4] Sengupta S, Caldwell C C, Nomellini V. Distinct Neutrophil Populations in the Spleen During PICS [J]. *Front Immunol*, 2020, 11(12): 804-806
- [5] Stiel CU, Ebenebe CU, Trochimuk M, et al. Markers of NETosis Do Not Predict Neonatal Early Onset Sepsis: A Pilot Study[J]. *PLoS One*, 2019, 7(9): 555-559
- [6] Cichon I, Ortmann W, Bednarz A, et al. Reduced Neutrophil Extracellular Trap (NET) Formation During Systemic Inflammation in Mice With Menkes Disease and Wilson Disease: Copper Requirement for NET Release[J]. *Front Immunol*, 2019, 10(8): 3021-3027
- [7] Collazos J, De La Fuente B, De La Fuente J, et al. Factors associated with sepsis development in 606 Spanish adult patients with cellulitis [J]. *BMC Infect Dis*, 2020, 20(1): 211-219
- [8] Cox LE. Neutrophil extracellular trap formation and nuclease activity in septic patients[J]. *Epidemiol Infect*, 2020, 20(1): 15-19
- [9] Ghosh A, Nanda P, Tripathy S, et al. Glycogen Accumulation in Neutrophil Can Be a Marker of Sepsis[J]. *Cells*, 2020, 10(1): 22-24
- [10] Gong Y, Li D, Cheng B, et al. Increased neutrophil percentage-to-albumin ratio is associated with all-cause mortality in patients with severe sepsis or septic shock[J]. *Crit Care*, 2020, 148(13): e87
- [11] Ho J, Chan H, Liang Y, et al. Cathelicidin preserves intestinal barrier function in polymicrobial sepsis[J]. *Stem Cell Res Ther*, 2020, 24(1): 47-49
- [12] Huggard D, Doherty D G, Molloy E J. Immune Dysregulation in Children With Down Syndrome [J]. *J Vet Intern Med*, 2020, 8(14): 73-76
- [13] Ismail Hassan F, Didari T, Khan F, et al. A Review on The Protective Effects of Metformin in Sepsis-Induced Organ Failure [J]. *Cell J*, 2020, 21(4): 363-370
- [14] Kikuchi S, Piraino G, O'connor M, et al. Hepatocyte-Specific Deletion of AMPK α 1 Results in Worse Outcomes in Mice Subjected to Sepsis in a Sex-Specific Manner [J]. *Front Immunol*, 2020, 11(12): 210-214
- [15] Marki A, Ley K. Leaking chemokines confuse neutrophils [J]. *J Clin Invest*, 2020, 130(5): 2177-2179
- [16] 王海波, 徐丽娟, 李克鹏, 等. KDIGO 标准 APACHE II 与 SOFA 评分对脓毒症急性肾损伤患者的预后评估 [J]. *中国急救医学*, 2013, 33(6): 499-502
- [17] Carroll GM, Burns GL, Petit JA, et al. Does postoperative inflammation or sepsis generate neutrophil extracellular traps that influence colorectal cancer progression? A systematic review[J]. *Surg Open Sci*, 2020, 2(2): 57-69
- [18] Martin-Fernandez M, Vaquero-Roncero LM, Almansa R, et al. Endothelial dysfunction is an early indicator of sepsis and neutrophil degranulation of septic shock in surgical patients[J]. *BJS Open*, 2020, 4(3): 524-534
- [19] Moffet JR, Mahadeo KM, Mcarthur J, et al. Acute respiratory failure and the kinetics of neutrophil recovery in pediatric hematopoietic cell transplantation: a multicenter study [J]. *Bone Marrow Transplant*, 2020, 55(2): 341-348
- [20] Monari E, Troia R, Magna L, et al. Urine neutrophil gelatinase-associated lipocalin to diagnose and characterize acute kidney injury in dogs[J]. *J Vet Intern Med*, 2020, 34(1): 176-185
- [21] Nesargi P, Niranjani HS, Bandiya P, et al. Neutrophil Volume, conductivity and scatter (VCS) as a screening tool in neonatal sepsis[J]. *Sci Rep*, 2020, 10(1): 4457-4459
- [22] 孙志刚, 赵志红, 马燕, 等. 血清 NT-proBNP、尿液 NGAL 对脓毒血症患儿继发急性肾损伤的早期预测价值 [J]. *山东医药*, 2017, 57(28): 60-62
- [23] Peters AL, Straat M, Vlaar AP, et al. Reactive oxygen species induce antibiotic tolerance during systemic *Staphylococcus aureus* infection [J]. *Transfusion*, 2020, 5(2): 282-290
- [24] Polilli E, Sozio F, Frattari A, et al. Comparison of Monocyte Distribution Width (MDW) and Procalcitonin for early recognition of sepsis[J]. *PLoS One*, 2020, 15(1): e0227300
- [25] Walstein K, Völlger L, Reuner F, et al. The diagnostic and prognostic values of serum and urinary kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin in sepsis induced acute renal injury patients[J]. *BMC Anesthesiol*, 2020, 24(10): 5604-5617
- [26] Yin WP, Li JB, Zheng XF, et al. Effect of neutrophil CD64 for diagnosing sepsis in emergency department[J]. *World J Emerg Med*, 2020, 11(2): 79-86
- [27] Yong H, Wu G, Chen J, et al. lncRNA MALAT1 Accelerates Skeletal Muscle Cell Apoptosis and Inflammatory Response in Sepsis by Decreasing BRCA1 Expression by Recruiting EZH2[J]. *Mol Ther Nucleic Acids*, 2020, 19(8): 97-108
- [28] Yao Q, Wang P, Wang X, et al. A retrospective study of risk factors for severe acute respiratory syndrome coronavirus 2 infections in hospitalized adult patients[J]. *Nat Microbiol*, 2020, 130(5): 390-399
- [29] Ahn SY, Maeng YS, Kim YR, et al. In vivo monitoring of dynamic interaction between neutrophil and human umbilical cord blood-derived mesenchymal stem cell in mouse liver during sepsis [J]. *Stem Cell Res Ther*, 2020, 11(1): e44
- [30] Aldecoa C, Heredia-Rodríguez M, Ren C, et al. Sepsis-associated encephalopathy: a vicious cycle of immunosuppression[J]. *BJS Open*, 2020, 17(1): 14-19
- [31] Agapito Fonseca J. Timing of Initiation of Renal Replacement Therapy in Sepsis-Associated Acute Kidney Injury [J]. *Intensive Care Med*, 2020, 9(5): 112-118
- [32] Antal O, Ștefănescu E, Mleşnițe M, et al. Hemodynamic Predictors for Sepsis-Induced Acute Kidney Injury: A Preliminary Study [J]. *J Clin Med*, 2020, 9(1): 221-229

(下转第 2220 页)

- regenerative medicine[J]. *Acta Biochim Pol*, 2015, 62(3): 329-337
- [10] Säljö K, Barone A, Mölne J, et al. HLA and Histo-Blood Group Antigen Expression in Human Pluripotent Stem Cells and their Derivatives[J]. *Sci Rep*, 2017, 7(1): 13072
- [11] Fujii S, Yoshida S, Inagaki E, et al. Immunological Properties of Neural Crest Cells Derived from Human Induced Pluripotent Stem Cells[J]. *Stem Cells Dev*, 2019, 28(1): 28-43
- [12] Mora C, Serzanti M, Consiglio A, et al. Clinical potentials of human pluripotent stem cells[J]. *Cell Biol Toxicol*, 2017, 33(4): 351-360
- [13] Shahjalal HM, Abdal Dayem A, Lim KM, et al. Generation of pancreatic beta cells for treatment of diabetes: advances and challenges [J]. *Stem Cell Res Ther*, 2018, 9(1): 355
- [14] Päch G, Perakakis N, Mantzoros CS, et al. Stem cells in the treatment of diabetes mellitus - Focus on mesenchymal stem cells [J]. *Metabolism*, 2019, 90: 1-15
- [15] Ilic D, Ogilvie C. Concise Review: Human Embryonic Stem Cells-What Have We Done? What Are We Doing? Where Are We Going?[J]. *Stem Cells*, 2017, 35(1): 17-25
- [16] Halevy T, Urbach A. Comparing ESC and iPSC-Based Models for Human Genetic Disorders[J]. *J Clin Med*, 2014, 3(4): 1146-1162
- [17] De Filippis L, Zalfa C, Ferrari D. Neural Stem Cells and Human Induced Pluripotent Stem Cells to Model Rare CNS Diseases [J]. *CNS Neurol Disord Drug Targets*, 2017, 16(8): 915-926
- [18] Geis FK, Galla M, Hoffmann D, et al. Potent and reversible lentiviral vector restriction in murine induced pluripotent stem cells[J]. *Retrovirology*, 2017, 14(1): 34
- [19] Ouyang X, Telli ML, Wu JC. Induced Pluripotent Stem Cell-Based Cancer Vaccines[J]. *Front Immunol*, 2019, 10: 1510
- [20] Robinton DA, Daley GQ. The promise of induced pluripotent stem cells in research and therapy[J]. *Nature*, 2012, 481: 295-305
- [21] Stewart SA, Dykxhoorn DM, Palliser D, et al. Lentivirus-delivered stable gene silencing by RNAi in primary cells [J]. *RNA*, 2003, 9: 493-501
- [22] Rizzino A, Wuebben EL. Sox2/Oct4: A delicately balanced partnership in pluripotent stem cells and embryogenesis[J]. *Biochim Biophys Acta*, 2016, 1859(6): 780-791
- [23] Karagiannis P, Takahashi K, Saito M, et al. Induced Pluripotent Stem Cells and Their Use in Human Models of Disease and Development [J]. *Physiol Rev*, 2019, 99(1): 79-114
- [24] Trusler O, Huang Z, Goodwin J, et al. Cell surface markers for the identification and study of human naive pluripotent stem cells[J]. *Stem Cell Res*, 2018, 26: 36-43
- [25] Malecki M, Anderson M, Beauchaine M, et al. TRA-1-60 (+), SSEA-4(+), Oct4A(+), Nanog(+) Clones of Pluripotent Stem Cells in the Embryonal Carcinomas of the Ovaries [J]. *J Stem Cell Res Ther*, 2012, 2(5): 130
- [26] Xu J, Yu L, Guo J, et al. Generation of pig induced pluripotent stem cells using an extended pluripotent stem cell culture system [J]. *Stem Cell Res Ther*, 2019, 10(1): 193
- [27] Zeevaert K, Elsafi Mabrouk MH, Wagner W, et al. Cell Mechanics in Embryoid Bodies[J]. *Cells*, 2020, 9(10): 2270
- [28] Pettinato G, Wen X, Zhang N. Engineering Strategies for the Formation of Embryoid Bodies from Human Pluripotent Stem Cells [J]. *Stem Cells Dev*, 2015, 24(14): 1595-609
- [29] Schroder ARW, Shinn P, Chen HM, et al. HIV-1 integration in the human genome favors active genes and local hotspots [J]. *Cell*, 2002, 110: 521-529
- [30] Mitchell RS, Beitzel BF, Schroder ARW, et al. Retroviral DNA integration: ASLV, HIV, and MLV show distinct target site preferences [J]. *Plos Biology*, 2004, 2: 1127-1137

(上接第 2252 页)

- [33] Hag ğu N, Wen X, Li S, et al. Time-dependent effects of histone deacetylase inhibition in sepsis-associated acute kidney injury [J]. *J Clin Med*, 2020, 8(1): 9-18
- [34] 邓龙天, 余灿. 脓毒症患者并发急性肾损伤危险因素分析[J]. *现代医药卫生*, 2020, 36(10): 1481-1484
- [35] Nandagopal N, Reddy PK, Ranganathan L, et al. Comparison of Epidemiology and Outcomes of Acute Kidney Injury in Critically Ill Patients with and without Sepsis[J]. *J Clin Med*, 2020, 24(4): 258-262
- [36] Tang W, Huang J, Huang X, et al. Effect of alkaline phosphatase on sepsis-associated acute kidney injury patients: A systematic review and meta-analysis [J]. *Medicine (Baltimore)*, 2020, 99 (4): 18788-18792
- [37] Zhang CF, Wang HJ, Tong ZH, et al. The diagnostic and prognostic values of serum and urinary kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin in sepsis induced acute renal injury patients[J]. *Eur Rev Med Pharmacol Sci*, 2020, 24(10): 5604-5617