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Relationship Between Beta Cell Dysfunction and Severity of Disease Among Critically Ill Children

A STROBE-Compliant Prospective Observational Study

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Abstract: Although beta cell dysfunction has been proved to predict prognosis among humans and animals, its prediction on severity of disease remains unclear among children. The present study was aimed to examine the relationship between beta cell dysfunction and severity of disease among critically ill children.

This prospective study included 1146 critically ill children, who were admitted to Pediatric Intensive Care Unit (PICU) of Hunan Children's Hospital from November 2011 to August 2013. Information on characteristics, laboratory tests, and prognostic outcomes was collected. Homeostasis model assessment (HOMA)-β, evaluating beta cell function, was used to divide all participants into 4 groups: HOMA-β = 100% (group I, n = 339), 80% ≤ HOMA-β < 100% (group II, n = 71), 40% ≤ HOMA-β < 80% (group III, n = 293), and HOMA-β < 40% (group IV, n = 443). Severity of disease was assessed using the worst Sequential Organ Failure Assessment (SOFA) score, Pediatric Risk of Mortality (PRISM) III score, incidence of organ damage, septic shock, multiple organ dysfunction syndrome (MODS), mechanical ventilation (MV) and mortality. Logistic regression analysis was used to evaluate the risk of developing poor outcomes among patients in different HOMA-β groups, with group I as the reference group.

Among 1146 children, incidence of HOMA-β < 100% was 70.41%. C-peptide and insulin declined with the decrement of HOMA-β ($P < 0.01$). C-reactive protein and procalcitonin levels, rather than white blood cell, were significantly different among 4 groups ($P < 0.01$). In addition, the worst SOFA score and the worst PRISMIII score increased with declined HOMA-β. For example, the worst SOFA score in group I, II, III, and IV was 1.55 ± 1.85, 1.71 ± 1.93, 1.92 ± 1.63, and 2.18 ± 1.77, respectively. Furthermore, patients with declined HOMA-β had higher risk of developing septic shock, MODS, MV, and mortality, even after adjusting age, gender, myocardial injury, and lung injury. For instance, compared with group I, the multivariate-adjusted odds ratio (95% confidence interval) for developing septic shock was 2.17 (0.59, 8.02), 2.94 (2.18, 6.46), and 2.76 (1.18, 6.46) among patients in group II, III, and IV, respectively.

Beta cell dysfunction reflected the severity of disease among critically ill children. Therefore, assessment of beta cell function is critically important to reduce incidence of adverse events in PICU.

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Abbreviations: CRP = C-reactive protein, HOMA = homeostasis model assessment, MODS = multiple organ dysfunction syndrome, MV = mechanical ventilation, PCT = procalcitonin, PICU = pediatric intensive care unit, PRISM = pediatric risk of mortality, SOFA = Sequential Organ Failure Assessment, WBC = white blood cells.

INTRODUCTION

Hyperglycemia has been identified as a significant risk factor for poor disease prognosis among critically ill children.[1,2] The incidence was estimated to be 20% among all admissions of critical ill children.[3] Therefore, glycemic management of pediatric patients was substantially different from that in adults. Studies revealed that pancreatic beta cell dysfunction may play an important role on hyperglycemia development and further influence disease prognosis.[4] Beta cell dysfunction is characterized by anomalies of secretory phase and decreased quality of insulin secretion and beta cell numbers, which further result in absolute or relative insulin deficiency and blood glucose increment. As an important hormone, insulin has acute and potent anti-inflammatory effects, regulates blood glucose and promotes the synthesis of adipose, protein, and nucleic acid.[5,6] Van Waardenburg et al[7] observed meningococcal septic shock among children with hypoinsulinemia and hyperglycemia. Our previous study has also observed the beta cell dysfunction among critically ill children, especially children with septic shock.[8] In addition, the prediction of beta cell dysfunction on poor prognosis in humans and animals with multiple organ dysfunction syndrome (MODS) has already been proved.[9,10] However, effect of beta cell dysfunction on diseases prognosis has not been well examined, especially among children. Therefore, the present study was aimed to examine the relationship between beta cell dysfunction and severity of disease among critical ill children in China.

METHODS

Study Participants

A prospective observational study was performed among pediatric patients ages from 1 month to 15 years, who were admitted to the Pediatric Intensive Care Unit (PICU) of Hunan Children's Hospital between November 2011 and August 2013. Children were not eligible for the present study if they had diabetes, pancreatitis, mumps, a history of insulin injection, or

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blood transfusions, or have been treated with oral or intravenous glucose, or chemotherapy within the last 6 months, or took food within 6 h before admission.

The study was approved by the Investigation and Ethics Committee of the Hunan Children's Hospital. Parents or their legal guardians have given parental permissions for their participation in the study.

Data Collection

Information on characteristics, laboratory tests, and outcome of patients were collected, including age, gender, fasting glucose, insulin, C-peptide, white blood cells (WBC), C-reactive protein (CRP), procalcitonin (PCT), disease status within the first 24 h of admission, organ damage, septic shock, MODS, mechanical ventilation (MV), and mortality. All laboratory tests were performed according to strict protocol by the same staff. Blood glucose was measured using glucose oxidase method by an automatic biochemical analyzer (ADVIA2400, Tarrytown, USA), and insulin and C-peptide were measured using chemiluminescence method by an automatic immune analyzer (ADVIA centaur, New Jersey, USA). Homeostasis model assessment (HOMA)-β was used to evaluate beta cell function in the present study. Although the hyperinsulinemic euglycemic clamp technique is the ''gold standard'' for evaluating insulin secretion, it is not commonly used in pediatric patients. However, HOMA-β is highly correlated with results from the hyperinsulinemic euglycemic clamp and has been widely used in clinical practice.[11] HOMA-β was calculated according to the following formula: HOMA-β = fasting insulin (mU/mL) × 20/(fasting glucose [mmol/mL] − 3.5). Its normal value is 100%, and decreased HOMA-β means impaired islet beta cell function. Due to insufficient evidence on the cut-point of HOMA-β to evaluate severity of beta cell dysfunction among critically ill children, we divided all patients into 4 groups according to the following criteria: HOMA-β = 100% (group I), 80% ≤ HOMA-β < 100% (group II), 40% ≤ HOMA-β < 80% (group III), and HOMA-β < 40% (group IV).

Outcome Assessment

Clinical severity of disease was assessed using the worst Sequential Organ Failure Assessment (SOFA) score, Pediatric Risk of Mortality (PRISM) III score, and incidence of adverse events. The adverse events were assessed by 2 investigators independently and any discrepancies were discussed with another investigator.

Statistical Analysis

Median (P5, P95) or percentages were used to present continuous and categorical variables, respectively. Differences among groups were examined by the nonparamentric Wilcoxon test due to non-normal distribution and the Chi-squared test for continuous and categorical variables, respectively. In addition, the Spearman correlation was used to determine the correlation between quantitative variables. Logistic regression analysis was used to estimate odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) of developing poor prognosis among different HOMA-β groups, with group I as the reference group. Sensitivity analysis was conducted to assess the influence of baseline myocardial injury and lung injury on the overall findings. A 2-sided P value <0.05 was considered statistically significant and all statistical analyses were performed using SPSS 13.0.

RESULTS

Patient Characteristics

A total of 1146 children (760 boys and 386 girls) were included in the present study, with an average age of 1.83 years (range: 1 month to 15 years). All patients were classified into 4 groups, with 339, 71, 293, and 443 patients in group I, group II, group III, and group IV, respectively. The average age and gender proportion were both similar across 4 groups ($P > 0.05$). A total of 70.41% patients had their HOMA-β < 100%. The admission disease included respiratory diseases (56.98%), nervous system diseases (23.21%), accident injury (8.29%), digestive system diseases (4.36%), and others (7.16%; Table 1).

Relationship of HOMA-β Index With C-Peptide, Insulin, and Infectious Indicators Among Critically Ill Children

HOMA-β index was positively correlated with C-peptide and insulin levels (C-peptide: $r = 0.443$, $P < 0.01$; insulin:

TABLE 1. Characteristics of Study Participants According to HOMA-β Levels

Variables	Total (n = 1146)	Group I (n = 339)	Group II (n = 71)	Group III (n = 293)	Group IV (n = 443)	P
Age, y	0.83 (0.33–2.06)	0.66 (0.30–2.03)	0.58 (0.25–2.10)	0.83 (0.41–2.60)	0.91 (0.33–2.06)	0.145
Males, n (%)	733 (63.96)	209 (18.24)	47 (4.10)	182 (15.88)	295 (25.74)	0.558
Admission disease, n (%)						0.117
Respiratory disease	653 (56.98)	193 (56.94)	42 (59.15)	168 (57.34)	250 (56.43)	
Nervous system disease	266 (23.21)	89 (26.25)	18 (25.35)	78 (26.62)	81 (18.28)	
Accident injury	95 (8.29)	20 (5.90)	6 (8.45)	22 (7.51)	47 (10.61)	
Digestive system diseases	50 (4.36)	9 (2.65)	2 (2.82)	10 (3.41)	29 (6.55)	
Others	82 (7.16)	28 (8.26)	3 (4.23)	15 (5.12)	36 (8.13)	
WBC, $\times 10^9$	9.99 (7.06–14.42)	9.29 (6.96–13.5)	10.32 (7.21–14.06)	10.1 (6.86–14.71)	10.6 (7.30–15.08)	0.099
CRP, mg/L	3.35 (0.84–16.30)	2.44 (0.84–9.17)	2.1 (0.84–7.89)	3.89 (0.85–21.72)	4.24 (0.85–18.97)	0.011
PCT, ng/mL	0.17 (0.05–1.38)	0.12 (0.05–0.73)	0.14 (0.06–0.84)	0.17 (0.05–1.08)	0.23 (0.06–2.53)	0.006

CRP = C-reactive protein, HOMA = homeostasis model assessment, PCT = procalcitonin, WBC = white blood cell.

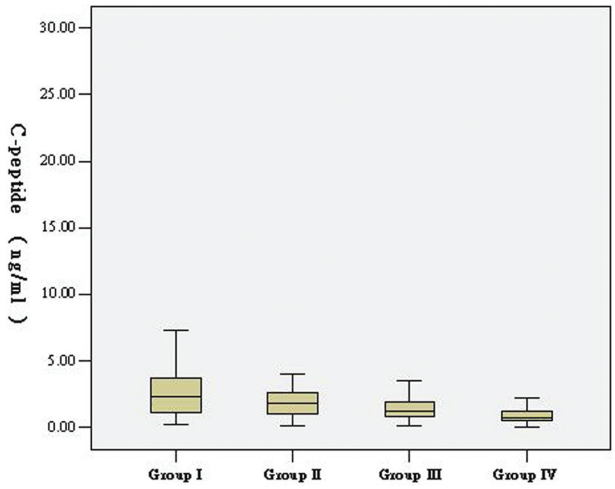

FIGURE 1. Levels of C-peptide across 4 groups.

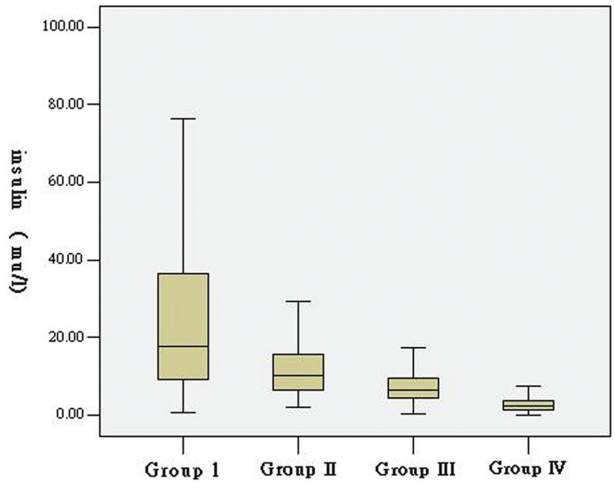

FIGURE 2. Levels of insulin across 4 groups.

$r = 0.443$, $P < 0.01$), while it was negatively correlated with WBC, CRP, and PCT levels (WBC: $r = -0.082$, $P = 0.006$; CRP: $r = -0.102$, $P < 0.001$; and PCT: $r = -0.105$, $P < 0.001$). In addition, significant positive correlation between insulin and C-peptide was also found ($r = 0.601$, $P = 0.001$). Furthermore, the median level of C-peptide decreased with declined HOMA-β index and that was 2.30 (1.16–3.76), 1.82 (1.03–2.72), 1.21 (0.79–1.91), and 0.76 (0.53–1.25) ng/mL in group I, group II, group III, and group IV, respectively. The similar trend was also observed for insulin, with the median level of 17.61 (8.90–36.59), 10.0 (6.4–15.7), 6.46 (4.30–9.74), and 2.19 (1.22–3.77) mIU/L in group I, group II, group III, and group IV, respectively. In addition, significant difference of C-peptide and insulin was observed across 4 groups ($P < 0.001$; Figures 1 and 2). CRP and PCT levels increased with declined HOMA-β ($P < 0.01$), while WBC level did not differ among 4 groups ($P = 0.099$; Table 1).

Situation of Organ Damage on Admission

The total incidence of myocardial injury, hepatic injury, lung injury, renal injury, stress ulcer, cranial pressure syndrome, and blood coagulation dysfunction among children with HOMA-β ≥ 100% was 24.3%, 17.5%, 29.5%, 2.9%, 3.3%, 18.4%, and 11.40%, respectively. Incidence of myocardial injury and lung injury differed among 4 groups ($P < 0.05$). Incidence of hepatic injury, renal injury, stress ulcer, cranial pressure syndrome, or blood coagulation dysfunction did not differ among 4 groups ($P > 0.05$; Table 2).

Worst SOFA, PRISMIII Score on Admission

The worst SOFA score increased with worsening HOMA-β (1.55 ± 1.85, 1.71 ± 1.93, 1.92 ± 1.63, and 2.18 ± 1.77 in group I, group II, group III, and group IV, respectively, $P = 0.011$). Similarly, the worst PRISMIII score also increased with declined HOMA-β levels (2.57 ± 3.06, 3.20 ± 3.85, 3.91 ± 1.92, and 4.36 ± 2.06 in group I, group II, group III, and group IV, respectively, $P = 0.041$). The worst SOFA and PRISMIII score in group IV were significantly higher than those in group I, respectively ($P < 0.01$; Figure 3).

Incidence of Septic Shock, MODS, MV, and Mortality

Patients with declined HOMA-β had higher incidence of lung injury. Incidences of stress ulcer and blood coagulation dysfunction in declined HOMA-β group were marginally higher than those with HOMA-β of 100%. In addition, incidence of septic shock, MODS, MV, and mortality was also significantly higher in declined HOMA-β group. For example, the incidence of septic shock was 2.06%, 5.63%, 5.80%, and 7.22% in group I, group II, group III, and group IV, respectively (Table 3).

Furthermore, after adjustment of age and gender, patients with declined HOMA-β had higher risk of developing septic shock ($P = 0.004$), MODS ($P = 0.013$), and MV ($P < 0.001$).

TABLE 2. Incidence of Organ Damage on Admission Among 4 Groups

Variables	Group I (n = 339)	Group II (n = 71)	Group III (n = 293)	Group IV (n = 443)	*P*
Myocardial injury, n (%)	82 (24.3)	17 (23.9)	69 (23.5)	144 (32.7)	0.014
Hepatic injury, n (%)	59 (17.5)	13 (18.3)	46 (15.8)	80 (18.2)	0.854
Lung injury, n (%)	100 (29.5)	29 (40.8)	95 (32.4)	168 (37.9)	0.049
Renal injury, n (%)	10 (2.9)	2 (2.8)	10 (3.4)	17 (3.8)	0.910
Stress ulcer, n (%)	11 (3.3)	5 (7.1)	13 (4.4)	30 (6.8)	0.119
Cranial pressure syndrome, n (%)	62 (18.4)	12 (16.9)	47 (16.0)	90 (18.5)	0.491
Blood coagulation dysfunction, n (%)	26 (7.7)	7 (9.9)	26 (8.9)	59 (13.4)	0.055

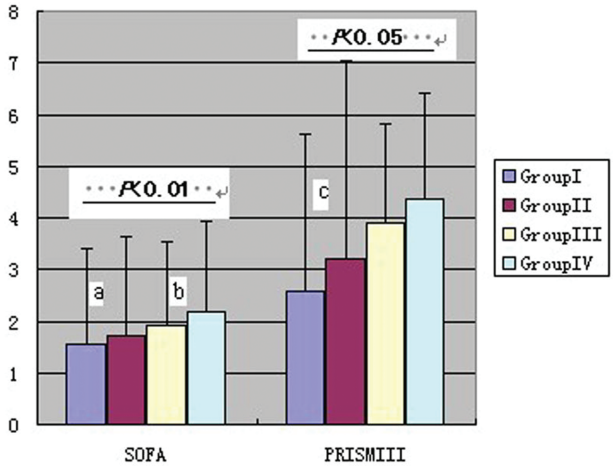

FIGURE 3. Worst SOFA and PRISMIII score on admission across 4 groups. PRISMIII = Pediatric Risk of Mortality III, SOFA = Sequential Organ Failure Assessment.

Further adjustment of myocardial injury and lung injury did not substantially change the results. For example, compared with group I, the multivariate-adjusted OR (95% CI) for developing septic shock was 2.17 (0.59, 8.02), 2.94 (2.18, 6.46), and 2.76 (1.18, 6.46) among patients in group II, III, and IV, respectively (Table 4).

DISCUSSION

Our study showed that incidence of HOMA-β < 100% is 70.41% among critically ill children. With declined HOMA-β index, the C-peptide and insulin levels have parallel downtrend. Positive correlations of insulin and C-peptide levels with HOMA-β were also found. These findings supported that decline of HOMA-β was very common among critically ill children and HOMA-β index could reflect the severity of pancreatic beta cells impairment.

Endocrine dysfunction is an important feature among critically ill children and impaired hormone homeostasis often results in poor prognosis.[12,13] In normal circumstances, pro-insulin was converted to insulin and C-peptide via PC1, PC2, and carboxypeptidase in pancreatic beta cells. However, beta cells secretory granules was affected under condition of poor perfusion, oxidative stress, or infections, which might change the process of converting pro-insulin to insulin and C-peptide and further result in pancreatic beta cells dysfunction.[14,15]

It has been identified that critical ill patients with insulin resistance often have decreased or normal insulin level.[16–18] Previous studies believed that this phenomenon may be a result of reduced suppression of insulin sensitivity, a status caused by increased catecholamines and cortisol levels.[18,19] In addition, evidence supported that the pancreatic beta cells dysfunction may be attributed to hyperglycemia, hypoinsulinemia, or low C-peptide.[20,21] Beta cell dysfunction is the performance of pancreatic damage among critical ill children. In our previous study, we found that critically ill children (those with disseminated tuberculosis, fulminant hepatitis, and other severe infection) had their pancreas with inflammatory cells infiltration, hemorrhage, necrosis, and other organic damage.[22] Pancreatic pathological anatomy of 44 critically ill children after death showed that secondary pancreatic injury and inflammatory cells infiltration were observed among 61.4% of cases.[23] Insulin secretion is inhibited by inflammatory factors, such as TNF-α, and IL-1, in the process of the inflammatory response in vivo.[24] For example, negative correlation between TNF-β and HOMA-β index has been identified. Inflammatory response could also affect the secretion function of beta cell among critical ill patients.[25] High levels of CRP and PCT, high incidence of septic shock, and low HOMA-β level are also compatible with an inhibitory effect of the inflammatory response on insulin secretion and beta cell dysfunction.

The condition of critical ill children with secondary pancreatic injury deteriorated quickly, being accompanied with single or multiple organ damage, especially the heart and lung.[26] Our research identified the rate of organ damage varied from 3.59% to 36.18% among children whose HOMA-β was <100%, and incidences of myocardial injury and lung injury plasma were significantly different across 4 groups. The present study identified the role of beta cell dysfunction on prognosis prediction, which suggested attention should be paid to critical ill children with pancreatic injury, especially those accompanied by myocardial injury or lung injury. These children tend to have aggravating illness and MODS. Although animal models have confirmed that pancreas was actively involved in the acute phase reaction in sepsis of remote origin,[27,28] effect of pancreas injury on MODS should be further investigated in humans.

The SOFA, PRISMIII score are considered to be important indicators to evaluate disease severity among critically ill children.[29,30] Septic shock and MODS are important performances in critical condition,[31] and MV is an essential treatment method. Our data showed that incidences of septic shock, MODS, MV, and mortality were significantly different among 4 groups, the worst SOFA, PRISMIII score from group I to group IV showed an increasing trend with worsening HOMA-β.

The present study provided first evidence on relationship between beta cell dysfunction and poor outcomes in Chinese children. However, some limitations should be addressed. First, the inclusion of only patients from Hunan Children's Hospital limited the generalization of the current findings and further

TABLE 3. Incidence of Septic Shock, MODS, MV, and Mortality Among 4 Groups

Variables	Group I (n = 339)	Group II (n = 71)	Group III (n = 293)	Group IV (n = 443)	*P*
Septic shock, n (%)	7 (2.06)	4 (5.63)	17 (5.80)	32 (7.22)	0.014
MODS, n (%)	42 (12.39)	15 (21.12)	38 (12.97)	89 (20.09)	0.007
MV, n (%)	26 (7.67)	23 (32.39)	62 (21.16)	123 (27.77)	<0.001
Mortality, n (%)	24 (7.08)	9 (12.67)	15 (5.12)	49 (11.06)	0.014

MODS = multiple organ dysfunction syndrome, MV = mechanical ventilation.

TABLE 4. Odds Ratio* of Group II, Group III, and Group IV for Incident Septic Shock, MODS, MV, and Mortality

Outcome	Group I (n = 339)	Group II (n = 71)	Group III (n = 293)	Group IV (n = 443)	$P_{\text{for trend}}$
Model 1					
Septic shock	1.00	2.87 (0.82, 10.12)	2.90 (1.18, 7.09)	3.48 (1.51, 8.02)	0.004
MODS	1.00	1.97 (1.02, 3.81)	1.03 (0.64, 1.67)	1.80 (1.20, 2.69)	0.013
MV	1.00	5.90 (3.10, 11.23)	3.23 (1.98, 5.28)	4.63 (2.94, 7.29)	<0.001
Mortality	1.00	1.93 (0.85, 4.36)	0.70 (0.36, 1.37)	1.22 (0.79, 1.88)	0.156
Model 2					
Septic shock	1.00	2.17 (0.59, 8.02)	2.94 (1.18, 7.33)	2.76 (1.18, 6.46)	0.020
MODS	1.00	1.65 (0.82, 3.33)	0.97 (0.59, 1.59)	1.51 (0.99, 2.31)	0.101
MV	1.00	6.92 (3.15, 15.22)	4.03 (2.30, 7.09)	5.54 (3.29, 9.32)	<0.001
Mortality	1.00	1.40 (0.58, 3.36)	0.59 (0.29, 1.18)	1.23 (0.72, 2.13)	0.626

Model 1 = adjustment for age and gender, Model 2 = adjustment for age, gender, myocardial injury, and lung injury, MODS = multiple organ dysfunction syndrome, MV = mechanical ventilation.
* Multivariable-adjusted odds ratio.

investigation in a country-wide study with a much larger sample size and is highly needed. Second, this is a hospital-based study, and information was collected from medical records of eligible patients. Therefore, plasma levels of IL-6, TNF, and IL-1 which were not routine measurements, could not be obtained from the medical record. Considering the correlation of IL-6, TNF, and IL-1 with HOMA, insulin levels and the severity of the diseases, further studies are warranted to illustrate their influence on the relationship between beta cell dysfunction and clinical prognosis. However, the relationship of CRP and PCT with HOMA levels in the present study might have partly reflected the inhibitory effect of inflammatory response on beta cell dysfunction.

CONCLUSION

The present study suggests that beta cell dysfunction reflects the severity of disease among critically ill children, and assessment of beta cell function is critically helpful for pediatricians to evaluate the disease status. Therefore, treatment targeting on the primary disease and appropriate insulin treatment might be important to reduce adverse events in PICU.

REFERENCES

1. Wintergerst KA, Foster MB, Sullivan JE, et al. Association of hyperglycemia, glucocorticoids, and insulin use with morbidity and mortality in the pediatric intensive care unit. *J Diabetes Sci Technol.* 2012;6:5–14.
2. Kyle UG, Coss Bu JA, Kennedy CE, et al. Organ dysfunction is associated with hyperglycemia in critically ill children. *Intensive Care Med.* 2010;36:312–320.
3. Preissig CM, Hansen I, Roerig PL, et al. A protocolized approach to identify and manage hyperglycemia in a pediatric critical care unit. *Pediatr Crit Care Med.* 2008;9:581–588.
4. Verhoeven JJ, den Brinker M, Hokken-Koelega AC, et al. Pathophysiological aspects of hyperglycemia in children with meningococcal sepsis and septic shock: a prospective, observational cohort study. *Crit Care.* 2011;15:R44.
5. Dandona P, Aljada A, Bandyopadhyay A. The potential therapeutic role of insulin in acute myocardial infarction in patients admitted to intensive care and in those with unspecified hyperglycemia. *Diabetes Care.* 2003;26:516–519.
6. Jeschke MG, Klein D, Bolder U, et al. Insulin attenuates the systemic inflammatory response in endotoxemic rats. *Endocrinology.* 2004;145:4084–4093.
7. van Waardenburg DA, Jansen TC, Vos GD, et al. Hyperglycemia in children with meningococcal sepsis and septic shock: the relation between plasma levels of insulin and inflammatory mediators. *J Clin Endocrinol Metab.* 2006;91:3916–3921.
8. Liu P, Zhu Y, Xiao Z, et al. Relationship between hyperglycemia and pancreatic beta cell dysfunction in critically ill children. *Chin Pediatr Emerg Med.* 2014;21:550–553.
9. Das S, Misra B, Roul L, et al. Insulin resistance and beta cell function as prognostic indicator in multi-organ dysfunction syndrome. *Metab Syndr Relat Disord.* 2009;7:47–51.
10. Shi S, Lin C, Lin X. Ultrastructural and functional changes of pancreatic beta cells in rats with MODS. *Chin J Emerg Med.* 2009;18:1026–1030.
11. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care.* 2004;27:1487–1495.
12. Penesova A, Galusova A, Vigas M, et al. The role of endocrine mechanisms in ventilator-associated lung injury in critically ill patients. *Endocr Regul.* 2012;46:161–166.
13. Marquardt DJ, Knatz NL, Wetterau LA, et al. Failure to recover somatotropic axis function is associated with mortality from pediatric sepsis-induced multiple organ dysfunction syndrome. *Pediatr Crit Care Med.* 2010;11:18–25.
14. Liang GY, Wu HS, Li J, et al. Role of insulin receptors in myocardial ischaemia-reperfusion injury during cardiopulmonary bypass. *Acta Cardiol.* 2011;66:323–331.
15. Hiltebrand LB, Krejci V, Banic A, et al. Dynamic study of the distribution of microcirculatory blood flow in multiple splanchnic organs in septic shock. *Crit Care Med.* 2000;28:3233–3241.
16. Clowes GH Jr, Martin H, Walji S, et al. Blood insulin responses to blood glucose levels in high output sepsis and spetic shock. *Am J Surg.* 1978;135:577–583.
17. Dahn MS, Jacobs LA, Smith S, et al. The relationship of insulin production to glucose metabolism in severe sepsis. *Arch Surg.* 1985;120:166–172.
18. Mizock BA. Alterations in fuel metabolism in critical illness: hyperglycaemia. *Best Pract Res Clin Endocrinol Metab.* 2001;15:533–551.
19. Pretty C, Chase JG, Lin J, et al. Impact of glucocorticoids on insulin resistance in the critically ill. *Comput Methods Programs Biomed.* 2011;102:172–180.
20. Ballestero Y, Lopez-Herce J, Gonzalez R, et al. Relationship between hyperglycemia, hormone disturbances, and clinical

evolution in severely hyperglycemic post surgery critically ill children: an observational study. *BMC Endocr Disord.* 2014;14:25.

21. Preissig CM, Rigby MR. Hyperglycaemia results from beta-cell dysfunction in critically ill children with respiratory and cardiovascular failure: a prospective observational study. *Crit Care.* 2009;13:R27.
22. Zhu YM, Liu F, Zhou XY, et al. Clinical and pathologic characteristics of pancreatic necrosis in critically ill children. *World J Emerg Med.* 2011;2:111–116.
23. Chen W, Zhu Y, Zhou Z, et al. Pathological characteristic of pancreatic tissue injury in pediatric death cases with critical illness. *J Clin Pediatr.* 2012;30:29–32.
24. Mehta VK, Hao W, Brooks-Worrell BM, et al. Low-dose interleukin 1 and tumor necrosis factor individually stimulate insulin release but in combination cause suppression. *Eur J Endocrinol.* 1994;130:208–214.
25. Ma C, Cao X. An investigation of the relationship of inflammatory response and insulin and its components during stress hyperglycemia in critically ill patients. *Chin Crit Care Med.* 2011;23:169–172.
26. Sandri M, Berchialla P, Baldi I, et al. Dynamic Bayesian Networks to predict sequences of organ failures in patients admitted to ICU. *J Biomed Inform.* 2014;48:106–113.
27. Hirano T. Pancreatic injuries in rats with fecal peritonitis: protective effect of a new synthetic protease inhibitor, sepinostat mesilate (FUT-187). *J Surg Res.* 1996;61:301–306.
28. Tribl B, Filipp D, Bodeker H, et al. *Pseudomonas pneumonia*-mediated sepsis induces expression of pancreatitis-associated protein-I in rat pancreas. *Pancreas.* 2004;29:33–40.
29. Khajeh A, Noori NM, Reisi M, et al. Mortality risk prediction by application of pediatric risk of mortality scoring system in pediatric intensive care unit. *Iran J Pediatr.* 2013;23:546–550.
30. Ha EJ, Kim S, Jin HS, et al. Early changes in SOFA score as a prognostic factor in pediatric oncology patients requiring mechanical ventilatory support. *J Pediatr Hematol Oncol.* 2010;32:e308–e313.
31. Proulx F, Fayon M, Farrell CA, et al. Epidemiology of sepsis and multiple organ dysfunction syndrome in children. *Chest.* 1996;109:1033–1037.