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.

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 al7 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
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. HOMA-β was calculated according to the following formula: HOMA-β = fasting insulin (mU/mL) × 20/ (fasting glucose [mmol/L] – 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 nonparametric 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 (%)   | 653 (56.98)     | 193 (56.94)      | 42 (59.15)       | 168 (57.34)        | 250 (56.43)       | 0.117|
| 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)         |      |
| WBC, ×10⁹                  | 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, mg/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.
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 (0.78–1.91), 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 (8.90–35.98), 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, PRISMIll 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 PRISMIll 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 PRISMIll 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).

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**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 |
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, carboxypeptidase in pancreatic beta cells. However, beta cell dysfunction is the performance of pancreatic beta cells impairment.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 were observed among 61.4% of cases.22 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

![FIGURE 3. Worst SOFA and PRISMIII score on admission across 4 groups. PRISMIII = Pediatric Risk of Mortality III, SOFA = Sequential Organ Failure Assessment.](image-url)
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.

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