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A novel prediction equation of resting energy expenditure for Japanese septic patients

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ABSTRACT

Estimating nutrient consumption and administering appropriate nutritional therapy is essential for improving clinical outcomes in critically ill patients. Various equations, such as the Harris-Benedict equation, have been developed to estimate the required calories. Previous equations, however, targeted Westerners, whose physical characteristics are likely different from those of Asians. Hence, it is unclear whether these equations can be used for Asian patients. This study focused specifically on sepsis patients admitted to a single Japanese ICU, and aimed to develop novel equations to estimate their total energy expenditure. A total of 95 sepsis patients were included in this study. We measured resting energy expenditure (REE) by using indirect calorimetry, and created equations to calculate basal metabolic rate (BMR) using height, weight and age as variables. REE was predicted by multiplying BMR by the novel equation with the stress factor of 1.4. The prediction error of our novel equations were smaller than those of other conventional equations. We further confirmed the accuracy of our equations and that they were unaffected by patient age and disease severity by using data obtained from another patient group. The current study suggested that these equations might allow accurate estimation of the total energy expenditure and proper management of nutritional therapy in Asian sepsis patients.

1. Introduction

Providing adequate caloric intake to patients hospitalized in the intensive care unit (ICU) is essential to improving clinical outcomes. However, it is not easy to achieve this, because critical illness and treatment interventions dynamically alter patient metabolism and energy expenditure [1–6]. Therefore, intensivists need to somehow estimate the amount of energy required by these patients.

Although indirect calorimetry (IC) is the gold standard for measuring resting energy expenditure (REE) in critically ill patients, IC is expensive and not available at all facilities. Alternatively, numerous mathematical equations for prediction of REE, including the Harris-Benedict, Ireton-Jones and Schofield equations, have been developed [7–10]. The original Harris-Benedict equation (HBE), published in 1919, was created based on data of healthy subjects [7]. We previously calculated basal metabolic rate (BMR) using the HBE and compared the results with REE measured by IC, and reported that the estimated stress factor (i.e., the ratio of measured REE to BMR) was around 1.1 [11]. However, this estimated stress factor was smaller than the values reported in previous studies, which ranged between 1.2 and 1.6 [3,12,13]. We considered the effect of sedation as a cause of this discrepancy, but could not find a relationship between the degree of sedation and estimated stress factor. Moreover, the estimated stress factor did not change with resolution of the illness [11]. We then hypothesized that this discrepancy might be caused by errors in estimation of BMR rather than in the values of the estimated stress factor. Hence, we aimed to create novel formulas for estimating BMR using data obtained from severely septic Japanese patients in this study. In addition, we compared the measured REE and estimated REE (i.e., BMR multiplied by the stress factor 1.4) in the same patients who were targeted for creating the estimation formulas. Subsequently, to confirm the accuracy of these novel formulas, measured and estimated REE were compared in a different group of septic patients admitted to the ICU.

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2. Materials and methods

2.1. Study design

This retrospective observational study was conducted at the intensive care unit (ICU) of Gunma University Hospital. The study was approved by the institutional ethics committee of our facility (No.2017–198). All procedures involving human participants performed in this study were in accordance with the ethical standards of Gunma University Hospital and with the 1964 Helsinki declaration and its later amendments. Moreover, information was published on the web page of our hospital to inform patients about the study protocol, and give them a chance to refuse inclusion in the study.

Adult patients (≥18 years of age) admitted to the ICU with a diagnosis of sepsis between April 2010 and March 2017 and who were mechanically ventilated were included. All the patients included in the study fulfilled the diagnostic criteria for severe sepsis [14,15]. While we conducted the study, a new definition of sepsis was announced [16]. Since the announcement was after we selected the patients, we decided to continue using the old definition. Mechanically ventilated patients who met one or more of the following criteria were excluded: fraction of inspired oxygen (FiO_2) ≥ 0.6, positive end expiratory pressure (PEEP) >12 cmH_2O, respiratory rate >35 breaths/min, and presence of a chest drain with leakage. In addition, patients on hemodialysis, continuous renal replacement therapy, or extracorporeal membrane oxygenation were excluded.

Sepsis patients who were admitted to our ICU and intubated during the period between April 2010 and March 2015 were assigned to group A, and those admitted between April 2015 and March 2017 were assigned to group B. Novel formulas to estimate BMR were created based on the data of group A. The accuracy of the formula was verified using the data obtained from group B patients.

2.2. Data collection

Acute Physiology and Chronic Health Evaluation (APACHE) II scores and Sequential Organ Failure Assessment (SOFA) scores were calculated for each patient at ICU admission.

Indirect calorimetry was performed using the M-COVX metabolic module (originally made by Datex-Ohmeda, Inc.) that was integrated with a mechanical ventilator (Engström Carestation®, GE Healthcare Japan). This module can automatically calculate and display REE using the Weir equation: REE (kcal/day) = (3.94 × VO2 + 1.10 × VCO2) × 1.44 − (2.17 × UN*) [17], where VO2: oxygen consumption (mL/min), VCO2: carbon dioxide production (mL/min), and UN: urinary nitrogen excretion (g). * In the M-COVX, the value of UN is fixed at 13 g/day.

The M-COVX with its data migration system enables continuous monitoring of REE. We selected the data measured at 2 a.m. on the first day of the intubation period [11]. The protocol required: (1) that patients be inactive and undisturbed for 30 min before testing and for the 15-minute duration of data collection, (2) an interval of at least 30 min between changes in ventilator settings and measurements, and (3) an interval of at least 4 h between changes in the feeding method and measurements. When the respiratory quotient (RQ) was <0.67 or >1.3, we discarded the values and instead incorporated the data obtained as close to 2 a.m. as possible [18–22]. We used any one or more of the following sedatives, as required: propofol, dexmedetomidine, midazolam and fentanyl. BMR was calculated by the Harris-Benedict equation, Ireton-Jones Energy Equations or Schofield equation using actual body weight and height on ICU admission.

2.3. Equations for prediction of energy requirements

Harris-Benedict equation (HBE) [7]:

$$\begin{aligned}\text{Males}: \text{BMR (kcal/day)} &= 66.5 + 13.8 \times \text{Weight (kg)} + 5.0 \\ &\times \text{Height (cm)} - 6.8 \times \text{age}\end{aligned}$$

$$\begin{aligned}\text{Females}: \text{BMR (kcal/day)} &= 655.1 + 9.6 \times \text{Weight (kg)} + 1.8 \\ &\times \text{Height (cm)} - 4.7 \times \text{age}\end{aligned}$$

Ireton-Jones Energy Equations 2002 version (IJEE) [9]:

$$\begin{aligned}\text{REE (kcal/day)} &= 1784 + 5 \times \text{Weight (kg)} - 11 \times \text{age} \\ &+ 244 \times \text{Gender} + (239 \text{ if trauma present}) \\ &+ (804 \text{ if burns present}) \\ &\times (\text{Gender}: \text{male} = 1, \text{female} = 0)\end{aligned}$$

Schofield equation (SE) [10]:

$$\begin{aligned}&\text{Males}: 18\text{–}30 \text{ years old}: \text{BMR (kcal/day)} \\ &= 15.057 \times \text{Weight (kg)} + 692.2, 30\text{–}60 \text{ years old} \\ &: \text{BMR (kcal/day)} = 11.472 \times \text{Weight (kg)} \\ &+ 873.1, >60 \text{ years old} \\ &: \text{BMR (kcal/day)} = 11.711 \times \text{Weight (kg)} + 587.7\end{aligned}$$

$$\begin{aligned}&\text{Females}: 18\text{–}30 \text{ years old}: \text{BMR (kcal/day)} \\ &= 14.818 \times \text{Weight (kg)} + 486.6, 30\text{–}60 \text{ years old} \\ &: \text{BMR (kcal/day)} = 8.126 \times \text{Weight (kg)} \\ &+ 845.6, >60 \text{ years old} \\ &: \text{BMR (kcal/day)} = 9.082 \times \text{Weight (kg)} + 658.5\end{aligned}$$

Penn State University Equation 2003a version (PSU) [23]

$$\begin{aligned}\text{REE (kcal/day)} &= 0.85 \times \text{HBE [7]} + 33 \times \text{Minute volume (L/ min)} \\ &+ 175 \times \text{Body temperature (°C)} - 6433\end{aligned}$$

Body temperature was defined as the highest body temperature during the 24 h study period, and minute volume was read from the ventilator at the time of measurement.

Faisy Fagon Equation (FE) [24]

$$\begin{aligned}\text{REE (kcal/day)} &= 8 \times \text{Weight (kg)} + 14 \times \text{Height (cm)} + 32 \\ &\times \text{Minute volume (L/ min)} + 94 \\ &\times \text{Body temperature (°C)} - 4834\end{aligned}$$

Body temperature was measured at the time of measurement, and minute volume was read from the ventilator at the time of measurement.

A 40% stress factor was applied to estimates of BMR derived from the HBE and SE.

$$\text{Estimated REE (eREE)} = \text{BMR} \times \text{stress factor (1.4 for sepsis)}$$

We calculated total energy intake from the doctor's order sheet. The decision regarding parenteral and/or enteral nutrition was made at a conference between the attending physician and ICU doctors. REE values measured by IC (mREE) were not utilized in decision-making. Generally, for subjects with a good nutritional status, we prescribed mainly enteral nutrients and the total energy intake was gradually increased over time. For subjects in a poor state of nutrition, on the other hand, intravenous feeding solutions were predominantly administered.

2.4. Statistical analysis

Data analysis was performed using SigmaPlot 13 (Systat Software, Inc., San Jose, CA) and GraphPad Prism 5 (GraphPad Software, Inc., La

Jolla, CA). Quantitative variables were described as means and standard deviations. The accuracy of the different equations was assessed by a similar way to the past study [25]. Briefly, bias was calculated as the mean difference of eREE and mREE. eREE was considered unbiased if the bias was <10% of mREE [26]. Precision was quantified as the SD of the bias and the limits of agreement. SDs of the different equations were compared using Levene's test for equality of variances. Bland-Altman plots were used to graphically represent bias and the limits of agreement. Accuracy was further quantified by accuracy rates, which we defined as the proportion of patients for which eREE predicted EE within 10% and 15% of mREE. We calculated >25% and >30% inaccuracy rates to quantify the occurrence of large errors, as the proportion of patients for which eREE differed by >25% or >30% from mREE. Differences between groups were compared using Mann-Whitney *U* test, paired *t*-test, Fisher's exact test, one-way ANOVA post hoc test. $P < .05$ was considered significant.

3. Results

A total of 95 patients with sepsis who were admitted to our ICU were included in this study. Groups A and B included 66 patients (42 men and 24 women) and 29 patients (19 men and 10 women), respectively. The demographic data of the patients in groups A and B are shown in Tables 1 and 2, respectively.

First, the values of REE estimated by the conventional equations were compared. They varied by equations both in group A and B, as shown in Supplemental Table 1. This variation suggested the need for a novel REE prediction equation.

Next, linear regression analysis was performed using the data of group A patients to create novel equations for estimation of REE.

Table 1
Demographics, nutritional characteristics and clinical outcomes of group A sepsis patients.

	Male	Female
Number of patients	42	24
Age (years)	68 (14)	60 (16)
Height (cm)	164 (8)	151 (8)
Weight (kg)	60 (14)	48 (16)
BMI (kg/m^2)	22.2 (4.7)	20.4 (5.3)
APACHEII score	24.2 (5.8)	27.6 (6.0)
SOFA score	11.6 (3.7)	13.0 (4.5)
Energy intake (kcal/day)	445 (303)	537 (227)
Respiratory quotient	0.78 (0.09)	0.77 (0.09)
ICU day of measurement	3.1 (9.8)	1.3 (0.7)
ICU LOS (day)	14.1 (15.5)	22.3 (11.6)
ICU mortality rate	7.1%	25.0%
EN	2.4%	0.0%
PN	52.4%	45.8%
EN + PN	45.2%	54.2%
Minimal nutrition	0.0%	0.0%
Recieving inotropes	78.6%	75.0%
Recieving CVP monitoring	54.8%	45.8%
CVP (if monitored) (mmHg)	10.5 (7.5)	9.1 (6.3)
BT, at the time of measurement (°C)	37.4 (0.8)	37.7 (1.2)
BT, maximum, previous 24 h (°C)	37.8 (0.9)	37.9 (1.3)
PaO2/FiO2	217 (87)	240 (101)
Heart rate (beat/min)	92 (21)	98 (22)
mABP, at the time of measurement (mmHg)	74 (14)	73 (16)
Primary site of infection		
Respiratory	26 (61.9%)	10 (41.7%)
Skin and joint	6 (14.3%)	5 (20.8%)
Abdominal	7 (16.7%)	6 (25.0%)
Blood stream	0 (0.0%)	2 (8.3%)
Urinary	3 (7.1%)	1 (4.2%)

Data are expressed as mean values. Standard deviations are shown in parentheses. BMI: body mass index, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, ICU: intensive care unit, LOS: length of stay, EN: enteral nutrition, PN: parenteral nutrition, Minimal nutrition: nutrients whose calories is <50 kcal/day, CVP: central venous pressure, BT: body temperature, PaO_2: partial pressure of arterial oxygen, FiO_2: fraction of inspiratory oxygen, mABP: mean arterial blood pressure.

Table 2
Demographics, nutritional characteristics and clinical outcomes of group B sepsis patients.

	Male	Female
Number of patients	19	10
Age (years)	66 (13)	56 (15)
Height (cm)	164 (7)	155 (4)
Weight (kg)	62 (10)	60 (17)
BMI (kg/m^2)	23.0 (2.9)	25.1 (7.1)
APACHEII score	26.9 (5.7)	34.8 (8.0)
SOFA score	12.7 (2.9)	14.3 (4.2)
Energy intake (kcal/day)	436 (268)	367 (320)
Respiratory quotient	0.81 (0.11)	0.76 (0.12)
ICU day of measurement	2.0 (2.2)	1.6 (1.3)
ICU LOS (day)	19.4 (24.3)	19.5 (14.6)
ICU mortality rate	5.3%	30.0%
EN	0.0%	0.0%
PN	89.5%	90.0%
EN + PN	5.3%	0.0%
Minimal nutrition	5.3%	10.0%
Recieving inotropes	89.5%	90.0%
Recieving CVP monitoring	21.1%	20.0%
CVP (if monitored) (mmHg)	7.8 (5.7)	13.5 (0.7)
BT, at the time of measurement (°C)	37.9 (1.2)	37.1 (1.6)
BT, maximum, previous 24 h (°C)	38.4 (1.4)	37.7 (1.9)
PaO2/FiO2	241 (73)	235 (114)
Heart rate (beat/min)	107 (18)	108 (25)
mABP, at the time of measurement (mmHg)	70 (11)	71 (13)
Primary site of infection		
Respiratory	3 (15.8%)	2 (20.0%)
Skin and joint	3 (15.8%)	2 (20.0%)
Abdominal	7 (36.8%)	2 (20.0%)
Blood stream	4 (21.1%)	3 (30.0%)
Urinary	2 (10.5%)	1 (10.0%)

Data are expressed as mean values. Standard deviations are shown in parentheses. BMI: body mass index, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, ICU: intensive care unit, LOS: length of stay, EN: enteral nutrition, PN: parenteral nutrition, Minimal nutrition: nutrients whose calories is <50 kcal/day, CVP: central venous pressure, BT: body temperature, PaO_2: partial pressure of arterial oxygen, FiO_2: fraction of inspiratory oxygen, mABP: mean arterial blood pressure.

These equations were created based on four factors that are also used in the HBE, namely sex, height, weight and age of the patients. As a result of these analysis, we obtained the following novel equation, named as Kamiyama-Takemae equation (KTE): BMR for males (kcal/day) $= -122.7 + 8.6 \times$ weight (kg) $+ 5.0 \times$ height (cm) $- 3.5 \times$ age ($R = 0.77$), BMR for females (kcal/day) $= -190.6 + 6.6 \times$ weight (kg) $+ 4.4 \times$ height (cm) $+ 0.78 \times$ age ($R = 0.82$). As in our previous study on septic patients, we calculated BMR first and obtained REE values by multiplying BMR with the stress factor of 1.4 [11].

To compare the predictive accuracy of the novel and conventional equations, we calculated the difference between mREE and eREE obtained with each equation, i.e. the prediction errors. mREE was an actual value measured by an indirect calorimeter. We found that the prediction error of KTE was smaller than that of all other conventional equations in male group A patients (Fig. 1A, $p < .05$, one-way ANOVA with post hoc Newman-Keuls test). This was also true for female patients in group A (Fig. 1B, $p < .05$, one-way ANOVA with post hoc Newman-Keuls test). These results seemed to be reasonable, because we applied the new equations to the same patient group as that targeted for creating the equations.

In order to confirm the accuracy of the new equations, we decided to apply these equations to a patient group different from the one used for creating the equations, namely group B. As in group A, the prediction error of KTE was smaller than that of the other conventional equations in both male and female patients in group B (Fig. 2A and B, $p < .05$, one-way ANOVA with post hoc Newman-Keuls test).

Next, we investigated the relationship between eREE and mREE. Both eREE by HBE and KTE were plotted against mREE in male (Fig. 3A) and female (Fig. 3B) patients. HBE was chosen as representative of calculation equations other than the KTE. For this purpose, the

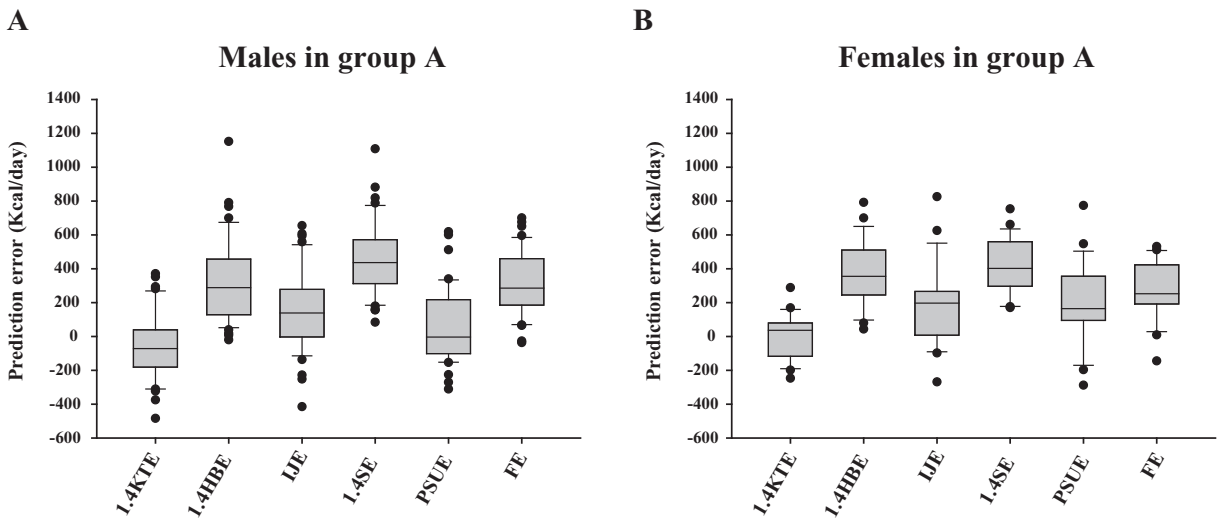

Fig. 1. Comparison of the difference between resting energy expenditure measured by indirect calorimetry (IC) and estimated by the Kamiyama-Takemae Equation (KTE), Harris-Benedict Equation (HBE), Ireton-Jones Equation 2002 (IJE), Schofield Equation (SE), Penn State University Equation 2003a (PSUE), and Faisy Fagon Equation (FE) in group A. The Y axis indicates the prediction error (kcal/day): estimated – measured resting energy expenditure (REE). Estimated REE by KTE, HBE, and SE was obtained by multiplying BMR by 1.4, as a tentative stress factor. Other equations did not require stress factor multiplication. The prediction error of KTE was smaller than that with other conventional eqs. ($P < .05$, One-way ANOVA with post hoc Newman-Keuls test). There was no significant difference among the values calculated using the conventional equations.

data obtained from patients in group A and B were integrated. We obtained the following equations by linear regression analysis for male patients (Fig. 3A): eREE by HBE = 1.26 × mREE, eREE by KTE = 0.97 × mREE. For female patients, the equations we obtained by linear regression analysis were similar to those for male patients (Fig. 3B): eREE by HBE = 1.25 × mREE, eREE by KTE = 0.96 × mREE. These results indicated that the eREEs by KTE were closer to mREE than were those by HBE.

We further investigated the relationship between REE and patient age. This was done to determine why KTE showed a smaller prediction error than the other conventional equations. This investigation revealed that although eREE by HBE was always greater than that by KTE regardless of patient age, the difference decreased with advancing patient age (Fig. 3C). The relationship between mREE and patient age is shown in Fig. 3D. Comparing these results, we found that the relationship between eREE by KTE and patient age was similar to that between mREE and patient age.

We examined whether prediction of REE by KTE is affected by the severity of sepsis. APACHE II and SOFA scores were adopted as indices of disease severity. There was no relationship between the prediction error of KTE and APACHE II score (Supplemental Fig. 1A). This was also true for HBE. A similar result was obtained for SOFA score (Supplemental Fig. 1B). Regardless of the severity of sepsis, the prediction error was less for KTE than for HBE. These results suggest that REE prediction by KTE is more accurate regardless of the severity of sepsis.

Finally, we evaluated the accuracy of all equations by calculating bias, precision, and accuracy and inaccuracy rates as shown in Table 3. Statistical analysis was performed to compare KTE and all other equations. Bland-Altman plot was also made to assess agreement between mREE and eREE calculated by each equation (Fig. 4). Bias of KTE was smaller than any other equations ($p < .001$, one-way ANOVA with post hoc Newman-Keuls test). KTE was the only equation that met the

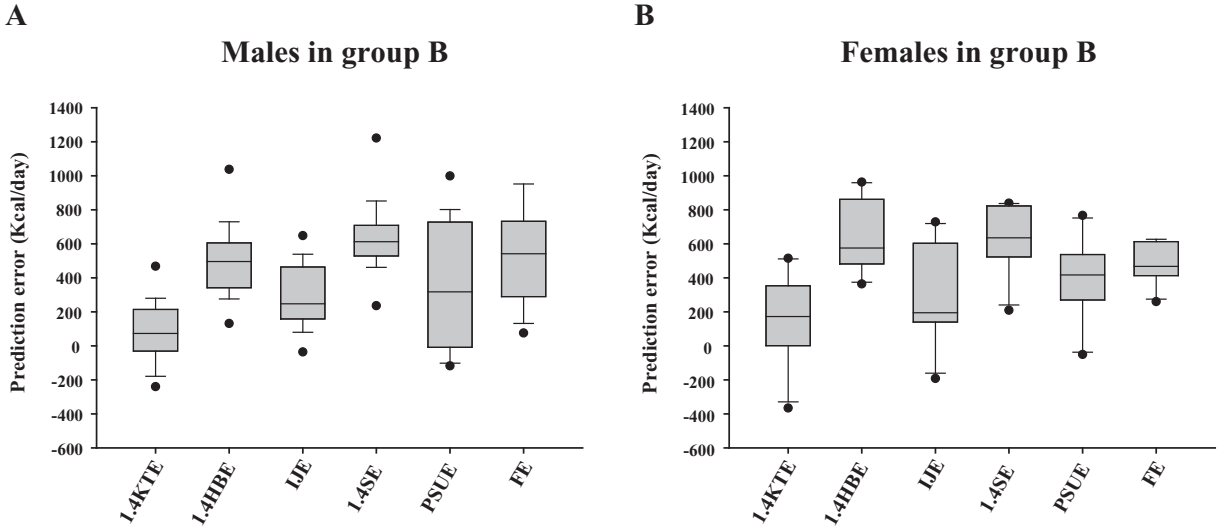

Fig. 2. Comparison of the difference between resting energy expenditure measured by indirect calorimetry (IC) and estimated by the Kamiyama-Takemae Equation (KTE), Harris-Benedict Equation (HBE), Ireton-Jones Equation 2002 (IJE), Schofield Equation (SE), Penn State University Equation 2003a (PSUE), and Faisy Fagon Equation (FE) in group B. The Y axis indicates prediction error (kcal/day): estimated – measured resting energy expenditure (REE). Estimated REE by KTE, HBE, and SE was obtained by multiplying BMR by 1.4, as a tentative stress factor. Other equations did not require stress factor multiplication. The prediction error of KTE was smaller than that with other conventional eqs. ($P < .05$, One-way ANOVA with post hoc Newman-Keuls test). There was no significant difference among the values calculated using the other conventional equations.

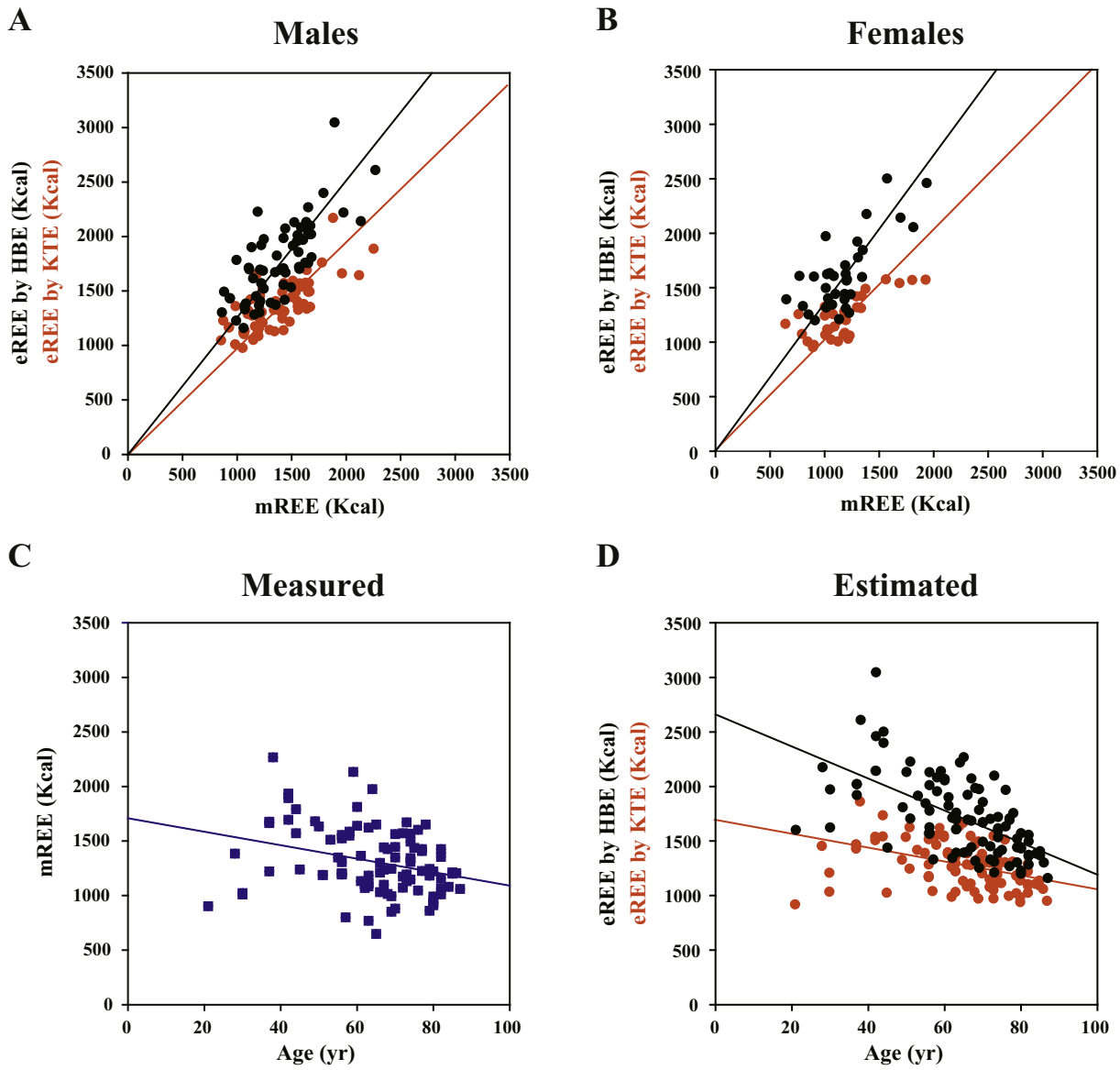

Fig. 3. Relationship between measured resting energy expenditure (mREE) and estimated REE (eREE) by the Harris-Benedict Equation (HBE) and Kamiyama-Takemae Equation (KTE) (A and B), and relationship between age and resting energy expenditure (REE) (C and D). In both males (A) and females (B), eREE by HBE (black circles) was greater than eREE by KTE (orange circles) in almost all cases. Measured REE (blue squares) declined with age (C). Fig. D indicates the age-related decline in estimated REE calculated using the HBE (black circles) and KTE (orange circles). HBE: Harris-Benedict equation, KTE: Kamiyama-Takemae equation.

prediction accuracy criteria, with a bias defined to be <10%. Bland-Altman limit of agreement was smallest for KTE. <10% and <15% accuracy rates of KTE were significantly higher than those of any other equations ($p < .05$, Fisher's exact test). Moreover, >25% and >30% inaccuracy rates of KTE were significantly lower than those of any other equations ($p < .01$, Fisher's exact test). These results suggested the superiority of KTE in terms of REE prediction.

4. Discussion

We created novel prediction equations for REE in this study. The prediction error of our novel equations is smaller than that of other conventional equations. This result suggests the high accuracy of estimation by the novel equations. Moreover, the accuracy appears to remain constant regardless of gender, age and severity of sepsis.

One characteristic of the novel equations, i.e. KTEs, is that they were created using data of patients who mainly consist of aged individuals. This is likely a common feature of sepsis patients in modern Asian countries. For example, a recent retrospective observational study that was conducted in 42 ICUs throughout Japan demonstrated that the average age of sepsis patients was 70.0 years [27]. Likewise, another study conducted in a Thailand ICU showed that the average age of sepsis patients was 71.6 years [28]. Average patient age in these studies were comparable to those in the current study, as shown in Tables 1 and 2. Conversely, sepsis patients admitted to the ICU in Western countries are reportedly younger [29–31]. The HBE was created based on data of subjects below the age of 70 years [7], and the average age of patients included in studies for creating IJEE1992 was 43 years [8]. Since many sepsis patients over 70 years of age are admitted to the ICU in modern times, we believe that this study has significance.

In addition to patient age, another important factor in calorimetric calculations is the weight of the patient. Most studies conducted in Western countries showed that the mean body mass index (BMI) of sepsis patients ranges between 26 and 28 kg/m^2 [29–31], while the mean BMI was 22.0 kg/m^2 in the study conducted in Thailand [28]. This value is equivalent to a body weight of 56.3 kg in a person whose height is 160 cm. In the Japanese study mentioned above, the average weight of sepsis patients was 56.1 kg [27]. Since these average weights

Table 3
Accuracy of the methods used to assess energy expenditure, expressed as bias, precision, and accuracy and inaccuracy rates.

Method	Bias		Precision		Accuracy quantified			
	Mean difference in kcal/day, 95%CI	Mean difference (% of mREE)	SD of bias (Levene's F test)	Bland-Altman limits of agreement	Accuracy rates		Inaccuracy rates	
					< 10%	< 15%	> 25%	> 30%
1.4KTE	5, −35 to 45	2.5%	196	−379 to 389	59%	72%	13%	7%
1.4HBE	404, 355 to 453	33.5%	272 (F = 1.93)	32 to 1097	5%	7%	89%	79%
	$p < .001$	$p < .001$	$p < .001$		$p < .001$	$p < .001$	$p < .001$	$p < .001$
IJE	208, 160 to 256	18.9%	234 (F = 1.42)	−250 to 666	34%	51%	33%	24%
	$p < .001$	$p < .001$	$p < .05$		$p < .001$	$p < .01$	$p < .001$	$p < .01$
1.4SE	505, 461 to 549	42%	216 (F = 1.21)	82 to 929	4%	12%	79%	72%
	$p < .001$	$p < .001$	$p = .17$		$p < .001$	$p < .001$	$p < .001$	$p < .001$
PSUE	191, 132 to 250	16.7%	287 (F = 2.14)	−371 to 250	39%	55%	37%	28%
	$p < .001$	$p < .001$	$p < .001$		$p < .01$	$p < .05$	$p < .001$	$p < .001$
FE	368, 323 to 413	31.3%	223 (F = 1.30)	−69 to 805	16%	26%	57%	51%
	$p < .001$	$p < .001$	$p = .10$		$p < .001$	$p < .001$	$p < .001$	$p < .001$

Biases between mREE and eREE were calculated, and those of KTE and other equations were compared by one-way ANOVA with post hoc Kruskall-Wallis test. <10% and <15% accuracy rates represent the proportion of patients for which each equation predicted EE within 10% and within 15%, respectively, of mREE. >25% and >30% inaccuracy rates represent the proportion of patients for which eREE differed by >25% and >30%, respectively, from mREE. Accuracy and inaccuracy rates in KTE and other equations were compared by Fisher's exact test. All p values are relative to KTE. $P < .05$ was considered significant.
CI: confidence interval, mREE: measured resting energy expenditure, KTE: Kamiyama-Takemae Equation, HBE: Harris-Benedict Equation, IJE: Ireton Jones Equation 2002, SE: Schofield Equation, PSUE: Penn State University Equation 2003a, FE: Faisy Fagon Equation.

are comparable to those of patients in the current study, KTE is likely applicable to other ICUs in Asian countries.

The total energy expenditure of a patient might change according to the state of metabolism. The amount of energy consumed does not have to be 100% compensated by external nutrition, but also relates to endogenous energy production [32]. Indeed, critically ill patients have extremely diverse metabolic responses, ranging from hypometabolic to hypermetabolic [33]. For example, a past report suggested a correlation

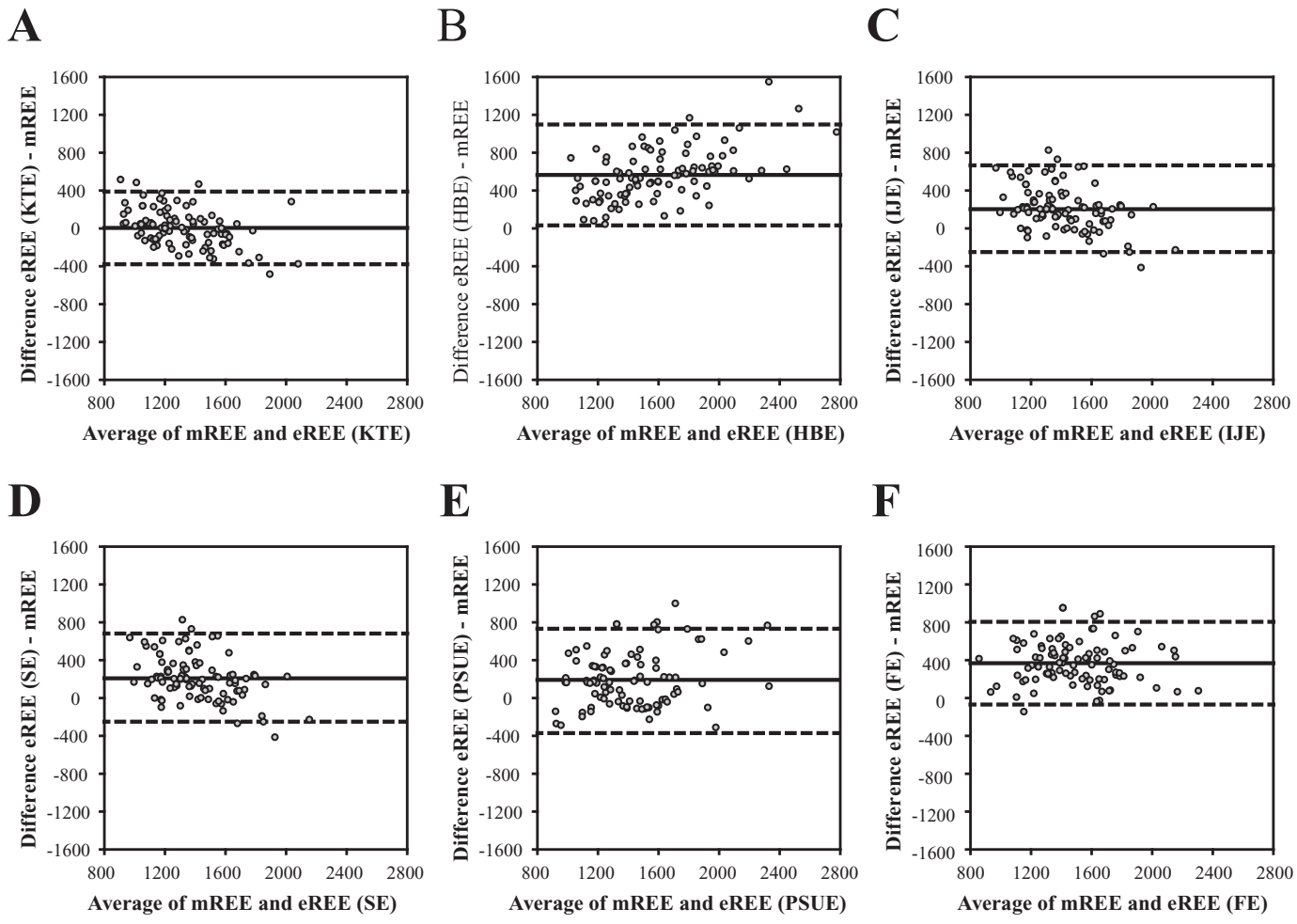

Fig. 4. Bland-Altman plots to assess agreement between measured resting energy expenditure (mREE) and estimated REE (eREE). The solid lines indicate the bias (mean difference with mREE). The dashed lines indicate the limits of agreement (bias ±2 standard deviations). Every dot represents 1 of 95 patients. The X axis represents the mean of mREE and eREE. The Y axis represents the difference between mREE and eREE. Figs. A-F show the results of KTE, HBE, IJE, SE, PSUE, and FE, respectively. KTE: Kamiyama-Takemae Equation, HBE: Harris-Benedict Equation, IJE: Ireton Jones Equation 2002, SE: Schofield Equation, PSUE: Penn State University Equation 2003a, FE: Faisy Fagon Equation.

between the severity of sepsis and REE [34]. We considered the severity of sepsis as a possible factor to explain such diversity, and demonstrated that the prediction error of KTE was affected by neither APACHE II nor SOFA scores. This result suggests that the predictive accuracy of KTE is independent of severity of sepsis.

The Deltatrac II metabolic monitor has been validated and widely used as an indirect calorimeter to measure respiratory gas exchange in critically ill patients. A previous study compared the performance of Deltatrac and the M-COVX metabolic monitor that was used in this study [35]. The authors concluded that they found no clinically significant bias between the two devices in VCO_2 or VO_2 over an FiO_2 range of 0.3–0.7. Since patients who had an FiO2 of ≥0.6 were not included in this study, the measurement accuracy of the M-COVX metabolic monitor can be guaranteed. Nevertheless, comparisons of the KTE-calculated REE with the measurement by other ICs including Deltatrac would be necessary, because past studies suggested poor agreement among the measurements by different ICs including M-COVX and Deltatrac [36,37]. Furthermore, the validity of KTE will need to be confirmed with a new generation of IC that is currently developing by an initiative of the International Multicentric Study Group for Indirectly Calorimetry [38].

The current study has another several limitations. We did not have a specific protocol for nutrition control while the patients were intubated. Therefore, there may have been inter-individual differences in the types of nutrients that were administered to the patients. In theory, mREE might fluctuate with this uncontrolled factor, because RQ depends on the class of nutrient consumed. To overcome this issue, prospective studies including patients under uniform nutrition control should be performed in future. Furthermore, since this study only included patients with sepsis, it should be clarified whether the KTE can be applied to patients admitted to the ICU with other conditions.

A possible additional limitation of this study is the small number of REE data acquired per day. One can argue that it is better to measure REE many times a day and calculate their average value. As the amount of activity during the day varies from patient to patient, we adopted an REE value that was measured at a single time point (2 a.m.) every day. Since most patients are asleep at this time point, we believe that variations in REE due to patient activity were minimized [11].

5. Conclusions

BMR prediction equations were created using REE measurement by an indirect calorimeter in Japanese sepsis patients. These equations might be a more useful tool than conventional equations for REE prediction and proper nutrition management in septic patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2020.01.021.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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