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Nutritional assessment formulae for nutritional requirement determination in severe trauma

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Running title: Indirect calorimetry in multiple trauma

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ABSTRACT

Background and Objectives: It is often difficult to assess the nutritional requirements of severely injured patients. In this study, we aimed to determine whether various nutritional assessment formulas are accurate at assessing the nutritional requirements of trauma patients. **Methods and Study Design:** We recruited trauma patients who were admitted to a trauma centre in 2018 and were identified as being at high risk for malnutrition. Energy expenditure was calculated using commonly used prediction equations, and the results were compared to resting energy expenditures measured using indirect calorimetry. **Results:** Sixty-nine patients (78.9% men; mean age, 53.6 years) collectively underwent 95 indirect calorimetry assessments. The average resting energy expenditure was 1761.8±483.8 kcal/day, and the average respiratory quotient was 0.8±0.2. The correlations between the measured resting energy expenditures and nutritional requirements estimated by each formula were significant but weak (i.e., r-values <0.8). The Penn State formula had the highest r-value (0.742; 95% confidence interval [CI], 0.6359–0.8210), followed by the Faisy formula (0.730; 95% CI, 0.620–0.812). **Conclusions:** The formula-predicted nutritional requirements did not adequately correlate with the resting energy expenditures measured by indirect calorimetry. Therefore, we recommend using indirect calorimetry to assess the nutritional requirements of severely injured patients.

Key Words: indirect calorimetry, multiple trauma, energy metabolism, nutritional requirements, precision medicine

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INTRODUCTION

Severe trauma patients, like other critically ill patients in the intensive care unit (ICU), develop severe metabolic disorders characterised by rapid oxidative stress and early hypermetabolism.[1,2] Further, it may be difficult to accurately assess their nutritional requirements as well as provide them with adequate nutrition, owing to several reasons. Recent studies have found a possible association between nutritional imbalances and the final prognosis of severe trauma patients. Huang et al found that over 90% of ICU patients developed malnutrition within 14 days of ICU admission.[3] Malnutrition in these patients is known to increase hospital stay, infection rates, morbidity, and mortality; it also results in specific negative clinical consequences for trauma patients, such as muscle weakness and delayed wound healing.[4] Although most trauma patients have no nutrition disorders on admission, they are at an increased risk of malnutrition owing to trauma-related neurohormonal changes and rapid pathophysiological changes caused by cytokine secretion.[5] Hypercatabolism, which develops after injury as by-products of amino acids are used to synthesise acute phase reactants and proteins for wound recovery, and hypermetabolism (via gluconeogenesis) occur simultaneously.[5] In addition, it is difficult to predict the nutritional requirements of trauma patients because their metabolic rates change rapidly in response to several factors, such as multiple procedures, drugs, and infection. To overcome this challenge, energy requirements can be accurately assessed using indirect calorimetry (IC). However, access to IC is limited in most medical centres, and intensivists either follow the nutritional support guidelines recommendation of 25–30 kcal/kg/day[6] or use the Harris-Benedict formula to estimate nutritional requirements.[7] It is important to recognise that the energy requirements measured by IC in adult trauma patients differ from the values calculated by using the nutritional support guidelines or other formulas. The aim of this study was to measure the resting energy expenditure (REE) in trauma patients by using IC and analysing the factors that may influence it. We compared various nutritional assessment formulas to identify their accuracy at determining the nutritional requirements of trauma patients. We also attempted to evaluate the adequacy of nutritional support for adult trauma patients.

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MATERIALS AND METHODS

Patient selection

This study included trauma patients who were admitted to a 100-bed trauma centre between March and December 2018. Patients who were admitted to the ICU for less than 72 h were excluded from the study. We included patients who were identified as being at a high risk for malnutrition, by the nutrition support team, and who underwent IC. We recorded the sex, age, anthropometric data (height, weight, and body mass index [BMI]), Glasgow coma scale (GCS) score, systolic blood pressure, respiratory rate (RR), Revised Trauma Score (RTS), Abbreviated Injury Scale score, and Injury Severity Score (ISS) for all patients included in the study.

Indirect calorimetry

IC was performed under the direction of the nutrition support team, and it was performed only for patients with unavoidable prolongation of ICU stay and who needed mechanical ventilation. IC is generally considered safe because there are no specific contraindications; however, it is not routinely performed in clinical practice as its reliability is not guaranteed.

The measurements were performed in patients under mechanical ventilation at 50% of the fraction of inspired oxygen (FiO_2), checking during respiration balance does not last more than 5 min. We ensured that the patients were in clinically stable states, and their RRs were kept below 25 breaths/min throughout the measurement period. However, patients with un-cuffed endotracheal tubes, continuous air leaks from the airway or chest tube, a positive end-expiratory pressure of more than 10 mmHg, and those receiving extracorporeal membrane oxygenation were excluded from the study.

IC was performed using Quark RMR™ (COSMED, Rome, Italy). This indirect calorimeter is guaranteed to obtain reliable values when applied to patients with a FiO_2 <70%. Measurements were performed in patients who were sufficiently stable for at least 48 h following trauma and hospitalisation. After a minimum of 6 h following surgery, invasive testing and dietary changes were performed. The mean REE (mREE) was calculated after approximately 40 min of testing, excluding the calibration time. The whole-body oxygen consumption (VO_2), carbon dioxide output (VCO2), respiratory quotient (RQ), energy expenditure (EE) mean body temperature, mean minute ventilation, and mean RR were measured and recorded.

Measured energy expenditure (MEE) was calculated using the Weir equation:[8]

MEE (kcal/day) = $3.9 \times VO_2 + 1.1 \times VCO_2$

Nutritional requirements were predicted using commonly used formulas, including the Harris-Benedict,[9] Penn State,[10] Mifflin St. Jeor,[11] 1997 Ireton-Jones,[12] Faisy,[13] and American College of Chest Physicians' (ACCP) 25 kcal/kg formulas.[14]

Statistical analysis

All statistical analyses were performed using the Statistical Product and Service Solution version 23.0 (SPSS, Inc., Chicago, IL, USA). The Student's t-test and analysis of variance were used for quantitative data, and the chi-square test were used for qualitative data. p-value <0.05 was considered statistically significant. Among the descriptive statistics, normally distributed data were presented as means ± standard deviations, and nonparametric data were presented as median values. The energy requirements predicted by the MEE and the respective formulas were compared using scatter plots. The correlations were tested with Pearson correlation analysis for normally distributed data and Spearman correlation analysis for nonparametric data. The correlation was considered strong at an r-value ≥0.8. The correlations were confirmed using Deming multivariate linear regression with jackknife standard errors. The Bland-Altman plots were used to graphically represent the deviations and

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limits of agreement between the MEE and energy requirements predicted by the respective formulas. Subgroup correlation tests were performed based on age, sex, BMI, admission time, and ISS to evaluate the characteristic correlation of each equation in specific subgroups.

Ethical approval

This retrospective study was approved by the Institutional Review Board of our institution, Ajou University Hospital (Approval number: AJIRB-MED-MDB-18-288). The need for informed consent was waived by the board owing to the observational design of the study.

RESULTS

Study population

A total of 95 IC tests were performed for 69 trauma patients. Seven of the patients had the highest number of assessments performed (3 or more), followed by 10 patients who had two assessments performed. Forty-nine (78.9%) of the patients were men. The study population had a mean age of 53.6 years, mean ISS of 30.3±13.0, mean RTS of 6.3±1.4, and mean GCS on admission of 9.75±4.4 (Table 1).

Energy expenditure

IC was carried out following a mean hospitalisation period of 18.6±17.7 days. The mREE was 1761.8±483.8 kcal/day, and the mean RQ was 0.8±0.2. The mean nutritional requirements calculated by the various formulas were as follows: Harris-Benedict, 1444.1±240.3 kcal/day; Ireton-Jones, 1856.8±257.4 kcal/day; Mifflin St. Jeor, 1425.4±241.2 kcal/day; Penn State, 1707.0±287.4 kcal/day; ACCP, 1563.4±267.9 kcal/day; and Faisy, 1922.8±313.7 kcal/day (Table 1). The scatter plots comparing the MEE and the formula-predicted nutritional requirements are presented in Figure 1.

Although the correlation between the nutritional requirements predicted by each formula (Table 2) and the MEE was statistically significant, none of the formulas showed a strong correlation ($r > 0.8$). Among the formulas, the Penn State formula had the highest r-value (0.742; 95% confidence interval [CI], 0.6359–0.8210), followed by the Faisy formula (0.730; 95% CI, 0.620–0.812) (Table 3).

Further analysis was conducted to examine the correlation between formula-predicted nutritional requirements and MEE among specific subgroups. The Faisy formula had the highest r-value (0.626) in the non-obese subgroup (BMI <25 kg/m^2), while the Penn State formula had the highest r-value (0.870) in the obese subgroup (BMI >25 kg/m^2). In the

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analysis based on admission time, the Penn State formula had the highest r-value in the early admission (before two weeks) subgroup, while the Faisy formula had the highest r-value in the late admission (after two weeks) subgroup. The Penn State formula had the highest r-values for both men (0.702) and women (0. 623). In age-based analysis, the Penn State and Faisy formulas had the highest r-values for the younger (0.842) and older groups (0.644), respectively. In the analysis based on injury severity, there were very few patients with an ISS <16 for the analysis; however, in patients with an ISS ≥16, the Faisy formula had the highest r-value (0.756) (Table 5). The correlation strength analysis using Deming linear regression revealed that the Faisy formula had the strongest correlation among all the formulas (coefficient, 1.5423; 95% CI, 0.9022–2.1823; jackknife standard error, 0.3323). Other formulas had relatively higher coefficients and standard errors (Table 4). Regarding the Bland-Altman analysis, the mean difference between the REE calculated with the Faisy formula and the mREE was -161.0 (range: 824.9–502.9), which is fairly wide. The mean difference between REE calculated with the Penn State formula and mREE was the least among the differences between formulas-based predictions and mREE (54.8 kcal/day; range: -595.9–705.5) (Figure 2).

DISCUSSION

This study provides evidence that some of the commonly used formulas for estimating energy requirements in trauma patients are not adequately accurate. The results of the Harris-Benedict equation, a traditionally used tool, and the ACCP 25 kcal/kg formula, which is widely used, were both found to be considerably different from the results of IC, which is the gold standard for the measurement of EE. In addition to several studies, various nutritional estimation formulas have been published for several specific patient groups, some of which are used in clinical practice; however, there are limited studies concerning critically ill trauma patients receiving mechanical ventilation.

Severe trauma patients differ from other patient populations, owing to their unique metabolic demands and dramatic changes in energy requirements during the postoperative healing phase.[15] Since most trauma patients are oedematous, these formulas fail to calculate metabolic rates that reflect changes in lean body mass and fluid shifts.[16] The Harris-Benedict, Mifflin St. Jeor, and ACCP 25 kcal/kg formulas were primarily developed to calculate the nutritional needs of healthy adults by using weight, height, age, sex, and fat-free mass. Therefore, they cannot provide an accurate estimation of nutritional requirements in severe

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trauma patients. Several studies have also concluded that prediction equations were not accurate in determining the nutritional requirements of middle-aged patients.[17-20]

In more recent publications concerning the Penn State (2003b) 10 and Faisy 13 formulas, the measured results of IC through multivariate analysis from minute volume and body temperature data were included. Our study found that these two formulas had relatively higher correlations with the results of IC than with the results of the other formulas. However, even the Penn State formula, which had the highest correlation (r = 0.742), did not have an r-value above 0.8. Further, regarding the Bland-Altman plot testing, the mean difference between the Penn State formula-predicted result and mREE was 54.8 kcal/kg (range: -595.9–705.5), which is not a narrow range of agreement. Although the Faisy and Penn State formulas were found to have relatively higher correlations in the subgroup analysis, the sample sizes were not adequate to support statistical significance.

Our findings indicate that the formulas analysed in our study were not accurate in estimating the complex nutritional requirements of severe trauma patients. Therefore, it may be necessary to calculate nutritional requirements using IC to support the nutritional needs of such patients. Further, to achieve optimal energy prescription and improved prognosis, these measurements may have to be repeated at several instances to account for the rapid changes in energy demands during wound recovery and rehabilitation This may be the basis for the existing report.[21]

IC has several limitations, such as the need for expensive equipment, prolonged measurement time (30–40 min), and the need for trained manpower. Further, there is inadequate evidence supporting the role of accurate measurements of EE in improving the final outcome of patients. A small-sized randomised clinical trial demonstrated that IC contributed to a positive outcome.[22] Apart from this, only a few retrospective analyses have supported the use of IC in clinical practice.[23] Future large-scale prospective studies may be able to demonstrate the benefit of accurate measurements of EE in improving outcomes in critically ill patients, including trauma patients. Such studies may also enable the development of guidelines for customised nutritional prescriptions, as well as the development of IC methods that are inexpensive and simple to perform.

This study had a few limitations. First, it was a small retrospective study from only one trauma centre and may therefore have inherent biases. Second, although we identified the target group as those with major trauma, the patient population was heterogeneous, and the clinical significance of the measured values may be questionable. Third, since this was a

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retrospective study, there may have been unrecognised quality issues in the performance of IC, which could have affected our results.

Based on a study that reported several positive results, we adopted a protocol to implement IC for patients who are expected to stay in the ICU with a mechanical ventilator for more than 5 days. For patients whose nutritional requirements are difficult to calculate using equations, such as obese or major burn patients, the first IC measurement was performed before 48 hours of admission to the ICU. For patients with rapidly changing metabolic demands, such as those in septic conditions, follow-up tests should be performed at least twice a week (figure 3).

In conclusion, there was an inadequate correlation between the commonly used formulas for the estimation of nutritional requirements and mREE, as measured by IC, in severe trauma patients. Our study demonstrates that IC cannot be replaced by the various formulas for nutritional requirement estimation. We therefore recommend that IC should be used for estimating the nutritional requirements of severe trauma patients who are critically ill. Additionally, there is a need for further research to establish the role that the exact prediction of nutritional requirements has on improving the outcomes of critically ill patients.

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AUTHOR DISCLOSURE

None of the authors have any other personal or financial conflicts of interest.

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Table 1. Demographic, clinical characteristics of trauma patients

Classification	
No. of cases	95
No. of patients	69
Age (years)	53.6±20.5
Sex (F)	20 (21.1%)
BMI (kg/m^2)	23.3±3.7
Cause of injury	
MVC†	61
Crushing	7
Fall down	23
Others	4
ISS	30.3±13.0
MREE (kcal/day)	1761.8±483.8
PE (kcal/kg/day)	
Harris-Benedict	1444.1±240.3
Ireton-Jones (1997)	1856.8±257.4
Mifflin St. Jeor	1425.4±241.2
Penn State	1707.0±287.4
25 kcals/kg formulas	1563.4±267.9
Faisy	1922.8±313.7
Test day	18.6±17.7

MVC: motor vehicle collision; ISS: injury severity score; MREE: measured resting energy expenditure; PE: predictive equation.

Table 2. Correlation between MREE and PEE

	Test used	r-value	95% confidence interval	*p*-value
Harris-Benedict	Spearman	0.541	0.381 to 0.669	<0.001
Ireton-Jones (1997)	Spearman	0.376	0.189 to 0.537	0.005
Mifflin St Jeor	Spearman	0.614	0.471 to 0.726	<0.001
Penn State	Pearson	0.742	0.6359 to 0.8210	<0.001
25 kcal/kg	Spearman	0.502	0.334 to 0.639	<0.001
Faisy	Spearman	0.730	0.620 to 0.812	<0.001

MREE: measured resting-energy expenditure; PEE: predictive energy expenditure.

Table 3. Deming regression between MREE and PEE

	Coefficient	Jack-knife standard error	95% confidence interval
Harris-Benedict	2.0138	0.3138	1.3907 to 2.6369
Ireton-Jones (1997)	1.8783	0.5672	0.7522 to 3.0044
Mifflin St Jeor	2.0059	0.3027	1.4048 to 2.6070
Penn State	1.6833	0.1390	1.4074 to 1.9593
25 kcal/kg	1.8058	0.5491	0.7155 to 2.8961
Faisy	1.5423	0.3223	0.9022 to 2.1823

MREE: measured resting-energy expenditure; PEE: predictive energy expenditure.

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Table 4. Subgroup analysis about correlation between MREE and PEE

	Non-obese (BMI <25) (n=67)		obese (BMI ≥ 25) (n=28)		<2 weeks (n=49)		≥ 2 weeks (n=46)	
	r-value	*p*-value	r-value	*p*-value	r-value	*p*-value	r-value	*p*-value
Harris-Benedict	0.404	0.001	0.686	<0.001	0.538	<0.001	0.542	<0.001
Ireton-Jones (1997)	0.153	0.218	0.683	<0.001	0.261	0.070	0.521	<0.001
Mifflin St Jeor	0.488	<0.001	0.767	<0.001	0.572	<0.001	0.659	<0.001
Penn State	0.602	<0.001	0.870	<0.001	0.755	<0.001	0.737	<0.001
25 kcal/kg	0.435	<0.001	0.578	0.001	0.601	<0.001	0.434	0.003
Faisy	0.626	<0.001	0.845	<0.001	0.709	<0.001	0.739	<0.001

	Men (n=75)		Women (n=20)		Age <54 (n=42)		Age ≥ 55 (n=53)	
	r-value	*p*-value	r-value	*p*-value	r-value	*p*-value	r-value	*p*-value
Harris-Benedict	0.450	<0.001	0.496	0.026	0.734	<0.001	0.303	0.027
Ireton-Jones (1997)	0.408	<0.001	-0.002	0.995	0.233	0.138	0.507	<0.001
Mifflin St Jeor	0.553	<0.001	0.490	0.028	0.716	<0.001	0.501	<0.001
Penn State	0.702	<0.001	0.623	0.003	0.824	<0.001	0.600	<0.001
25 kcal/kg	0.396	<0.001	0.283	0.227	0.774	<0.001	0.251	0.070
Faisy	0.700	<0.001	0.465	0.039	0.787	<0.001	0.644	<0.001

	ISS <16 (n=9)		ISS ≥ 16 (n=86)	
	r-value	*p*-value	r-value	*p*-value
Harris-Benedict	0.244	0.527	0.535	<0.001
Ireton-Jones (1997)	0.300	0.433	0.369	<0.001
Mifflin St Jeor	0.467	0.205	0.607	<0.001
Penn State	0.386	0.305	0.748	<0.001
25 kcal/kg	0.150	0.700	0.542	<0.001
Faisy	0.217	0.576	0.756	<0.001

MREE: measured resting-energy expenditure; PEE: predictive energy expenditure.

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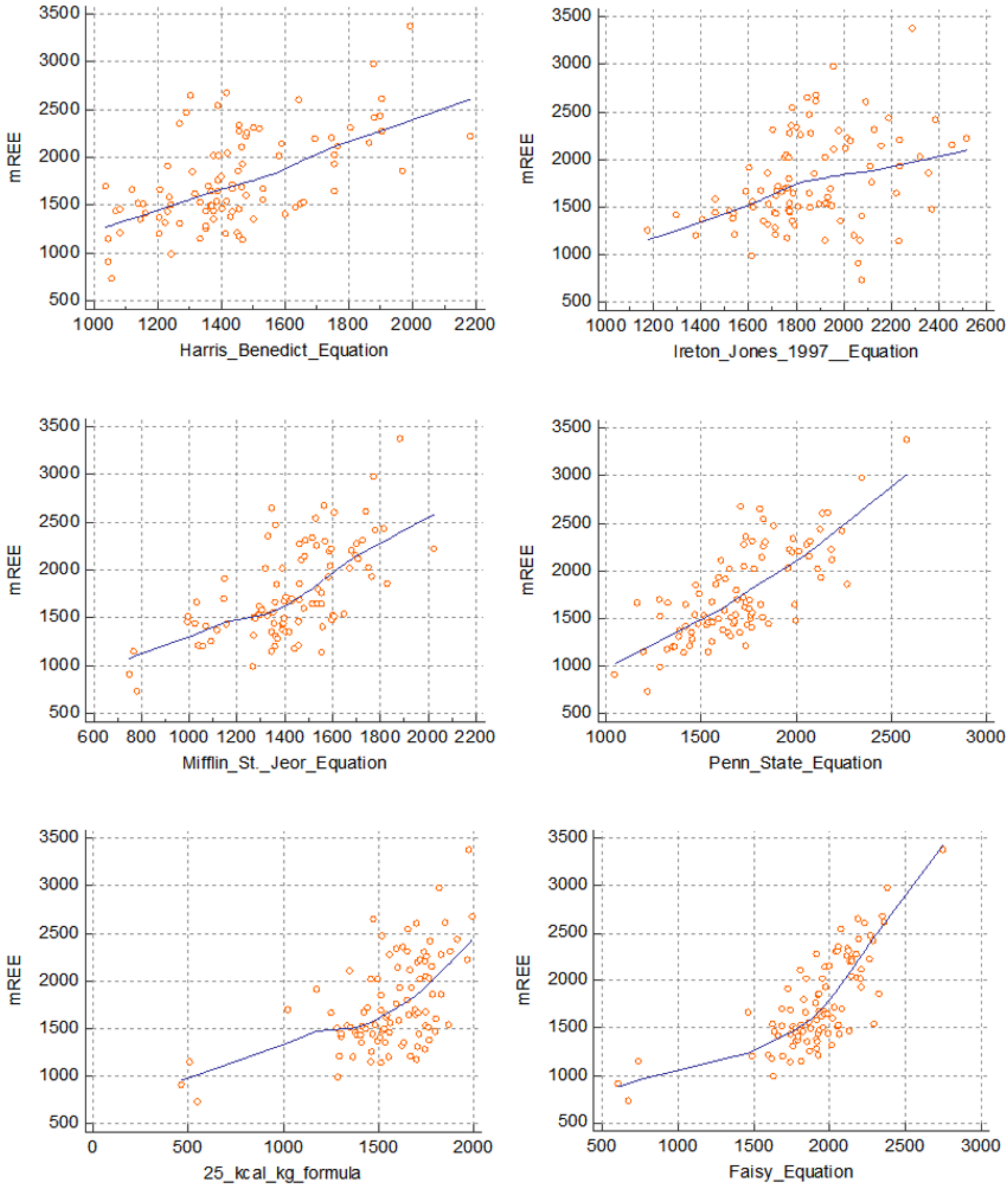

Figure 1. Scatter diagram. Scatter plots comparing the mREE and formula-predicted nutritional requirements: a. mREE vs. the Harris-Benedict equation; b. mREE vs. the Ireton-Jones formula; c. mREE vs. the Penn State formula; d. mREE vs. the Mifflin formula with stress factor; e. mREE vs. the ACCP 25 kcal/kg formula; f. mREE vs. the Faisy formula.

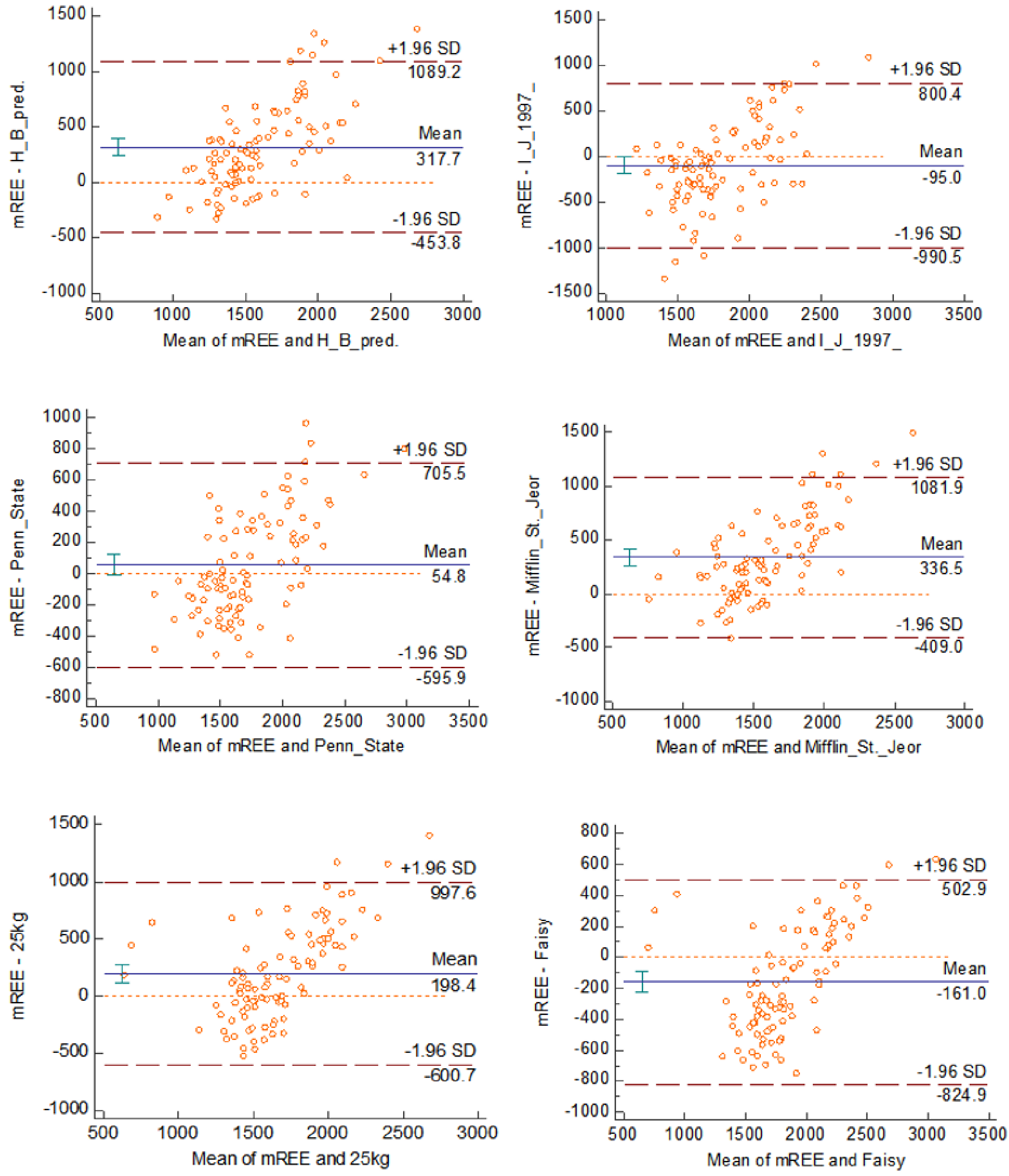

Figure 2. Bland-Altman plots. Differences between the measured mREE and estimated energy expenditure using different prediction equations: a. measured mREE vs. the Harris-Benedict equation; b. measured mREE vs. the Ireton-Jones formula; c. measured mREE vs. the Penn State formula; d. measured mREE vs. the Mifflin formula with stress factor; e. measured mREE vs. the ACCP 25 kcal/kg formula; f. measured mREE vs. the Faisy formula. On the x-axis, average values are presented. On the y axis, the differences between 2 methods (measured and estimated REE) are plotted. The limits of agreements are presented (i.e., average difference + 1.96 SD and average difference - 1.96 SD).

Indirect Calorimetry, Who and When ?

Who		anticipated to stay in ICU for more than **5 days** with **Mechanical ventilation**
	INCLUSION	**Obese** : BMI > 25 **Malnourished** : BMI < 18 Difficulty determining nutritional requirements **Major Burn** **Septic condition**
	EXCLUSION	**> 60%** of the fraction of inspired oxygen (**FiO^2**) **Air leaks** from the airway or chest tube **> 10 mmHg** of positive end-expiratory pressure (**PEEP**) Extracorporeal membrane oxygenation(**ECMO**)

When	**Initial Assessment**	Within 48 hours of ICU admission
	Follow-up Assessment	Twice a week if the clinical situation has changed

Figure 3. Patient selection and examination timing of indirect calorimetry test.

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