ARTICLE

Genomics and personalized strategies in nutrition

Do we need different predictive equations for the acute and late phases of critical illness? A prospective observational study with repeated indirect calorimetry measurements

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BACKGROUND: Predictive equations (PEs) for estimating resting energy expenditure (REE) that have been developed from acute phase data may not be applicable in the late phase and vice versa. This study aimed to assess whether separate PEs are needed for acute and late phases of critical illness and to develop and validate PE(s) based on the results of this assessment.
METHODS: Using indirect calorimetry, REE was measured at acute (≤5 days; $n = 294$) and late (≥6 days; $n = 180$) phases of intensive care unit admission. PEs were developed by multiple linear regression. A multi-fold cross-validation approach was used to validate the PEs. The best PEs were selected based on the highest coefficient of determination (R^2), the lowest root mean square error (RMSE) and the lowest standard error of estimate (SEE). Two PEs developed from paired 168-patient data were compared with measured REE using mean absolute percentage difference.
RESULTS: Mean absolute percentage difference between predicted and measured REE was <20%, which is not clinically significant. Thus, a single PE was developed and validated from data of the larger sample size measured in the acute phase. The best PE for REE (kcal/day) was 891.6(Height) + 9.0(Weight) + 39.7(Minute Ventilation)−5.6(Age) – 354, with $R^2 = 0.442$, RMSE = 348.3, SEE = 325.6 and mean absolute percentage difference with measured REE was: 15.1 ± 14.2% [acute], 15.0 ± 13.1% [late].
CONCLUSIONS: Separate PEs for acute and late phases may not be necessary. Thus, we have developed and validated a PE from acute phase data and demonstrated that it can provide optimal estimates of REE for patients in both acute and late phases.
TRIAL REGISTRATION: ClinicalTrials.gov NCT03319329.

BACKGROUND

Indirect calorimetry (IC) is the reference standard for measuring the energy expenditure of critically ill patients in the intensive care unit (ICU) [1, 2]. Optimizing energy provision with daily IC measurements in the ICU may confer clinical benefits [3–5]. However, IC is not commonly used [6]. This is due to the high cost, poor insurance reimbursement, and lack of trained personnel to operate the equipment and to interpret the results [7, 8]. Hence, clinicians need to rely on predictive equation (PE) for estimating patients' energy expenditure.

In the ICU, resting energy expenditure (REE) is calculated using PEs with variables such as weight, height, age, sex, body temperature and minute ventilation [9]. PEs developed in healthy populations, such as the Harris-Benedict [10] and Mifflin-St. Jeor equations [11], are widely used in the ICU setting. While PEs developed in the critically ill population, such as the Penn State [9], Swinamer [12], and Faisy [13] equations, were developed from Caucasians and data of patients in the acute phase (≤5 days). Our recent study found that none of the commonly used PEs could optimally estimate measured REEs of patients in different phases of critical illness [14]. Furthermore, we found that REE during the acute phase of critical illness is generally lower than the late phase (6–10 days), while REE in the chronic phase (≥11 days) was not significantly different from the late phase [14]. Based on these results, we hypothesized that the use of separate PE for the acute (≤5 days) and later phases (≥6 days; collectively known as the late

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phase) would further optimize the nutrition care of critically ill patients, especially in the setting where IC is not available. However, the PermiT trial [15] found a difference of ~25% of the calculated caloric requirement did not result in any differences in clinical outcomes. Therefore, this study has two objectives: (a) to assess whether separate PEs for acute and late phases are needed, (b) to recommend the best PE(s) for our population based on the result of the first objective. A priori, we set a mean absolute percentage difference threshold of ≥20% between the predicted REE calculated from the developed PEs with the measured REE at acute and late phases. If the predicted REE calculated by the acute PE and measured REE in the late phase has an absolute mean difference of ≥20% or vice versa, then two PEs at different phases may be needed. Otherwise, a single PE will be sufficient.

METHODS

Study design and subjects
A prospective observational study was conducted from December 2016 to November 2018 in a mixed medical-surgical ICU at the University of Malaya Medical Centre (UMMC), Malaysia. The study protocol was approved by the Medical Research Ethics Committee (MREC), UMMC (MREC ID NO: 20161024-4407) and registered with the National Medical Research Register (NMRR) Malaysia (NMRR.ID: NMRR-16-2030-33143) and Clinical-Trials.gov (NCT03319329). Informed consent was obtained from the patients or their legal representative. The inclusion and exclusion criteria are the same as our previous study [14]. In this study, we further excluded patients with extreme body mass index (BMI), <15 kg/m² or > 40 kg/m², as their metabolic requirement might be very different from that of other patients [16].

Sample size estimation
The sample size for the development of new PEs was estimated based on the assumptions that minimum squared multiple correlation coefficients of 0.15, [13] and PEs have at least three predictor variables with a significance level (α) at 0.05, and power of the study at 80% [17]. The calculated sample size was 220 patients. However, with an estimated non-response or drop-out rate of 30%, the sample size required was 315 patients.

Besides, the sample size for comparison of mean absolute percentage difference and validation of newly developed PEs was estimated based on the assumption that the intra-class correlation coefficient (ICC) between predicted and measured REE was expected to be about 0.9. We further assumed that the lower limit of expected ICC would be 0.8, two measurements of REE would be conducted on each patient, together with a significance level (α) at 0.05, and power of the study at 80%, the minimum sample size was 134 patients [18]. With an estimated non-response or drop-out rate of 20%, the sample size required for paired comparison and validation was 168 patients.

Measurements and instrumentation
REE was measured using COSMED Quark RMR 2.0 (COSMED srl, Rome, Italy). The standard protocol for conducting the measurement was followed [7, 19]. Most of the IC measurements were performed in the morning (between 08:00 and 12:00). The REE was recorded after a 30 min non-fasting steady state, in accordance with standard protocol and manufacturer instructions. Respiratory variables [oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory quotient (RQ)] were collected during the IC measurements. IC measurement was conducted in the acute phase (≤5 days), and in the late phase (≥6 days) if the patient was still mechanically ventilated in the ICU, up to 14 days.

Patient data
The list of data collected is in the Supplementary Appendix. All data were recorded in a standardized case report form.

Statistical analysis for model development and validation
All statistical analysis was performed using SPSS for Windows (version 24.0, SPSS Inc., Chicago, Il, USA). Statistical significance was defined as two-tailed $p < 0.05$. Descriptive statistics were used to describe demographic, nutritional, respiratory, and clinical characteristics.

The multi-fold cross-validation approach was employed to develop and validate the PEs among the patients who have a measured REE in both the acute and later phases ($n = 168$) [20, 21]. The fivefold cross-validation approach was used to develop and validate PE for both phases, whereby subjects were randomly divided into five groups. PEs were then generated five times for each phase, each time with four groups as the validation group (training folds) and the one remaining group as the cross-validation group (test fold).

Simple linear regression (SLR) analysis was applied to identify the demographic, nutritional, respiratory, and clinical characteristics variables that were significantly associated with measured REE. These variables were then entered into multiple linear regression (MLR) analysis. The stepwise selection of variables was applied in MLR analysis to generate the PE. To develop the best PE, the variable which had contributed to the model with changes in the coefficient of determination (R^2) of <0.05 was removed from the MLR model. The final model was checked for interactions and multicollinearity among the independent variables. The final model was then cross-validated with the cross-validation group. The PEs with the highest R^2, the lowest root mean square error (RMSE) and the lowest standard error of estimate (SEE), for acute and late phases, were identified as the best PEs. R^2 was prioritised as the SE or RMSE can be reduced or minimised with a large sample while R^2 is not affected by sample size. In addition to these statistical considerations, other factors considered when selecting the independent variables to be used in the PE were: (i) the variable should be practical and correspond with the physiological concept, (ii) the final PE should be simple to apply in the ICU settings, and (iii) the variable should contribute towards the accuracy of predicting the REE.

The predicted REE calculated from the developed PEs were then compared with measured REE during the acute and late phases by looking at the mean absolute percentage difference. Overestimation or underestimation was defined as a percentage difference of >10% or >−10% [22, 23], respectively, between the predicted and the measured REE.

We found that the mean absolute percentage difference was <20% between the calculated REE for the acute phase with REE measured during the acute and late phases. Similarly, the calculated REE for the late phases and REE measured during the acute and late phases also had mean absolute percentage difference of <20%. Hence, we decided to develop only one PE with a larger sample of patients from the acute phase ($n = 294$). Tenfold cross-validation was used because a higher number of folds leads to a less biased predictive model for larger sample sizes. The best PE were selected based on the aforementioned method.

RESULTS
During the study period, a total of 2504 patients were admitted to the ICU. After screening for eligibility, 315 patients were recruited. Twenty-one patients were excluded from the study due to missing data ($n = 6$), technical issues ($n = 4$), BMI < 15 kg/m² ($n = 3$) and BMI > 40 kg/m² ($n = 8$). A total of 294 (acute phase) and 180 (late phase) patients were included in the final analysis (Fig. 1). Demographic and nutritional characteristics of eligible patients at two different phases of critical illness are presented in Table 1. There were 168 patients who had REE measured in both the acute and late phases. Mean REE was significantly lower in the acute (1747 ± 429 kcal) compared to the late phase (1865 ± 462 kcal) ($p < 0.001$). Data on respiratory support and clinical variables recorded during IC measurements are summarized in Table S1.

In the SLR analysis among 168 patients, the association between measured REE and 15 quantitative variables in the acute phase were statistically significant (Table S2). Among the 15 quantitative variables, variables with the highest correlation coefficients (r) with REE were height ($r = 0.524$, $p < 0.001$), weight ($r = 0.477$, $p < 0.001$), sex ($r = -0.398$, $p < 0.001$) and minute ventilation (Ve) ($r = 0.394$, $p < 0.001$). In the late phase, we found statistically significant relationships between measured REE and 15 quantitative variables. Among the 15 quantitative variables, variables with the highest correlation coefficients with REE were weight ($r = 0.512$, $p < 0.001$), height ($r = 0.498$, $p < 0.001$), energy intake in the previous 24 h ($r = 0.496$, $p < 0.001$), and maximum minute ventilation in the previous 24 h (VeMax) ($r = 0.418$, $p <$
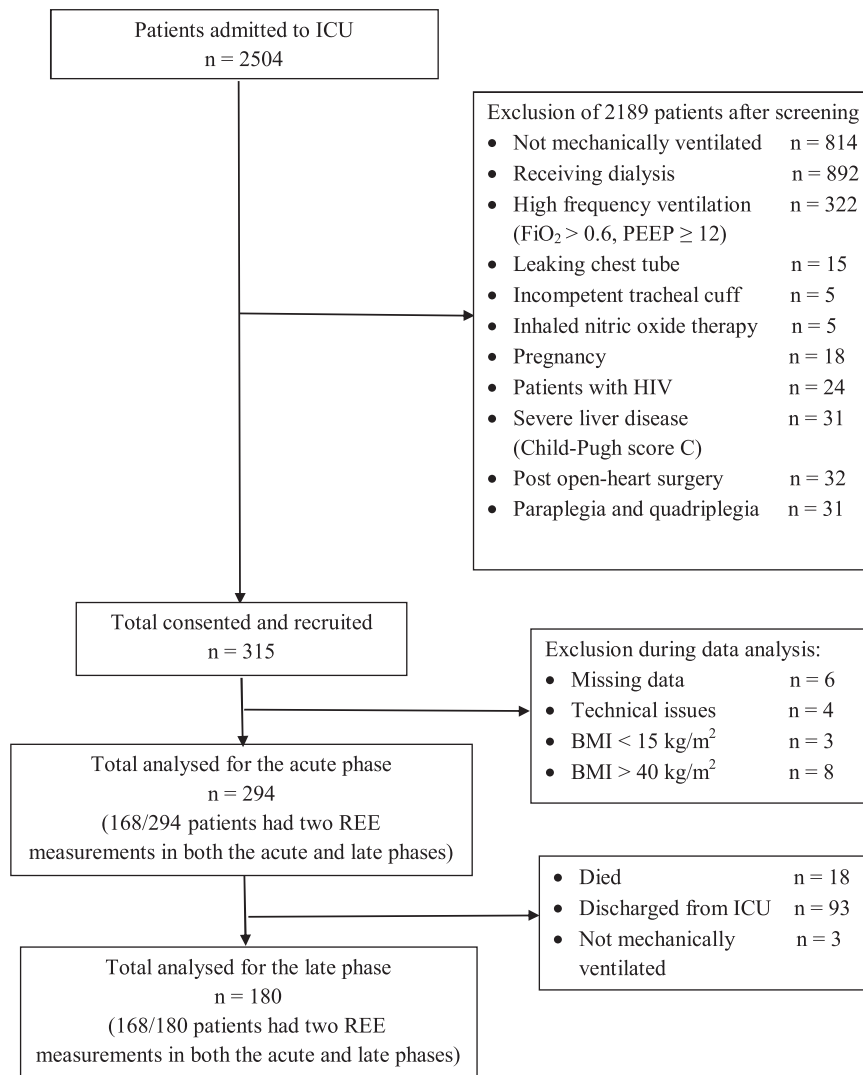
Fig. 1 Exclusion flow diagram. BMI body mass index, FiO$_2$ inspired oxygen, HIV human immunodeficiency virus, IC indirect calorimetry, ICU intensive care unit, PEEP positive end-expiratory pressure, REE resting energy expenditure.

0.001). For the 294 patients in the acute phase, we found statistically significant associations between measured REE and 18 quantitative variables (Table S3). Among the 18 quantitative variables, variables with the highest correlation coefficients (r) with REE were height ($r = 0.515$, $p < 0.001$), weight ($r = 0.487$, $p < 0.001$), sex ($r = 0.425$, $p < 0.001$) and Ve ($r = 0.412$, $p < 0.001$).

In the acute phase among 168 patients with REE measurement in both phases, MLR analysis and fivefold cross-validation were performed and the developed PEs are reported in Table 2A. The best PE for estimating REE (kcal/day) was 1627.8 (Height in m) + 25.3 (Maximum minute ventilation 24 h) + 8.4 (Weight in kg)—1830.3, with $R^2 = 0.414$, RMSE = 294.0, SEE = 343.7. R^2 for equations 2a and 3a are almost similar but equation 2a has a much lower RMSE; hence, equation 2a was selected. In the late phase, MLR analysis and fivefold cross-validation were performed and the developed PEs are shown in Table 2B. The best PE for REE was 1008.3 + 14.4 (Weight in kg) + 26.1 (Maximum minute ventilation 24 h)—7.9 (Age), with $R^2 = 0.498$, RMSE = 423.6, SEE = 335.9. These PEs are known as PE(acute) and PE(late).

Comparison of PEs developed among the 168 patients for the acute and late phases with measured REE during the acute and late phases is shown in Table 3. When comparing with measured

REE during the acute phase, PE(acute) and PE(late) had mean absolute percentage differences of 15.2 ± 13.8% and 18.6 ± 17.7%, respectively. PE(acute) underestimated 25.6% and overestimated 30.4%, while PE(late) underestimated 15.5% and overestimated 45.8% of the subjects' measured REE. When compare with measured REE during the late phase, PE(acute) and PE(late) had a mean absolute percentage difference of 15.7 ± 12.1% and 14.7 ± 14.7%, respectively. PE(acute) underestimated 39.9% and overestimated 22.6%, while PE(late) underestimated 18.5% and overestimated 32.7% of the subjects' measured REE. As the mean absolute percentage difference threshold of ≥20% between the predicted energy requirement from the developed PEs with the measured REE at acute and late phases did not exceed the threshold of 20% determined a priori, we developed a single PE among all patients with REE measured in the acute phase, as it has a larger sample size ($n = 294$) and hence better statistical precision.

Among the 294 patients, MLR analysis and ten-fold cross-validation was performed and the developed PEs are reported in Table 4. The best PE for estimating REE (kcal/day) was 891.6 (Height in m) + 9.0 (Weight in kg) + 39.7 (Minute Ventilation)—5.6 (Age)—354, with $R^2 = 0.442$, RMSE = 348.3, SEE = 325.6. This PE is known as PE(all). A comparison of measured with predicted REE

Table 1. Demographic, nutritional, and descriptive characteristics.

Variable	All patients (n = 294)	Patients with measured REE for 2 phases		
		Acute (n = 168)	Late (n = 168)	p value
Age, years	54.3 ± 18.6	54.1 ± 19.0		—
Sex				—
Male	192 (65.3%)	111 (61.7%)		
Female	102 (34.7%)	69 (38.3%)		
Race			—	
Malay	90 (30.6%)	56 (31.1%)		
Chinese	108 (36.7%)	70 (38.9%)		
Indian	77 (26.2%)	42 (23.3%)		
Others	19 (6.5%)	12 (6.7%)		
Admission category			—	
Medical	159 (54.1%)	101 (56.1%)		
Surgical	85 (28.9%)	50 (27.8%)		
Trauma	50 (17.0%)	29 (16.1%)		
Weight, kg	68.9 ± 15.7	69.0 ± 15.9	68.5 ± 15.8	0.005[a]
Height, m	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.319[a]
Body mass index (BMI), kg/m²	25.1 ± 5.0	25.2 ± 5.2	25.0 ± 5.1	0.034[a]
Measured REE, kcal	1757 ± 431	1747 ± 429	1865 ± 462	<0.001[a]
Route of nutrition (n = 291)				0.178[b]
Enteral nutrition	231 (79.4%)	136 (81.0%)	140 (83.3%)	
Parenteral nutrition	37 (12.7%)	19 (11.3%)	13 (7.7%)	
Enteral + Parenteral nutrition	23 (7.9%)	13 (7.7%)	15 (8.9%)	
Energy intake previous 24 h, kcal/day	1240 ± 586	1317 ± 518	1733 ± 457	<0.001[a]
Protein intake previous 24 h, g/day	50.9 ± 28.2	54.4 ± 24.2	79.3 ± 26.4	<0.001[a]
Body cell mass (BCM), kg	12.8 ± 3.2	12.7 ± 3.2	12.4 ± 3.2	0.006[a]
m-NUTRIC	5.6 ± 1.7	5.9 ± 1.7	5.7 ± 1.7	0.038[a]
Sepsis	101 (34.4%)	60 (35.7%)	65 (38.7%)	0.359[b]
SOFA	13.8 ± 3.0	14.2 ± 2.8	12.7 ± 3.1	<0.001[a]
APACHE II	23.4 ± 6.2	24.5 ± 6.5	22.2 ± 6.3	<0.001[a]
SAPS II	50.7 ± 13.5	53.7 ± 13.0	48.8 ± 13.3	<0.001[a]
Hospital day of measurement	4.0 (3.0–6.3)	5.0 (3.0–7.0)	8.0 (7.0–11.0)	<0.001[c]
ICU day of measurement	3.0 (2.0–4.0)	4.0 (3.0–5.0)	7.0 (6.0–7.8)	<0.001[c]
Vasopressor	141 (48.0%)	87 (51.8%)	47 (28.0%)	<0.001[b]
Sedation	160 (54.4%)	96 (57.1%)	81 (48.2%)	0.059[b]
Muscle relaxant	36 (12.2%)	20 (11.9%)	20 (11.9%)	0.804[b]

Acute phase, ≤5 days; *APACHE II* acute physiology and chronic health evaluation II score, *ICU* intensive care unit; late phase, ≥6 days, *m-NUTRIC* modified nutrition risk in critically ill score, *REE* resting energy expenditure, *SAPS II* simplified acute physiology score II, *SOFA* sequential organ failure assessment score.
Continuous variables are presented as Mean ± SD or Median (Q1–Q3).
Categorical variables are presented as number of subjects, n (%).
Significant difference, p < 0.05;
[a]paired *t*-test was performed to compare continuous paired data.
[b]McNemar test was performed to compare categorical paired data.
[c]Wilcoxon signed-ranked test was performed to compare non-parametric continuous paired data.

calculated from the PE(all) during the acute and late phases is shown in Table 5. The mean absolute percentage difference between the measured and predicted REE in the acute and late phases are 15.1 ± 14.2% and 15.0 ± 13.1%, respectively. In the acute phase, the calculations by PE(all) underestimated 23.5% and overestimated 32.0% of subjects' measured REE, with a mean percentage difference against the measured REE of −12.1 ± 8.4% and 17.6 ± 17.1%, respectively. In the late phase, a total of 33.3% and 22.2% of the subject's measured REE was underestimated and overestimated by PE(all), respectively, with a mean percentage difference against the measured REE of −13.5 ± 8.6% and 17.0 ±

17.2%, respectively. A simple Microsoft Excel Tah et al. equation calculator (Supplementary File) was developed as an aid for ease of application.

DISCUSSION
To the best of our knowledge, this is the first prospective study demonstrated that two separate predictive equations is not necessary for acute (≤5 days) and late (≥6 days) phases of critical illness. Hence, we have developed and internally validated a single PE and demonstrated that it is useful for estimating the REE of

Table 2. Fivefold cross-validation for predictive equations developed from same patients in the acute phase ($n = 168$) and late phase ($n = 168$).

A

Acute phase (<5 days)

Test set	Developed predictive equations	R^2	RMSE	SEE
1	REE = 1686.9Ht + 30.7VeMax + 8.0Wt - 1975.8	0.401	292.5	344.6
2	REE = 1627.8Ht + 25.3VeMax + 8.4Wt – 1830.3[a]	0.414	294.0	343.7
3	REE = 2048.8Ht + 115.7TMax + 7.1Wt – 6462.8	0.442	408.6	318.8
4	REE = 1542.8Ht + 23.4VeMax + 7.5Wt – 1629.1	0.395	381.9	322.4
5	REE = 1740.4Ht + 50.2PEEP + 34.6Ve – 1876.1	0.391	426.3	317.1

B

Late phase (≥ 6 Days)

Test set	Developed predictive equations	R^2	RMSE	SEE
1	REE = 919.1 + 12.0Wt + 43.1VeMax -7.9Age	0.491	412.4	328.5
2	REE = 1008.3 + 14.4Wt + 26.1VeMax– 7.9Age[a]	0.498	423.6	335.9
3	REE = 1143.3Ht + 11.2Wt – 8.9Age – 318.4	0.432	380.5	346.0
4	REE = 1244.6Ht + 10.6Wt – 6.9Age – 556.3	0.398	301.7	364.5
5	REE = 1445.3Ht + 9.3Wt + 27.6VeMax -1522.7	0.363	395.3	344.4

Acute phase, ≤5 days; *HR* heart rate (beats/min); *Ht*, Height (m); late phase, ≥6 days, *PEEP* positive end-expiratory pressure; R^2, coefficient of determination, *REE* resting energy expenditure, *RMSE* root mean square error, *SEE* standard error of the estimate, *TMax* maximum body temperature in the previous 24 h (°C), *VeMax* maximum minute ventilation in the previous 24 h (L/min), *Wt* weight (kg).
Multiple linear regression analysis was applied.
A stepwise method of variable selection applied. Model assumptions fulfilled.
No interactions between independent variables. No multicollinearity detected.
[a]The selected equation.

Table 3. Comparison of REE calculated from predictive equations developed from same patients with measured REE during the acute ($n = 168$) and late phases ($n = 168$).

	kcal/day	Mean absolute % difference	Underestimation		Overestimation	
			Mean % difference	> −10%	Mean % difference	> +10%
Measured REE during the acute phase = 1747 ± 429 kcal/day						
Predictive Equation (Acute)	1751 ± 275	15.2 ± 13.8	−11.7 ± 8.5 (range: −33.6 to −0.04; n = 82)	43/168 (25.6%)	18.4 ± 16.8 (range: 0.13 to 96.1; n = 86)	51/168 (30.4%)
Predictive Equation (Late)	1887 ± 302	18.6 ± 17.7	−10.3 ± 7.9 (range: −35.0 to −0.61; n = 55)	26/168 (15.5%)	22.7 ± 19.6 (range: 0.05 to 119.7; n = 113)	77/168 (45.8%)
Measured REE during the late phase = 1865 ± 462 kcal/day						
Predictive Equation (Acute)	1759 ± 276	15.7 ± 12.1	−14.2 ± 9.2 (range: −36.9 to −0.24; n = 106)	67/168 (39.9%)	18.3 ± 15.6 (range: 0.29 to 61.7; n = 62)	38/168 (22.6%)
Predictive Equation (Late)	1893 ± 313	14.7 ± 14.7	−10.4 ± 8.8 (range: −41 to −0.05; n = 79)	31/168 (18.5%)	18.6 ± 17.6 (range: 0.27 to 77.3; n = 89)	55/168 (32.7%)

Acute phase, ≤5 days; late phase, ≥6 days; *REE* resting energy expenditure.
Predictive Equation (Acute):1627.8Ht + 25.3VeMax + 8.4Wt – 1830.3.
Predictive Equation (Late):1008.3 + 14.4Wt + 26.1VeMax – 7.9Age.

both acute and late phases of critical illness in the Asian population.

Our previous study [14], which compared measured REEs using IC with predicted REEs from 15 commonly used PEs, showed that none of the REEs calculated using those PEs had very good accuracy and agreement at different phases of critical illness. Besides, we also found that patients in the acute phase had significantly lower mean REEs than patients in the late phase [14]. Considering the importance of these variations in energy requirements in different phases of critical illness, the recent ESPEN guidelines recommended a gradual increment of energy provision [2]. These provide us with the rationale to assess

metabolic determinants of REE for the acute and late phases of critical illness.

In this study, the predicted REE calculated from two separate PEs developed from patients that had two IC measurements in acute and late phases had mean absolute percentage differences of <20% when compared to measured REE in both phases, even though there appears to be a significant change in the severity of diseases between the two phases. In clinical practice, a 10–20% difference between predicted and measured REE has been considered acceptable. Based on the current literature, a difference of ±20% of energy intake does not produce any clinically meaningful difference in important outcomes [15, 25]. This

Table 4. Tenfold cross-validation for predictive equations developed from all patients ($n = 294$).

Test set	Developed predictive equations	R^2	RMSE	SEE
1	REE = 1710.8Ht + 7.3Wt + 26.6VeMax − 1906	0.417	391.1	328.7
2	REE = 891.6Ht + 9.0Wt + 39.7Ve − 5.6Age − 354[a]	0.442	348.3	325.6
3	REE = 2164.6Ht + 19.6BMI + 39.4Ve − 2651	0.397	325.3	338.8
4	REE = 2153.2Ht + 33.6Ve + 115.6TMax − 6423	0.401	356.6	338.9
5	REE = 1492.1Ht + 7.7Wt + 40.9Ve -1582	0.399	276.9	343.0
6	REE = 1785.9Ht + 7.4Wt + 31.0VeMax − 2087	0.426	349.0	334.3
7	REE = 1774.0Ht + 7.2Wt + 32.0VeMax − 2049	0.424	403.3	328.1
8	REE = 1405.7Ht + 8.1Wt + 37.1Ve − 1442	0.403	362.3	334.0
9	REE = 1564.2Ht + 7.9Wt + 28.7VeMax − 1727	0.396	338.1	335.3
10	REE = 1691.6 Ht + 7.8Wt + 23.3VeMax − 1878	0.390	397.9	328.0

BMI body mass index (kg/m²), *Ht* height (m), R^2 coefficient of determination, *REE* resting energy expenditure, *RMSE* root mean square error, *SEE* standard error of the estimate, *TMax* maximum body temperature in the previous 24 h (°C), *VeMax* maximum minute ventilation in the previous 24 h (L/min), *Ve* Minute Ventilation (L/min), *Wt* weight (kg).
Multiple linear regression analysis was applied.
A stepwise method of variable selection applied. Model assumptions fulfilled.
No interactions between independent variables. No multicollinearity detected.
[a]The selected equation.

Table 5. Comparison of REE calculated from predictive equation developed from all patients with measured REE during the acute ($n = 294$) and late phases ($n = 180$).

	kcal/day	Mean absolute % difference	Underestimation		Overestimation	
			Mean % difference	>−10%	Mean % difference	> +10%
Measured REE during the acute phase = 1757 ± 431 kcal/day						
Predictive Equation	1773 ± 284	15.1 ± 14.2	−12.1 ± 8.4(range: -36.8 to -1.1; $n = 130$)	69/294 (23.5%)	17.6 ± 17.1 (range: 0.1 to 113; $n = 164$)	94/294 (32.0%)
Measured REE during the late phase = 1886 ± 508 kcal/day						
Predictive Equation	1807 ± 315	15.0 ± 13.1	−13.5 ± 8.6 (range: -39.2 to -0.04; $n = 103$)	60/180 (33.3%)	17.0 ± 17.2 (range: 0.06 to 79.4; $n = 77$)	40/180 (22.2%)

Acute phase, ≤5 days; late phase, ≥6 days; REE, resting energy expenditure.
Predictive Equation (all patients in the acute phase, $n = 294$) :891.6Ht + 9.0Wt + 39.7Ve − 5.6Age − 354.

diminished the clinical reasoning for needing two separate equations for the different phases. A larger difference of measured REE between the acute and late phases may become more evident with a larger sample size and time-lapse. From these results, we decided to develop and validate a single PE among all patients with REE measured in the acute phase only, given the larger sample size. This single PE developed from the acute phase has been found to be optimal for estimating REE in both the acute and late phases.

Studies have shown that REE is influenced by many factors, including age, sex, body composition, body temperature, body movement, environmental temperature, heart rate, and disease status [26–28]. Pharmacological agents, such as analgesics, sedatives, and muscle relaxant reduce REE, while vasopressors increase REE [29]. REE can fluctuate throughout illness and can increase due to stress-induced metabolic effects in critically ill patients [30]. In this study, height, weight, minute ventilation and age were the main determinants of REE, and they explained about 44.2% of the variations in REE. The explanatory power of our variables is comparable with those reported in other studies that had developed PEs for ICU populations, such as Penn State [31], Raurich [32], Brandi [33], Faisy [13] and Swinamer [12], where the reported explanatory power ranges from 37% to 77%. The moderate performance of PEs developed for critically ill patients is expected as many factors will influence REE [26–30] and a PE estimates REE from only a few variables that are highly correlated with measured REE.

In the present study, weight and age were the 'static' variables selected for use in the prediction models of both the acute and

late phases. Older patients may have lower REEs partly because of age-associated changes in body composition and the relative size of fat-free mass (FFM) components [27, 34, 35]. Many studies have shown that body weight and FFM (the metabolizing mass of the body) correlate with REE [35–37]. However, the relationship between REE and body weight is nonlinear at the extremes of body weight [22, 27, 38]. A disturbance in the ratio of total body weight, organ, and muscle can distort the association between body weight and REE, especially among underweight, obese and muscular individuals [34, 36]. For these reasons, patients with BMI < 15 kg/m² and BMI > 40 kg/m² were excluded from this analysis.

In this study, multivariate analysis showed that the independent variables defining REE were those related to metabolism (age, weight, height, and minute ventilation). Of note, one "dynamic" variable which is minute ventilation was selected in the final prediction model. Minute ventilation, which is determined by the respiratory rate and tidal volume, depends on the sedation level or the ventilator setting. During the acute phase, patients are unstable, and the dynamic nature of minute ventilation may be able to better reflect the metabolic rate of the patients in this phase. Minute ventilation has also been included in previous equations for estimating the REE of critically ill patients [9, 13, 33]. Minute ventilation maintains acid-base homoeostasis and stable carbon dioxide status in an individual. The relationship between minute ventilation and REE is predicted because carbon dioxide production (VCO_2) is a part of the Weir equation (27, 28). Furthermore, the increase in REE with an increase of VCO_2 is the main cause for increased minute ventilation requirements in long-

staying mechanically ventilated patients [39]. Compared with PEs that use only 'static' variables, it is preferable to include dynamic variables in the PEs because PEs with "dynamic" variables are more consistent with REEs measured by IC [14].

The present study used predicted body cell mass (BCM) to explore the relationship between measured REE and body composition. This was a significant but weak correlation ($r = 0.234$ in the acute phase, $r = 0.257$ in late phase; $p < 0.05$) and thus was not selected for use in either of the prediction models. The probable reasons were that body composition values are influenced by stress conditions, injury and abnormal fluid status in critical illness [40, 41], and the predictive equation for calculating BCM [42] used in our study may be less accurate. The variable 'energy intake in the previous 24 h' was also not selected for use in the prediction model in the late phase even though statistically it is correlated with REE. This is because the problem of multicollinearity might exist as energy intake was guided by measured REE since early phase and use of this variable will lead to large variations of calculated REE as the variations in energy intake of patients can range from 0 kcal/day when nil by mouth to about 2000 kcal/day when given full feeding. Furthermore, the effect of DIT on REE is less than 5% when patients are not overfed and are on continuous nutrition support [43–45]. IC measurements in our study were performed without discontinuing nutrition support and patients were not overfed (mean energy adequacy $87.1 \pm 20.2\%$). The current study also did not include body temperature in the new predictive model because most of the patients were in normothermia condition (mean $36.71 \pm 0.86\,°C$) during IC measurements, although variations of 5% REE per degree Celsius has been found in other ICU studies [13, 32].

Recently, ventilator-derived VCO_2 has been proposed for estimating REE as it was shown to be more accurate than PEs [46, 47]. However, further validation showed that it has a low agreement with IC-measured REE [48]. Experts have also suggested that this simplistic approach cannot reflect the complex physiological changes that critically ill patients undergo [49]. Besides, this method needs a special ventilator that can measure VCO_2. Thus, PEs are still routinely used in daily practice and in critical care nutrition trials when IC is not feasible [15, 24].

This study has several limitations. First, the PEs generated in this single-centre study has limited generalizability. Second, as the measured or estimated body weight may not reflect actual weight (due to acute fluid shifts), this could have introduced errors in the prediction model. Third, despite efforts to ensure that every measurement was done in a standardized manner, the accuracy of IC measurements was inevitably influenced by metabolic factors, such as changes in body composition, medications, disease status, changes of ventilator mode, nutrients absorption and body temperature.

On the other hand, this study also has several strengths. First, the PE for critically ill Asian patients were developed and validated by considering the variable, dynamic, and complex nature of metabolic changes at different phases of critical illness. Second, this is a prospective study with a relatively large sample size and large number of variables in both the acute and late phases. Third, the use of multi-fold cross-validation is considered a robust internal-external validation method for the PEs, which can accurately predict out-of-sample accuracy and use data more efficiently as all observations are used for both testing and training [20, 21]. Fourth, the use of a single carefully calibrated device and the application of the standardized method for measuring REE minimized variations in the measurements. Lastly, a Microsoft Excel Tah et al. equation calculator (Supplementary File), which is a practical and simple-to-use tool is provided to facilitate the use of the developed PE in the ICU setting.

CONCLUSIONS

Two separate predictive equations for estimating REE in the acute (≤ 5 days) and late (≥ 6 days) phases of critical illness may not be necessary. An equation was developed and internally validated among patients with IC measurement in the acute phase. The equation is [891.6 (Height in m) + 9.0 (Weight in kg) + 39.7 (Minute Ventilation in L/min) − 5.6 (Age) − 354](Tah et al. equation). Comparison of the REE estimated from this new predictive equation with measured REE has demonstrated that it can provide optimal estimates of REE for patients in both acute and late phases. Thus, when IC measurement is not possible, this PE may be useful, especially for Asian critically ill patients. Future studies are needed to validate this newly developed PE externally.

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AUTHOR CONTRIBUTIONS
PCT, BKP, CCK, ZYL, VRHR, MBMN, MKZ, HAM and MSH contributed to the conceptualization and design of the study; PCT recruited the patients and collected the data; PCT, CCK and ZYL contributed to the acquisition and analysis of data; PCT, BKP, CCK, ZYL, HAM and MSH contributed to the interpretation of data; PCT drafted the manuscript; PCT and MSH contributed to the funding acquisition. All authors agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors have read and agreed to the published version of the manuscript.

COMPETING INTERESTS
The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
Ethics approval was granted by the Medical Research Ethics Committee (MREC), UMMC (MREC ID NO: 20161024-4407) and registered with the National Medical Research Register (NMRR) Malaysia (NMRR.ID: NMRR-16-2030-33143) and Clinical-Trials.gov (NCT03319329). Informed consent was obtained from the patients or their legal representative.

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