Measured resting energy expenditure via indirect calorimetry of critically ill patients: A comparison with predictive equations

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Running title: Measured REE vs predictive equations in ICU

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ABSTRACT

Background and Objectives: Assessing the resting energy expenditure (REE) of critically ill patients is essential for individual nutritional programs. We hypothesized that different evaluated ways for REE can be compared, and REE may be associated with disease severity and clinical prognosis. This study aimed to compare the differences between measured resting energy expenditure (m-REE) by indirect calorimetry and values estimated by predictive equations in critically ill patients, and to explore the correlations between REE and inflammatory status or clinical prognosis. **Methods and Study Design:** The patients in intensive care unit (ICU) were categorized based on APACHE II scores. REE was assessed using indirect calorimetry (m-REE) and compared with estimates from multiple equations including Harris-Benedict (H-B), adjusted H-B, Mifflin-St Jeor, WHO/FAO/UNU, Owen, Henry, and Weight-kilogram. Serum procalcitonin (PCT) and high-sensitivity C-reactive protein (hsCRP) were measured, and ICU staying days were recorded for correlation analysis. **Results**: Results showed that m-REE was significantly higher than most equation-predicted values (p <0.01) when APACHE II ≥15, while no significant differences were found with adjusted H-B, Owen, and Weight-kilogram equation. Additionally, m-REE was positively correlated with hsCRP, PCT, ICU staying days and hospital length (all p <0.05). When APACHE II <15, m-REE was generally lower than predicted values. **Conclusions**: The findings suggest that in the absence of indirect calorimetry, the adjusted H-B, Owen, and Weight-kilogram equations may be applicable for patients with APACHE II ≥15. Furthermore, m-REE may serve as a potential predictor of inflammatory status and clinical prognosis in critically ill patients.

Key Words: critical care, indirect calorimetry, resting energy expenditure, nutritional support, clinical prognosis

INTRODUCTION

Nutritional therapy is an important part of the comprehensive treatment for patients in the intensive care unit (ICU), most of whom have severe nutritional risk and a higher incidence of severe malnutrition.[1, 2] Given the great individual differences and complicated conditions of ICU patients, the primary problem for a reasonable nutritional treatment plan is to correctly assess the actual energy consumption of these patients.[3] In addition to being used for nutritional assessment and programs, the levels of energy consumption may also be associated with disease severity and inflammation levels, providing reference suggestions for evaluating the clinical prognosis of patients.[4]

At present, the calculated method with predictive equations is still widely used in the clinical estimation of patients' evaluation of energy consumption, including Harris-Benedict (H-B), adjusted H-B, Mifflin-St Jeor, World Health Organization/Food and Agriculture Organization of the United Nations/United Nations University (WHO/FAO/UNU), Owen, Henry, and Weight-kilogram equations. Although the equations mentioned above can be corrected by stress coefficients or other methods, there are still some calculation errors for severely malnourished patients, especially ICU patients.[5, 6]

Resting energy expenditure (REE) refers to the energy expenditure after fasting for more than 2 h and lying down at room temperature for 30 min. Compared to the strict requirements of basal metabolic rate detection, using REE to estimate the target value for energy of nutritional intervention in bedridden patients is more commonly recommended in clinical practice.[7] The advantage of indirect calorimetry is that it can detect the energy consumption of patients in real-time and is close to the actual energy consumption of bedridden patients. It can adjust the target energy in time according to the monitoring situation, which is of great significance for individualized nutrition plans for critically ill patients.[8] To date, there is still a lack of clinical studies on the differences between REE and predictive equations in the patients with different Acute Physiology and Chronic Health Evaluation II (APACHE II) scores in ICU, as well as the correlation between REE, inflammatory status, and clinical prognosis.

Therefore, we hypothesized that different evaluated ways for REE can be compared, and REE may be associated with disease condition (such as inflammation) and clinical prognosis. Given the above assumptions, the study stratified ICU patients according to the APACHE II, measured the REE of patients by indirect calorimetry, and compared the calculated results with different predictive equations. Meanwhile, the correlations of REE and serum high-sensitivity C-reactive protein (hsCRP), procalcitonin (PCT), and ICU staying days were also analyzed, providing new clinical proof for the assessment of energy consumption, clinical prognosis, and individualized nutrition project for ICU patients.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of the Eighth Affiliated Hospital of Sun Yat-sen University (No. ZDBY(L) 2020-051-01) and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. 60 patients who were admitted to the hospital from August 2022 to October 2024 were informed consent statements and taken as the subjects with the inclusion criteria, and were divided into two groups according to APACHEII ≥15 and APACHEII <15, with 30 patients in each group.

Inclusion criteria

Inclusion criteria for the study was as follow:

(1) Patients admitted to the ICU or EICU, aged 18 years or older, were either male or female.

(2) Understanding and willingness to participate in this study and providing signed informed consent by themselves or family members.

(3) The result of NRS2002 was more than three points, and the hospital stay was more than 24 hours, with hemodynamic stability and stable vital signs, including mean arterial pressure (MAP) ≥65 mmHg without escalating vasopressor support, heart rate between 60-120 bpm, stable oxygen saturation (SpO_2 ≥90% on stable ventilator settings), and no acute arrhythmias or significant hemodynamic events

requiring immediate intervention in the 4 hours preceding measurement.

(4) There was no need to adjust the ventilator parameters 2 h before or during the measurement.

Indirect calorimetric determination of REE

The patient's resting energy expenditure was measured using a mobile energy metabolism cart (CareFusion Vmax Encore). Standardized preparation was implemented before all measurements: (1) Patients were in a fasting state for at least 4 hours prior to measurement (enteral or parenteral nutrition was paused); (2) Measurements were performed with patients in a supine position, in a quiet and thermoneutral environment; (3) Patients were resting for at least 30 minutes before measurement; (4) Sedative and hypnotic drug administration was recorded (type and dosage), and measurements were avoided within 2 hours of bolus sedation; (5) No nursing procedures or physiotherapy were performed in the 30 minutes preceding measurement. All measurements were performed by professionals with strict training following instrument specifications. The test time for each patient was approximately 15 min after the instrument showed a steady state. The results were expressed as m-REE.

Predictive equations to calculate energy consumption

Seven commonly clinical-used equations, including Harris-Benedict, adjusted Harris-Benedict, Mifflin-St Jeor, WHO/FAO/UNU, Owen, Henry, and weight-kilogram equations were used for comparison with m-REE (Supplementary Table 1). The selection for the above predictive equations was based on: widespread use in ICU settings as previous reported; their representation of different methodological approaches (e.g., weight based; weight and sex based; height, weight, sex and age based), and their inclusion in previous comparative studies, allowing for contextualization of our findings.[9-12] The unit of calculation was kilocalorie per day (kcal/d) and the results were represented by abbreviations as hb-REE, ahb-REE, msj-REE, wfu-REE, o-REE, h-REE and w-REE, respectively.

Detection and records of inflammatory indicators and clinical prognosis

The levels of PCT and hsCRP were measured using a fully automated biochemical analyzer. The detection time for the above factors was the same as the resting energy measurement time (the difference should be less than 4 h). The clinical prognosis tracked included: (1) ICU length of stay (days from ICU admission to ICU discharge); (2) ICU mortality (death during ICU stay); (3) 28-day mortality (death within 28 days of ICU admission); and and (4) hospital length of stay.[1, 10] All patients were followed until hospital discharge or death.

Statistical analysis

The data were analyzed using SPSS 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and discontinuous variable are described as ratio (N%). Normality of data distribution was assessed using the Shapiro-Wilk test, and homogeneity of variances was evaluated using Brown-Forsythe and Bartlett's test. For inter-group comparisons (APACHE II ≥15 vs. APACHE II ≥15), one-way ANOVA was used for normally distributed data with homogeneous variances, or Welch ANOVA and Brown-Forsythe ANOVA for unequal variances with normal distribution. Bonferroni test (equal variances) or Dunnett’s T3 test (unequal variances) were used for pairwise comparisons. Spearman linear correlation analysis was performed to analyze: (1) the correlation between m-REE and serum hsCRP levels; (2) the correlation between m-REE and serum PCT levels; (3) the correlation between m-REE and ICU staying days; and (4) the correlation between m-REE and hospital length of stay. Differences were considered statistically significant when p <0.05. Results were plotted using GraphPad Prism 8 software (San Diego, CA, USA).

RESULTS

Comparison between indirect calorimetric measurement and calculated results of predictive equations.

The basic information, including sex, age, height, body weight, body mass index (BMI), nutrition intake and main clinical diagnose were shown in Supplementary Table 2. The m-REE measured by indirect calorimetry and the results calculated via different equations were shown in Table 1 and Figure 1. The results indicated that when APACHE II ≥15, the m-REE was higher than the hb-REE, msj-REE, wfu-REE, and h-REE (p <0.01). There were no statistically significant differences between the m-REE and ahb-REE (p = 0.80), o-REE (p = 0.35), or w-REE (p = 0.96). In patients with APACHE II <15, the m-REE was significantly lower than the results of the predictive equations (p <0.001). Further stratified analysis results by age and oxygen delivery pattern were presented in Supplementary Table 3.

Correlation analysis between resting energy consumption and serum hsCRP and PCT.

The correlation analysis between m-REE and serum hsCRP and PCT was shown in Figure 2 (Supplementary Table 4)**.** In the group with APACHE II ≥15, m-REE was positively correlated with serum hsCRP level (r = 0.721, p <0.01) and serum PCT level (r = 0.830, p <0.01). While in the APACHE II <15 group, m-REE was not associated with hsCRP (r = 0.196, p = 0.3) and PCT (r = 0.012, p = 0.949).

Correlation analysis between resting energy consumption and ICU staying days and hospital length of stay.

The correlation analysis between m-REE and ICU staying days and hospital length of stay were presented in Figure 3 (Supplementary Table 4)**.** REE was positively correlated with ICU staying day (r = 0.889, p <0.01) and hospital length of stay (r = 0.674, p <0.01) when APACHE II ≥ 15, and was not associated with ICU staying days (r = 0.260, p = 0.165) and hospital length of stay (r = 0.071, p = 0.711) in the group of APACHE II <15.

DISCUSSION

ICU patients, especially those with systemic inflammatory response syndrome and sepsis, often suffer from severe malnutrition, decreased immune function, poor wound healing, and other complications during clinical treatment, which is not favorable for the prognosis of the disease.[2, 13] Reasonable nutritional treatment can reduce the risk of ere malnutrition in ICU patients, improve clinical prognosis, and create favorable ditions for the treatment of patients. This is the first study to explore the accuracy of predictive equations of REE after APACHE II stratification, and to analyze the correlation between REE and hsCRP, PCT, and ICU staying days, which provides a new theoretical basis for nutritional treatment and clinical prognosis of ICU patients.

Because different predictive equations are based on data from different population, the energy consumption of ICU patients estimated via predictive equations may have some error with the actual energy consumption of patients.[8, 14] Studies have shown that when nutritional plans are calculated using predictive equations, approximately 50% of patients are in a state of overnutrition or malnutrition.[13] Compared to equation estimation, the determination of REE by indirect calorimetry has more advantages in terms of accuracy. Updated guideline recommendations for critical care nutrition have proposed that indirect calorimetry is recommended to measure energy expenditure when conditions permitted.[15-18] However, in actual clinical practice, owing to the limitation of instrument conditions, we have to adopt alternative methods to estimate the patient's energy expenditure. While European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines suggest the use of ventilator-derived VCO_2 or VO_2 from pulmonary artery catheters as alternatives to predictive equations, the application remains limited by diseases and vital signs of patients, and VCO_2 or VO_2 cannot be reliably recorded for the patients that not receiving mechanical ventilation. Therefore, in the absence of indirect calorimetry, VO_2 or VCO_2 measurements, the use of predictive equations may be preferred. In line with the pursuit of precision nutrition, emerging approaches such as deep learning-based predictive models have recently been proposed to optimize individualized energy delivery in septic patients, highlighting the potential of integrating advanced computational tools with metabolic monitoring in future critical care nutrition.[19]

The results of the APACHE II have been widely recognized for predicting clinical outcomes in ICU patients.[20] It was found that in patients with APACHE II ≥15, the m-REE was higher than the predicted value of the equations, which may be related to the elevated resting metabolism caused by the acute early infection stress response in critically ill patients.[21] The same results have also been obtained in studies of patients with liver transplant and septic shock.[11, 22] There was no statistically significant difference between m-REE and ahb-REE, o-REE and w-REE, suggesting that the calculated results of adjusted H-B, Owen, and Weight-kilogram might be served as the alternatives for patients without testing equipment. However, the weight-kilogram results have been inconsistent in some previous studies,[23] so further validation will be needed through methods such as enlarging the sample size and making disease stratification to ensure the accuracy of the results. In patients with APACHE II <15, the m-REE was lower than the predictive results of the equations. The reasons for this may be that the high stress level of the patients in the acute phase was corrected to certain extent, the energy consumption reduced adaptability.[24-26] The same results have also been found in the studies on chronic diseases such as cirrhosis and breast cancer.[14, 27-30]

Previous studies have explored the correlation between REE and C-reactive protein (CRP), and have found that REE is positively correlated with CRP and may also be associated with white blood cell count and neutrophil/lymphocyte ratio.[31] Critically ill patients release massive amounts of inflammatory factors due to trauma or infection, inducing the proliferation and recruitment of inflammatory cells, and the state of immune response also adaptively increases energy consumption.[26] PCT is also used to evaluate the infection status of the body, but few studies have focused on the correlation between REE and PCT in ICU patients.[21, 32] In this study, m-REE was found to be significantly positively correlated with hsCRP and PCT levels, ICU staying days and hospital length of stay when APACHE II ≥15. The possible mechanism is that pro-inflammation cytokines such as interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) may directly induce mitochondrial uncoupling in skeletal muscle and other tissues, where the energy from substrate oxidation is dissipated as heat rather than being efficiently stored as adenosine triphosphate (ATP), thereby increasing REE concurrently.[33] Moreover, systemic inflammation is associated with acquired resistance to anabolic hormones like growth hormone and IGF-1, which curtails protein synthesis and promotes a catabolic state, further contributing to the elevated energy demands observed in indirect calorimetry.[34] This sustained hypermetabolism, driven by unresolved inflammation, contributes to pathophysiological link between elevated REE and extended ICU or hospital staying length and poor prognosis.[35]

This study has some shortcomings that cannot be ignored. For example, because of the limited equipment used during data collection, the body composition of patients was not detected synchronously; therefore, the data that may affect the REE results, such as muscle, fat, and extracellular water, could not be included in the calculation. Furthermore, the inclusion of sample size and the complexity of diseases made it difficult to guarantee the accuracy further stratified analysis results, and affected the extrapolation of the study to some extent. Owing to the period for the inclusion of cases was mainly in the period of the COVID-19 epidemic, we could not measure the patients' REE several times to collect the longitudinal self-measurement data, which is more powerful to confirm the relationship between REE and changes in patients' clinical condition. We acknowledge that using APACHE II scores as the sole classification criterion may not fully capture disease heterogeneity. Future studies should focus on a single disease category (such as sepsis) with longitudinal REE measurements across different clinical stages and verify inflammatory-metabolic pathways in the above process, to better delineate the temporal relationship between energy metabolism and disease progression.

Conclusion

In conclusion, in the individualized nutritional treatment of critically ill patients, it is very important to correctly assess energy consumption. For patients with an APACHE II score ≥15, if there is no equipment condition, the adjusted H-B, Owen, and weight-kilogram equations may be used as an alternative. In the evaluation of disease, REE can reflect the level of infection and inflammation in ICU patients, and is a good predictor of disease condition and clinical prognosis.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

All the authors declare no conflict of interest.

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Table 1. The comparison of resting energy expenditure measured by indirect calorimetry and calculated via seven equations†

Groups	APACHEII ≥15	APACHEII <15
m-REE	1546±300	937±144
hb-REE	1221±174‡	1174±221§
ahb-REE	1461±209	1291±243§
msj-REE	1245±169‡	1168±229§
wfu-REE	1255±168‡	1202±215§
o-REE	1429±139	1376±178§
h-REE	1286±169‡	1225±225§
w-REE	1486±183	1431±223§

m-REE: REE measured by indirect calorimetry; hb-REE: REE calculated by Harris-Benedict; ahb-REE: REE calculated by adjusted H-B; msj-REE: REE calculated by Mifflin-St Jeor; wfu-REE: REE calculated by WHO/FAO/UNU; o-REE: REE calculated by Owen; h-REE: REE calculated by Henry; w-REE: REE calculated by Kilogram body weight equation; APACHE II: Acute Physiology and Chronic Health Evaluation II.

†The results were expressed as mean ± SD. Shapiro-Wilk test was used for energy expenditure measurement or calculated value in each group. The above variables all conformed to normal distribution. Brown-Forsythe and Bartlett's test for homogeneity of variances showed equal variances between groups for REE with APACHE II <15 and unequal variances between groups for REE with APACHE II ≥15 group. Welch ANOVA and Brown-Forsythe ANOVA for unequal variances with normal distribution. Dunnett's T3 test were used for pairwise comparisons.

‡ p <0.01 vs m-REE when APACHE II ≥15.

§ p <0.001 vs m-REE when APACHE II <15.

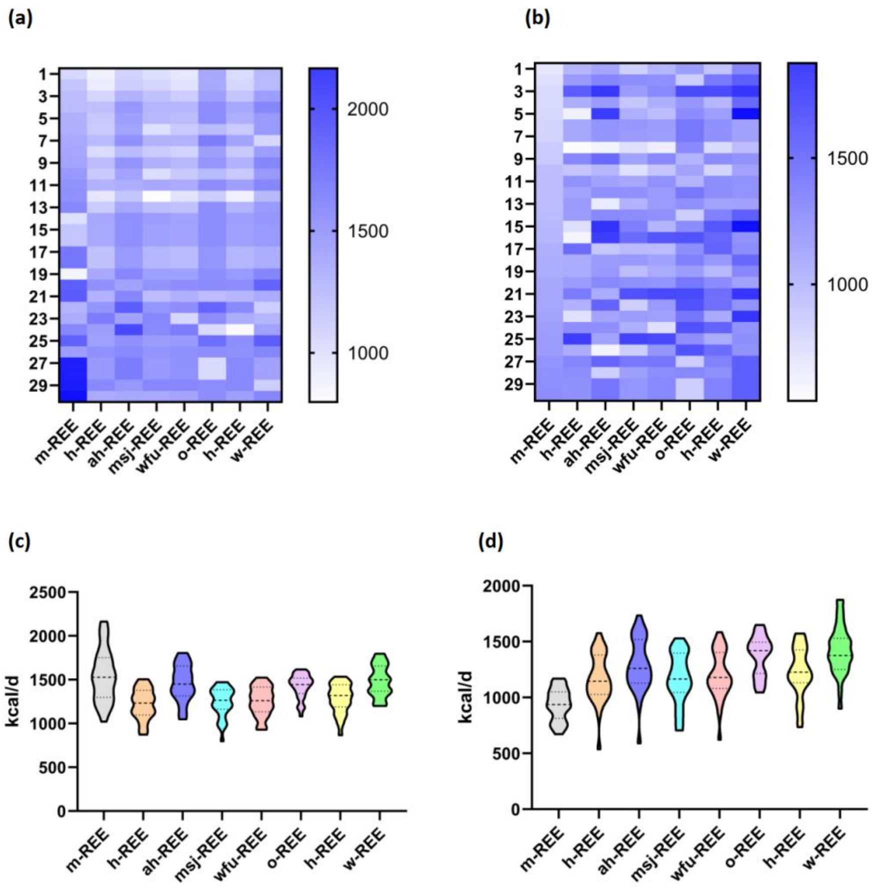

Figure 1. The comparison of indirect calorimetry and different predictive equations. The m-REE measured by indirect calorimetry and the results calculated via seven equations. (a) and (c): The m-REE was higher than the hb-REE, msj-REE, wfu-REE, and h-REE when APACHE II ≥15. (b) and (d): The m-REE was significantly lower than the results of the predictive equations when APACHE II <15. Abbreviations: m-REE (REE measured by indirect calorimetry), hb-REE (REE calculated by Harris-Benedict), ahb-REE (REE calculated by adjusted H-B), msj-REE (REE calculated by Mifflin-St Jeor), wfu-REE (REE calculated by WHO/FAO/UNU), o-REE (REE calculated by Owen), h-REE (REE calculated by Henry), w-REE (REE calculated by Kilogram body weight equation), APACHE II: Acute Physiology and Chronic Health Evaluation.

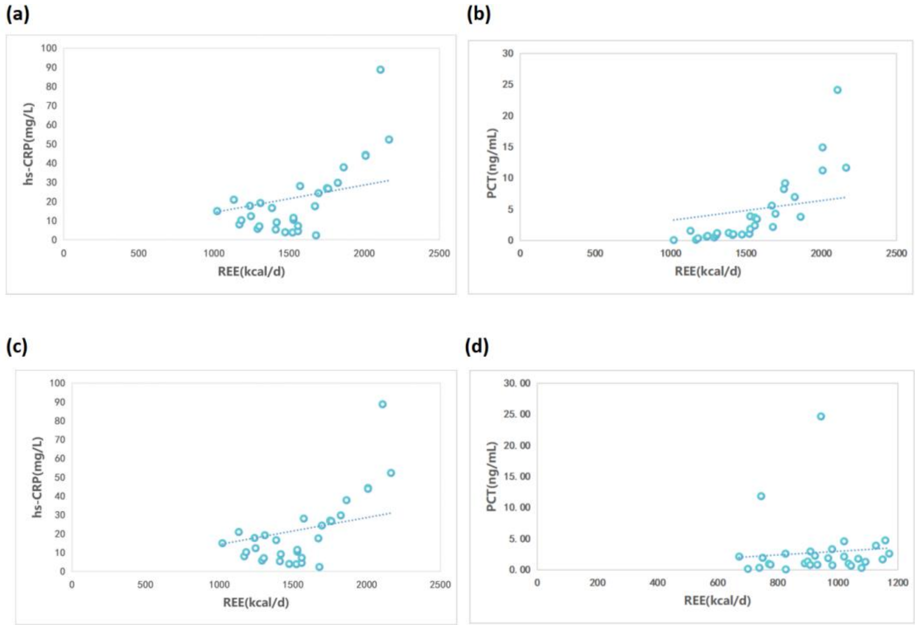

Figure 2. The the correlation analysis between resting energy expenditure and serum hsCRP and serum PCT. The REE was positively correlated with serum hsCRP level (a) and serum PCT level (b) when APACHEII ≥15. However, when APACHE II <15, REE was not associated with serum hsCRP levels (c) and serum PCT levels (d). Abbreviations: REE (resting energy expenditure measured by indirect calorimetry), procalcitonin (PCT) ,high-sensitivity C-reactive protein (hsCRP), APACHE II (Acute Physiology and Chronic Health Evaluation II).

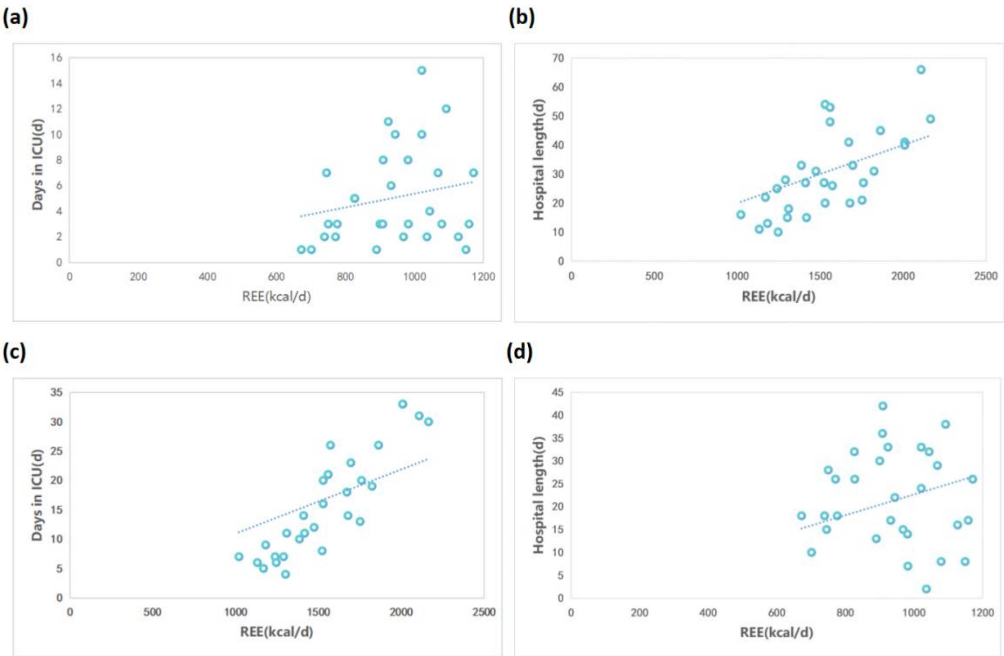

Figure 3. The the correlation analysis between resting energy expenditure and ICU staying days and hospital length of stay. The REE was positively correlated with ICU staying days (a) and hospital length of stay (b) when APACHEII ≥15, and REE was not associated with ICU staying days (c) and hospital length of stay (d) when APACHE II <15. Abbreviations: REE (resting energy expenditure measured by indirect calorimetry), APACHE II (Acute Physiology and Chronic Health Evaluation II).