Clinical application of a novel diagnostic scheme including pancreatic β-cell dysfunction for traumatic multiple organ dysfunction syndrome

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Received June 8, 2016; Accepted August 22, 2017

DOI: 10.3892/mmr.2017.7898

Abstract. A novel diagnostic scheme that includes pancreatic β-cell dysfunction analysis for the diagnosis of traumatic multiple organ dysfunction syndrome (MODS) was investigated to assist in the early diagnosis and detection of MODS. Early intervention and treatment of MODS has been associated with a reduced mortality rate. A total of 2,876 trauma patients (including patients post-major surgery) were admitted to the intensive care unit of the authors' hospital between December 2010 and December 2015 and enrolled in the present study. There were 205 cases where the patient succumbed to their injuries. In addition to the conventional diagnostic scheme for traumatic MODS, indexes of pancreatic β-cell dysfunction [fasting blood-glucose (FBG), homeostatic model assessment-β and (blood insulin concentration 30 min following glucose loading-fasting insulin concentration)/(blood glucose concentration 30 min following glucose loading-FBG concentration)] were included to establish an improved diagnostic scheme for traumatic MODS. The novel scheme was subsequently used in clinical practice alongside the conventional scheme and its effect was evaluated. The novel scheme had a significantly higher positive number of MODS diagnoses for all trauma patients compared with the conventional scheme (12.48 vs. 8.87%; P<0.01). No significant difference was identified in the final percentage of positive of MODS diagnoses for trauma-associated mortality patients between the novel (88.30%) and the conventional scheme (86.34%). The novel scheme had a significantly higher positive number of MODS diagnoses for trauma-associated mortality patients 3 days prior to patients succumbing to MODS compared with the conventional scheme (80.98 vs. 64.39%; P<0.01). The consensus of the MODS diagnosis of all trauma patients between the novel scheme and the conventional scheme was 100%; however, out of the patients diagnosed as positive by novel scheme 71.03% were positive by the conventional scheme. The consensus between the final MODS diagnosis and the MODS diagnosis 3 days prior to patients succumbing to their injuries between the novel scheme and the conventional scheme was 100%; however, out of the patients diagnosed as positive by novel scheme 97.79 were positive by the conventional scheme of the 205 patients who succumbed to MODS and out of the patients diagnosed as positive for MODS by novel scheme 3 days prior to succumbing, 79.52% were positive by the conventional scheme. The results of the present study demonstrated that the novel diagnostic scheme using the relevant indexes of pancreatic β-cell dysfunction for diagnosis of traumatic MODS, was able to diagnose MODS early without excessively extending the diagnostic scope. Its clinical application should be promoted.

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Key words: trauma, multiple organ dysfunction syndrome, diagnostic scheme, pancreatic β-cell dysfunction, blood glucose

Introduction

Multiple organ dysfunction syndrome (MODS) refers to a clinical syndrome in which dysfunction or disorder of ≥two organs or tissues occurs simultaneously or sequentially following severe trauma, infection or shock. It is a common complication of severe trauma in patients (including post-major operation patients). Characterized by acute onset, rapid progression, high mortality and difficult treatment, MODS, especially

at the later stages, seriously threatens the health and life of patients (1-4). To the best of the authors' knowledge, although there are various diagnostic methods for MODS following trauma, there is no recognized uniform standard for the diagnosis of MODS post severe trauma (including following major operations) (5-8).

It is important to possess an accurate concept of MODS and multiple organ failure (MOF) to establish an accurate and novel improved MODS diagnostic scheme for trauma patients. The concept of 'organ dysfunction' means 'organ function is deregulated or insufficient'. The concept of 'organ failure' means 'complete loss of organ function'. MOF and MODS are distinct. MOF is usually the exhibited in the later stage of MODS, so the mortality from MOF is higher than in the early stage of MODS. Mortality from MOF in the late stage of MODS following trauma may be up to 80-96% (9,10). Unlike MOF, organ dysfunction of MODS patients following trauma may be recoverable by early detection and timely clinical intervention. Therefore, it is of great importance to detect and intervene early in MODS, in order to prevent MODS from developing into MOF (11).

Organ dysfunction may demonstrate abnormal laboratory indexes prior to typical clinical manifestations of MODS. For example, the blood alanine aminotransferase level rises in certain patients with liver dysfunction, although there may be no clinical manifestations of liver dysfunction. Only when there is serious dysfunction or liver failure do typical clinical signs such as a hepatic coma occur. Instead of depending on clinical signs alone, clinical laboratory data analysis serves as a crucial approach for detecting MODS at an early stage (4).

Pancreatic islet β-cells are important cells and they continuously and rapidly secrete insulin in response to stimuli from the blood glucose level to maintain the blood glucose within a normal range. Systemic inflammatory response syndrome (SIRS) and lipopolysaccharides can cause an increase in a variety of inflammatory cytokines and impair the function of pancreatic islet β-cells by upregulating the nuclear factor-κB gene (12,13). An inflammatory response will promote diabetes, and anti-inflammatory treatment can be used to treat diabetes by improving β-cell dysfunction (14,15). However, in the field of traumatic MODS, inflammatory factors also exist and damage pancreatic islet β-cell function. In previous studies on diagnostic criteria for traumatic MODS although the relationship between hyperglycemia following severe trauma and MODS has been reported (16-20), dysfunction or failure of pancreatic islet β-cells was neglected or not considered. To the best of the authors' knowledge, there are no reports on the inclusion of pancreatic islet β-cell dysfunction into the MODS diagnostic scheme. In the present study, indexes associated with pancreatic β-cell function (21), including fasting blood-glucose (FBG), homeostatic model assessment (HOMA-β) and (blood insulin concentration 30 min following glucose loading-fasting insulin concentration)/(blood glucose concentration 30 min following glucose loading-FBG concentration; $\Delta INS_{30}/\Delta GLU_{30}$) were included in the diagnostic scheme for traumatic MODS, and it was demonstrated that the improved scheme could increase the diagnostic sensitivity of traumatic MODS, without excessively extending the diagnosis scope.

Materials and methods

Study participants. A total of 2,876 severe trauma patients (including patients following major operations) who were admitted to the intensive care unit (ICU) of the 94th Hospital of People's Liberation Army (Nanchang, China) between December 2010 and December 2015, were recruited as participants of the present study. There were 1,746 male and 1,130 female participants, aged 46.17±16.73 years old, including 205 deceased patients certified as brain dead. All subjects were hospitalized with severe trauma, and certain patients were comatose. All patients (or their next of kin for comatose or deceased patients) cooperated with the present study, and were emotionally stable during blood sampling.

The inclusion criteria were: Patients who had MODS caused by severe trauma and were hospitalized for >3 days. All recruited subjects were otherwise physically healthy and did not have diabetes or MODS prior to trauma. Brain death was considered a criterion of mortality. The study protocol was approved by the ethics committee of the 94th Hospital of People's Liberation Army (Nanchang, China) and informed consent was obtained from all participants when the participants were awake or their next of kin when the participants were comatose. Patients with the following conditions were excluded: Being hospitalized for ≤3 days for severe trauma, mortality due to hypovolemic shock caused by traumatic hemorrhage within 3 days, pre-trauma diabetes, impaired glucose tolerance and severe insulin resistance, currently receiving insulin therapy, FBG ≤3.5 mmol/l, body mass index >28 kg/m^2, severe insulin resistance, other metabolic diseases and pre-trauma liver, kidney or cardiac insufficiency.

Evaluation of pancreatic β-cell dysfunction. Unlike ordinary diabetic patients, not all methods of pancreatic β-cell function evaluation are suitable for critically ill patients during trauma surgery. MODS in trauma patients is characterized by the patient being in a critical condition with rapid progression. Therefore, easy, fast and minimally invasive methods of pancreatic β-cell function evaluation are favored for patients who are critically ill (21). MODS patients who already had diabetes and obesity before trauma were excluded, so the potential effect of insulin resistance on the evaluation indicators of pancreatic β-cell dysfunction was avoided. Many reports have been published regarding the evaluation of pancreatic β-cell dysfunction in diabetes (21-27). Considering the fast progression of MODS in trauma patients (28), early diagnosis of pancreatic β-cell dysfunction is necessary. To develop a suitable evaluation method for these patients FBG, HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$ evaluation was combined (22,23).

In the present study, patients were treated with saline, balanced salts, amino acids or fatty milk, according to the needs of the patient. If intravenous (IV) glucose was received, blood samples were collected following fasting or no IV glucose being administered for 12 h. The FBG and insulin level of the severe trauma patients was determined. The HOMA-β index [fasting insulin x20/(FBG-3.5)] was calculated. IV glucose was given at a dose of 75 g/60 kg weight, and then the blood glucose and the insulin levels were analyzed again 30 min later. The $\Delta INS_{30}/\Delta GLU_{30}$ [(blood insulin concentration 30 min following glucose loading-fasting insulin

concentration)/(blood glucose concentration 30 min following glucose loading-FBG concentration)] was calculated. The blood glucose and the insulin values used to calculate the HOMA-β index and in the $\Delta INS_{30}/\Delta GLU_{30}$ formula were the same/patient/time point. FBG was determined using the glucose oxidase method, The Beckman AU2700 automatic biochemical analyzer (Beckman Coulter, Inc., Pasadena, TX, USA) was used to measure blood glucose according to the manufacturer's protocol.

Conventional diagnostic scheme for traumatic MODS. Scoring for lung, kidney, liver, blood and brain dysfunction was performed according to previous studies (9,29-32) as was the scoring for post-traumatic cardiac dysfunction (9,10). In addition post-trauma gastrointestinal dysfunction was also scored according to previous studies (10,33). Each organ dysfunction was scored according to clinical manifestations or assessed continuously using simple, fast and objective laboratory inspection indicators (Table I).

Patients with dysfunction of ≥2 organs (excluding organ dysfunction prior to trauma and the primary organ dysfunction) can be diagnosed as traumatic MODS if the total score was >2.0. If one organ satisfied the requirements for all indicators, a full score for that organ was given; if only part of the requirements were satisfied, then a partial score was given. Evaluation indicators and scoring criteria of the conventional scheme for dysfunction of different organs is exhibited in Table I. The conventional diagnostic scheme (29) had been used for >5 years.

Novel diagnostic scheme for traumatic MODS. On the basis of the conventional diagnostic scheme for traumatic MODS, evaluation on indexes of pancreatic β-cell dysfunction (FBG, HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$) was performed and a new scheme was produced. If one out of the three indicators (FBG, HOMA-β, or $\Delta INS_{30}/\Delta GLU_{30}$) satisfied the criterion for pancreatic β-cell dysfunction, dysfunction was diagnosed; if all indicators satisfied the criteria, a full score was given; if a number of the indicators satisfied the criteria, a partial score was given (Table II). For most MODS patients following trauma, at least one of the three indicators (FBG, HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$) satisfied the criterion; and under most situations, the other two indicators also satisfied the criteria, and an increase in FBG was usually be accompanied by a decrease in HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$. The laboratory reference range for the normal levels of index of HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$ was 139 and 15.36, respectively (the means were determined according from 1,000 healthy subjects with normal FBG, fasting insulin, fasting blood lipid, and body mass index). Patients with dysfunction of ≥2 organs (excluding organ dysfunction before trauma and the primary organ dysfunction) can be diagnosed as exhibiting traumatic MODS, if the total score was >2 (Same as conventional diagnostic scheme for traumatic MODS, for several indicators of the same organ/tissues/cell, if all of them satisfied the criteria, then a full score was given; otherwise, a partial score was given). See Table II.

Evaluation of the diagnoses by both diagnostic schemes. All participants were evaluated for traumatic MODS using the conventional and novel diagnostic schemes. The positive rate of MODS diagnosis for all trauma patients (including patients post-major surgery), the final positive rate of MODS diagnosis for patients with trauma-related mortality and the positive rate of MODS diagnosis for patients with trauma-related mortality 3 days prior to patient mortality, using the novel scheme and the conventional scheme were calculated.

The percentage of MODS patients diagnosed using the novel scheme was calculated (the number of MODS positive patients diagnosed by novel scheme/the number of MODS positive patients diagnosed by conventional scheme). The percentage of MODS patients diagnosed by conventional scheme was calculated (the number of MODS positive patients diagnosed by conventional scheme/the number of MODS positive patients diagnosed by novel scheme).

Statistical analysis. SPSS version 11.0 (SPSS, Inc., Chicago, IL, USA) for Windows software was used for the chi-squared test of rates. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Novel scheme has a significantly higher number of positive MODS diagnoses compared with the conventional scheme. Among the 2,876 patients with severe trauma, the novel scheme diagnosed 359 patients as positive for MODS, whereas the conventional scheme diagnosed 255 patients as positive for MODS. The novel scheme had a significantly higher positive rate of MODS diagnosis for all trauma patients, compared with the conventional scheme ($P<0.01$; Table III and Fig. 1).

Consensus between the novel scheme and conventional scheme in traumatic MODS diagnosis. There were 255 patients diagnosed as positive for MODS by the conventional scheme, and all 255 patients were diagnosed as positive for MODS by the novel scheme. The consensus between the novel scheme and the conventional scheme was 100%. Out of the 359 patients diagnosed as positive for traumatic MODS by the novel scheme, 255 of them were diagnosed as positive by the conventional scheme. The consensus between the conventional scheme and the novel scheme was 71.03%. For the 2,876 trauma patients, the positive and negative cases diagnosed by the novel and conventional schemes are summarized in Table IV.

Final number of positive MODS diagnoses for trauma-associated mortality patients by the two schemes and analysis of their consistency. There were a total of 205 trauma-related patients who succumbed to MODS, the novel scheme diagnosed 181 of these patients as positive for MODS, whereas the conventional scheme diagnosed 177 as positive for MODS. No significant differences were identified in the number of positive diagnoses of MODS for all trauma-associated mortality patients between the novel scheme and the conventional scheme (Table V and Fig. 2).

Of the 177 individuals who succumbed and were diagnosed as positive for MODS by the conventional scheme, all were diagnosed as positive for MODS by the novel scheme. The positive consensus between the conventional scheme and the novel scheme was 100%. Conversely, the consensus between

the novel scheme and the conventional scheme for individuals who suffered mortality was 97.79% (Table VI).

The number of positive MODS diagnoses for patients that succumbed to trauma-associate injuries 3 days prior to mortality, by the two diagnostic schemes, and analysis of their consistency. Of the 205 patients who suffered trauma-related mortality, the novel scheme diagnosed 166 patients as positive for MODS 3 days prior to when they succumbed to their trauma-associated injuries, while the conventional scheme only diagnosed 132 patients as positive for MODS at the same time point. The novel scheme had a significantly higher positive rate of MODS diagnosis compared with the conventional scheme 3 days prior to patients succumbing, 80.98 vs. 64.39% respectively (P<0.01; Table VII and Fig. 3).

The consensus between the conventional scheme and the novel scheme was 100%, whereas the consensus between the novel scheme and the conventional scheme was 79.52% when compared at 3 days prior to patients succumbing to trauma-associated injuries (Table VIII).

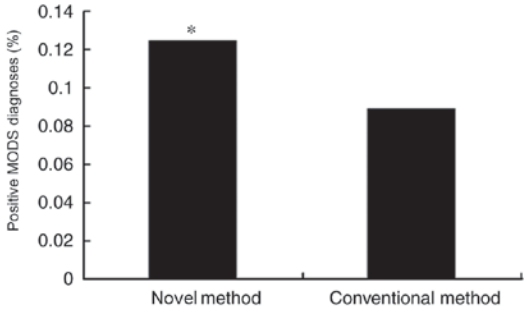

Figure 1. Change in the percentage of positive MODS diagnoses for 2,876 trauma patients using the novel and conventional methods. The novel scheme has a significantly higher positive rate of MODS diagnosis compared with the conventional scheme A total of 2,876 trauma patients were diagnosed using the conventional scheme and the novel scheme. The novel scheme diagnosed a higher percentage of individuals as being MODS positive. *P<0.01 vs. the conventional method. MODS, multiple organ dysfunction syndrome.

Discussion

The failure of tissues or organs of patients with MODS following severe trauma may not be a sudden occurrence. The dysfunction-to-failure of tissues or organs in MODS patients following severe trauma may be a progressive process, and take time to develop into MOF. Early MODS detection is more desirable than late diagnosis as the latter is associated with a high mortality rate (10,33,34) and early MODS detection and timely intervention may prevent MODS from developing into MOF (11). Early MODS may not present typical clinical symptoms, therefore, it should be diagnosed using clinical laboratory data, and not on clinical symptoms alone. The consequences of a missed diagnosis of severe traumatic MODS prior to MOF may be more severe than the consequences of widening the diagnosis range of MODS.

Since the mortality rate of traumatic MOF is so high, early diagnosis of MODS is very important (10). A uniform MODS diagnosis and scoring standard has yet to be established, and different assessment of the degree of organ damage, such as organ dysfunction, impairment and failure, as well as different types of organs involved in MODS, can result in distinct diagnostic criteria for MODS used in different areas or hospitals. The authors' hospital had long used the traumatic MODS diagnosis scheme, as a control scheme for the present study, proposed by professor of Zhengguo Wang of the Chinese Academy of Engineering (29). Certain diagnostic criteria are too conservative, and the MODS diagnosed by such criteria may have reached MOF, exhibiting the symptoms of advanced MODS and so the best opportunity for clinical intervention may be lost. Since early positive diagnosis of severe traumatic MODS may be difficult, the MOF mortality may be falsely regarded as the MODS mortality, which may be the reason for the high mortality (>80%) for traumatic MODS (10). Early diagnosis of MODS, allowing the best window of opportunity for treatment of MODS is an important measure to reduce the fatality rate of traumatic ICU patients (11,35).

Dysfunction indicates that although the organ is impaired, there may be no obvious clinical manifestations. Organ failure indicates that the organ is not functional, and it may be an indicator of organ death. Organ dysfunction without obvious clinical manifestations should be diagnosed as MODS. This conforms to the theory that early MODS can be recoverable (11), and adheres to the description of 'dysfunction'. Based on laboratory indicators, the scoring of MODS was adjusted to include patients with mild organ dysfunction within the scope of MODS diagnosis, and enabled earlier diagnosis of traumatic MODS. The present study puts forward a more sensitive diagnostic scheme for traumatic MODS, which includes pancreatic β-cell dysfunction. The utilization of the authors' novel scheme for diagnosis allows the early detection of traumatic MODS patients that have not advanced to MOF and may improve the therapeutic efficacy of MODS treatment in clinical practice (11).

The results of the present study demonstrated that the improved novel scheme utilizing pancreatic β-cells had an increased positive rate of traumatic MODS diagnosis compared with the conventional scheme. All positive patients diagnosed by the conventional scheme were also positive when diagnosed by the improved novel scheme. Among the positive patients diagnosed by the improved novel scheme, a few cases were diagnosed as negative by the conventional scheme. These results indicate that the improved novel diagnostic scheme for traumatic MODS may increase the sensitivity of MODS diagnosis and increase the positive rate of MODS diagnosis.

The pancreatic β-cell is the only cell that can secrete insulin that serves an important role in the post-traumatic metabolic reaction (21). Pancreatic β-cell dysfunction should be regarded as a part of MODS. Evaluation of the function of pancreatic β-cells should take into account both the initial stimulated level of blood glucose and the final level of blood glucose, including basal level of insulin secretion during FBG, early insulin secretion function as a result of stimulation by hyperglycemia, and FBG after stable secretion of insulin (21).

There are several methods of evaluation of pancreatic β-cell function for diabetic patients (36-39). Traumatic MODS patients are different from diabetic patients. Traumatic MODS patients are in pain, and some complex methods (such as frequent blood sampling) of evaluation of pancreatic β-cell function for diabetic patients may not be appropriate for MODS patients

Table I. Conventional diagnostic scheme for traumatic MODS.

	Evaluation indicators by score		
Affected system	0.5	1	2
Lung	Mild effusion from lung or exudation between lung lobes, respiration >30 times/min, PaO_2 <80 mmHg, PiO_2=0.5	Exudation from unilateral or bilateral alveoli, respiration >35 times/min, PaO_2 <55 mmHg, FiO_2=0.5, PEEP (<0.78 kPa) is required	Exudation from bilateral alveoli, respiration >40 times/min, PaO_2 <50 mmHg, FiO_2=1, PEEP (>0.78 kPa) is required pulmonary artery pressure increases
Kidney	Urine volume <500 ml/day, BUN 14.2-28.5 mmol/l, Scr 132.6-176.8 μmol/l	Urine volume <400 ml/day, BUN 28.5-42.8 mmol/l, Scr >176.8 μmol/l	Urine volume <300 ml/day, BUN >42.8 mmol/l, Scr >442 μmol/l, hemodialysis is required
Heart	Systolic blood pressure <80.0 mmHg, mild shock, pulse/systolic pressure >1.0	Systolic blood pressure <70.0 mmHg, medium shock, pulse/systolic pressure >1.5	Systolic blood pressure <60.0 mmHg, severe shock, pulse/systolic pressure >2.0
Liver	Hemobilirubin 20.5-34.2 μmol/l, blood ALT 40-100 U/l	Jaundice in clinic, hemobilirubin >34 μmol/l, blood ALT >100 U/l	Hepatic coma, increased blood ammonia, low protein, hemobilirubin >85 μmol/l, blood ALT >200 U/l
Brain	Slow response, be able to make a simple conversation and open eyes after awakening, disorientation	Have pain reflex, unable to talk, Glascow score <7	No response to language, pain reflex disappeared, Glascow score <3
Blood	Blood platelet <40x10^3/l, PT and APTT extend slightly, negative test results of 3P test, no DIC	Blood platelet <20x10^3/l, PT and APTT extend significantly, weakly positive result of 3P test, DIC earlier stage	Blood platelet <10x10^3/l, strong positive result of 3P test, DIC, clear systemic bleeding
Gastrointestinal tract	Abdominal distension, borborygmus weakness	Highly increased abdominal distension, borborygmus disappears, intestinal obstruction or diarrhea	Intestinal obstruction and no autonomous defecation following enema, or stress intestinal ulceration, intestinal tract bleeding
Others[a]		24 h following trauma or major surgery	

[a]Supplemented diagnostic criteria. PEEP, positive end-expiratory pressure; BUN, blood urea nitrogen; ALT, alanine aminotransferase; PT, prothrombin time; APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; 3P, plasma protamine paracoagulation; PiO_2, inspired oxygen; PaO_2, partial pressure of oxygen; FiO_2; fraction of inspired oxygen.

Table II. Improved diagnostic scheme for traumatic MODS involved in pancreatic β-cell dysfunction

	Evaluation indicators by score		
Affected system	0.5	1	2
Lung	Mild effusion from lung or exudation between lung lobes, respiration >30 times/min, PaO_2 <80 mmHg, PiO_2=0.5	Exudation from unilateral or bilateral alveoli, respiration >35 times/min, PaO_2 <55 mmHg, FiO_2=0.5, PEEP (<0.78 kPa) is required	Exudation from bilateral alveoli, respiration >40 times/min, PaO_2 <50 mmHg, FiO_2=1, PEEP (>0.78 kPa) is required, pulmonary artery pressure increases
Kidney	Urine volume <500 ml/day, BUN 14.2-28.5 mmol/l, Scr 132.6-176.8 μmol/l	Urine volume <400 ml/day, BUN 28.5-42.8 mmol/l, Scr >176.8 μmol/l	Urine volume <300 ml/day, BUN >42.8 mmol/l, Scr >442 μmol/l, hemodialysis is required
Heart	Systolic blood pressure <80.0 mmHg, mild shock, pulse/systolic pressure >1.0	Systolic blood pressure <70.0 mmHg, medium shock, pulse/systolic pressure >1.5	Systolic blood pressure <60.0 mmHg, severe shock, pulse/systolic pressure >2.0
Liver	Hemobilirubin 20.5-34.2 μmol/l, blood ALT 40-100 U/l	Jaundice in clinic, hemobilirubin >34 μmol/l, blood ALT >100 U/l	Hepatic coma, increased blood ammonia, low protein, hemobilirubin >85 μmol/l, blood ALT >200 U/l
Brain	Slow response, be able to make a simple conversation and open eyes after awakening, disorientation	Have pain reflex, unable to talk, Glascow score <7	No response to language, pain reflex disappeared, Glascow score <3
Blood	Blood platelet <40x10^3/l, PT and APTT extend slightly, negative test results of 3P test, no DIC	Blood platelet <20x10^3/l, PT and APTT extend significantly, weakly positive result of 3P test, DIC earlier stage	Blood platelet <10x10^3/l, strong positive result of 3P test, DIC, clear systemic bleeding
Gastrointestinal tract	Abdominal distension, borborygmus weakens	Highly increased abdominal distension, borborygmus disappears, intestinal obstruction or diarrhea	Intestinal obstruction and no autonomous defecation following enema, or stress intestinal ulceration, intestinal tract bleeding
Pancreatic β-cells[a]	Fasting blood glucose >8.0 mmol/l (last for >2 days), HOMA-β, $\Delta INS_{30}/\Delta GLU_{30}$ reduce to <50% of normal value	Fasting blood glucose >11.0 mmol/l (last for >2 days), HOMA-β, $\Delta INS_{30}/\Delta GLU_{30}$ reduce to <25% of normal value	Fasting blood glucose >15.0 mmol/l (last for >2 days), HOMA-β, ΔINS30/ΔGLU30 reduce to <12.5% of normal value
Others[a]		24 h following trauma or major surgery	

[a]Supplemented diagnostic criteria. HOMA, homeostatic model assessment; PEEP, positive end-expiratory pressure; BUN, blood urea nitrogen; ALT, alanine aminotransferase; PT, prothrombin time; APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; 3P, plasma protamine paracoagulation; PiO_2, inspired oxygen; PaO_2, partial pressure of oxygen; FiO_2; fraction of inspired oxygen.

Table III. The positive rate of multiple organ dysfunction syndrome diagnosis for trauma patients by the novel scheme and the conventional scheme.

Diagnostic method	Total cases, n	Positive cases, n	Percentage positive, %
Novel scheme	2,876	359	12.48[a]
Conventional scheme	2,876	255	8.87

[a]P<0.01 vs. the conventional scheme.

Table IV. Consistency of the novel scheme and conventional scheme in the diagnosis of multiple organ dysfunction syndrome for patients after trauma.

Criteria	Novel scheme	Conventional scheme
Positive cases (n)	359	255
Negative cases (n)	2,517	2,621
Total (n)	2,876	2,876
Positive consensus (%)	100	71.03

Table V. Comparison of final positive rate of multiple organ dysfunction syndrome diagnosis for patients who suffered trauma-associated mortality.

Diagnostic method	Mortality cases, n	Final positive cases, n	Percentage consensus, %
Novel scheme	205	181	88.30
Conventional scheme	205	177	86.34

following trauma due to the severity and rapid development of MODS in the present study. Simple and rapid evaluation methods of pancreatic β-cell function that are minimally painful, may be more suitable for MODS patients following trauma.

The included cases were physically healthy prior to trauma or they were inpatients following major surgery. Patients with severe insulin resistance, obesity, hypertension and diabetes prior to trauma were excluded. For diabetic and obese subjects, the effect of insulin resistance should be corrected for prior to the evaluation of pancreatic β-cell dysfunction, and the computation is usually complex (24,26). In the present study, only patients who were physically healthy and had no metabolic disorders prior to trauma were included. Therefore, the classical calculation formulae of HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$ indicator were applicable to these trauma patients.

Stress hormone levels usually increase following severe trauma, especially glucagon, which antagonizes insulin, causing insulin resistance. However, in a conventional sense,

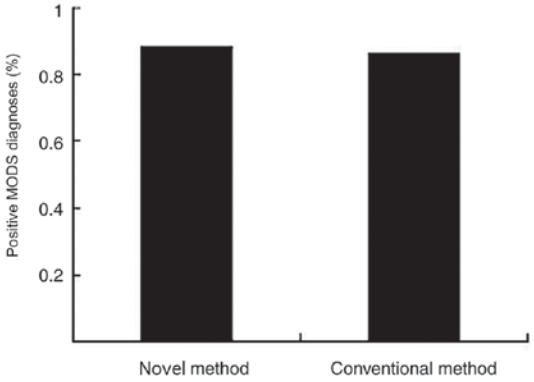

Figure 2. Final percentage of positive MODS diagnoses of the 205 trauma patients that succumbed to MODS using the novel and conventional methods. Novel and conventional diagnostic methods demonstrate similar effectiveness in diagnosing patients who succumb to mortality. A total of 205 patients succumbed to mortality, the novel and conventional methods of diagnosis for MODS diagnosed a similar number of patients as positive for MODS. MODS, multiple organ dysfunction syndrome.

insulin resistance refers to a decline in function per unit of insulin. Pancreatic β-cell function is defined as the level of insulin secretion by pancreatic β-cells under the stimulus of the same level of blood glucose. Therefore, insulin resistance and pancreatic β-cell function may not be correlated. The blood glucose level is the net result of interaction between pancreatic β-cell function and insulin resistance (21).

A continuous rise of FBG was considered as an indicator of pancreatic β-cell function in the present study, for the following reasons: i) By using the continuous rise of FBG for ≥2 days after fasting (including discontinuance of glucose nutrition for 12 h) as the indicator, the effect of transient increase of glucagon on FBG was precluded; ii) as none of the cases had diabetes or obesity-associated insulin resistance prior to trauma, an increase of glucagon and other hormone levels following trauma was considered secondary to the trauma. If the pancreatic β-cell function was normal, insulin resistance caused by glucagon increase could be counteracted. Therefore, FBG would remain normal with hyperinsulinemia and the diagnosis of pancreatic β-cell dysfunction was rejected; iii) in patients with MODS following trauma, a continuous high FBG level with pancreatic β-cell dysfunction is secondary to post-trauma infection and oxidative stress; and iv) this symptom does not exist prior to trauma. If pancreatic β-cell dysfunction is exhibited prior to trauma, diagnosis of post-trauma MODS cannot be made on this basis.

The HOMA-β index can be used to indicate the basic insulin secretory function of pancreatic β cells and $\Delta INS_{30}/\Delta GLU_{30}$ can serve as an index indicating the early insulin secretory function of pancreatic β-cells stimulated by the presence of blood glucose. Sustained hyperglycemia will appear in clinically only following pancreatic β-cell dysfunction and failure to maintain stable glucose metabolism (21). There is continuous hyperglycemic trauma in MODS patients, none of whom had diabetes before trauma combined with an apparent decline in the HOMA-β index and $\Delta INS_{30}/\Delta GLU_{30}$ (40). This is an important reason why a sustained FBG increase and a HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$ decline is used as an indicator of pancreatic β-cell function in post-trauma MODS patients.

Table VI. Positive and negative cases of multiple organ dysfunction syndrome diagnosed by the novel and conventional scheme for patients who suffered trauma-associated mortality.

Criteria	Novel scheme	Conventional scheme
Positive cases (n)	181	177
Negative cases (n)	24	28
Total (n)	205	205
Percentage consensus (%)	100	97.79

Table VIII. The multiple organ dysfunction syndrome positive and negative cases diagnosed by the novel scheme and the conventional scheme for patients who suffered trauma-related mortality, 3 days prior to mortality.

Criteria	Novel scheme	Conventional scheme
Positive cases, n	166	132
Negative cases, n	39	73
Total, n	205	205
Percentage consensus, %	100	79.52

Table VII. Comparison of the number of positive of multiple organ dysfunction syndrome diagnoses 3 days prior to day that patients suffered trauma-associated mortality.

Diagnostic method	Mortality cases, n	Positive cases 3 days prior to mortality, n	Final consensus, %
Novel scheme	205	166	80.98[a]
Conventional scheme	205	132	64.39

[a]P<0.01 vs. the conventional scheme.

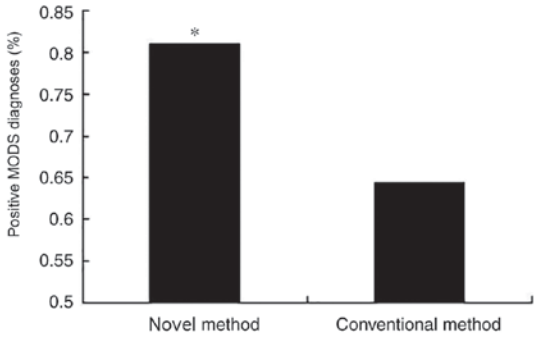

Figure 3. Number of positive MODS diagnoses of the 205 trauma patients that succumbed to MODS using the novel and conventional methods 3 days prior to mortality. At 3 days prior to mortality, the novel method diagnosed a significantly higher number of patients as being MODS positive compared with the conventional method. *P<0.01 vs. the conventional method.

The authors of the present study hypothesize that it is reasonable to include pancreatic β-cells of severe trauma patients into the MODS diagnosis. Following severe trauma, hyperglycemia occurs simultaneously, and the secretion of insulin declines compared with the increase in blood glucose (21,40-43). Severe traumatic infection and endotoxemia can induce the apoptosis and damage of pancreatic β-cells through the increase of inflammatory cytokines (40,44,45). Morphological alterations and dysfunction of pancreatic β-cells are present in traumatic MODS, and sustained hyperglycemia promotes the genesis and development of MODS (46-49). The conclusions of these studies provide a theoretical basis for the establishment of an improved diagnostic scheme for traumatic MODS involving pancreatic β-cell dysfunction. In addition, taking two blood samples can be sufficient for functional evaluation of pancreatic β-cells, i.e., evaluation based on indexes such as FBG, HOMA-β index and $\Delta INS_{30}/\Delta GLU_{30}$. It is non-invasive and can be easily tolerated by severe trauma patients. Therefore, the improved novel diagnostic scheme for traumatic MODS involved in pancreatic β-cell dysfunction established by us is practical, and easily applied.

The results of the present study demonstrated that the improved novel scheme had an increased positive rate of MODS diagnosis for trauma-associated mortality of patients 3 days prior to succumbing to MODS than the conventional scheme, which indicates that the improved novel scheme for traumatic MODS may improve the positive rate of early diagnosis for severe traumatic MODS patients. Hyperglycemia following trauma is positively correlated with the severity of MODS, and accompanies the process of MODS genesis and development (49-51). Severe trauma patients exhibit sustained hyperglycemia in an early stage, while this symptom may be associated with pancreatic β-cell dysfunction, which can serve as an early warning index for traumatic MODS (49). Continuous increase of FBG and a reduction of the HOMA-β index and $\Delta INS_{30}/\Delta GLU_{30}$ usually occurs at an early stage of severe traumatic MODS in patients that eventually pass away, and the dysfunction of pancreatic β-cell generally occurs before the failure of other organs following trauma (48-49), which may be an important reason why the modified novel diagnostic method may discover MODS 3 days earlier than the conventional diagnostic method.

The addition of pancreatic β-cell dysfunction to the conventional scheme for diagnosis of traumatic MODS, would not excessively extend the diagnosis scope for traumatic MODS. The improved novel diagnosis scheme for traumatic MODS includes 2 essential conditions: i) Dysfunction of ≥2 organs or histocytes occurs; and ii) the total score is >2. Traumatic MODS cannot be diagnosed only by pancreatic β-cell dysfunction. Pancreatic β-cell dysfunction cannot be diagnosed if the patient only has transient hyperglycemia, or hyperglycemia is not sustained >2 days or the HOMA-β index and $\Delta INS_{30}/\Delta GLU_{30}$ index does not obviously decrease. In addition, sustained hyperglycemia following trauma is also accompanied by hepatic and renal dysfunction. Pancreatic β-cell dysfunction, dysfunction of other organs and SIRS

following severe trauma are positively correlated with each other, and aggravate the condition of severe trauma patients (48,49).

Diagnostic methods for traumatic MODS in patients with pancreatic β-cell dysfunction following trauma should be employed flexibly and in combination with scoring. Scoring can be conducted based on laboratory data, clinical manifestations and objective indicators using a scale. If all indicators satisfy the diagnostic criteria for dysfunction of a specific organ, the full score is given; otherwise, a partial score is given. In the present study, the indicators considered were FBG, HOMA-β index and $\Delta INS_{30}/\Delta GLU_{30}$, which were used to assess the degree of pancreatic β-cell dysfunction in traumatic patients. If all of them satisfied the criteria, a full score (2) was given; if only one or two indicators did, a partial score was given (0.5 or 1; Table II).

It should be noted that pancreatic β-cell dysfunction following trauma may occur concurrently with or sequentially to dysfunction of other organs. FBG increase following trauma is usually accompanied by a reduction in the HOMA-β index and $\Delta INS_{30}/\Delta GLU_{30}$ (21,40,49). In addition, a high FBG following trauma can be differentiated from that in diabetic patients, as the FBG increase in diabetic patients is chronic and persistent. However for high FBG following trauma, if the traumatic MODS patients were properly treated, the high FBG would decrease to the pre-trauma normal level. In the trauma patients that had a poor prognosis or even succumbed to MODS, the FBG increase that is frequently accompanied by a reduction in HOMA-β index and $\Delta INS_{30}/\Delta GLU_{30}$, would not improve therefore allowing for differentiation from diabetic patients (48,49).

Scoring for organ dysfunction except for pancreatic β-cell dysfunction in MODS patients following trauma was performed using the conventional scheme (10,29,40,48,49) that has been tested following years of clinical practice. Not all patients with an FBG level >the upper limit (typically 6.1 mmol/l) of the Chinese normal range have MODS (21) and so pancreatic β-cell dysfunction following trauma would be not diagnosed if only the FBG level was elevated above the upper limit of the normal range. If 6.1 mmol/l FBG was designated as the cutoff value of pancreatic β-cell dysfunction, the novel scheme that included pancreatic β-cell dysfunction would cause misdiagnosis of MODS following trauma. Through surveying patients sustained FBG increase for 2 days and a level >8.0 mmol/l was identified as an appropriate cut-off value; the risk of MODS in those with FBG >8.0 mmol/l was greater than that in those with FBG <8.0 mmol/l. It was also demonstrated that FBG levels were >8.0 mmol/l, 11.0 mmol/l and 15.0 mmol/l, mild, moderate and severe dysfunction, respectively for over 2 days may be usually combined with varying degrees of organ dysfunction. That is why these FBG levels were designated as the cut-off values for the diagnosis of pancreatic β-cell dysfunction following trauma in patients with varying degree of organ dysfunction. So far, no standard normal ranges or means of HOMA-β index and $\Delta INS_{30}/\Delta GLU_{30}$ have been established yet, and different laboratories have different reference ranges. Therefore, it may be more reasonable to use the degree of reduction in HOMA-β index and $\Delta INS_{30}/\Delta GLU_{30}$ (expressed as a percentage) as the indicator used for assessment of the severity of different levels of pancreatic β-cell dysfunction. A variety of factors can result in elevated FBG, therefore FBG alone is not precise enough for a diagnosis of pancreatic β-cell dysfunction. The patient also had to demonstrate a reduction in the HOMA-β index and $\Delta INS_{30}/\Delta GLU_{30}$. Both the HOMA-β index and $\Delta INS_{30}/\Delta GLU_{30}$ are important indicators of the accurate assessment of pancreatic β-cell dysfunction.

In the present study, although the novel scheme had an increased positive rate of MODS diagnosis for severe trauma patients and had an increased positive rate of MODS diagnosis for trauma-associated mortality patients 3 days prior to succumbing to MOF than the conventional scheme, there was no difference in the final positive rate of MODS diagnosis for trauma-associated mortality patients between the novel scheme and the conventional scheme. These results suggest that compared with the conventional scheme, the improved novel diagnosis scheme for traumatic MODS only slightly advances the diagnosis of MODS, but does not excessively broaden the diagnosis range of traumatic MODS.

The improved novel diagnostic scheme for traumatic MODS suggest that attention should be given to the harm of sustained dysfunction of pancreatic β-cell and hyperglycemia to severe trauma patients. Control of hyperglycemia and pancreatic β-cell protection may be important measures to prevent and cure severe traumatic MODS (50-52). Insulin or glucose, insulin, potassium (GIK) not only could control the hyperglycemia of traumatic MODS, but also could protect the function of pancreatic β-cell of traumatic MODS by anti-inflammatory effect, and therefore insulin or GIK could be used as a drug for traumatic MODS patients (53-56). Further clinical study and improvement are required for the improvement of the novel traumatic MODS diagnostic scheme that includes pancreatic β-cell dysfunction, the novel scheme should be tested on patients suffering different types of injuries and from different ethnic subgroups.

Acknowledgments

The present study was supported by the National Science and Technology project (grant no. 2008BAI52B03), the Jiangxi Provincial Science and Technology Project (grant no. 2008BAO7400), Key Issues for the 'Eleventh Five-Year' in Nanjing Military Region (grant no. 06Z25) and the Health Science and Technology project in Jiangxi Province (grant no. 20082044).

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