Clinical Nutrition 38 (2019) 1899–1904

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Prognostic value of energy expenditure and respiratory quotient measuring in patients with liver cirrhosis

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ARTICLE INFO

Article history:
Received 16 January 2018
Accepted 1 July 2018

Keywords:
Cirrhosis
Indirect calorimetry
Resting energy expenditure
Predictive equations
Respiratory quotient

SUMMARY

Background & aims: Resting energy expenditure (REE) and respiratory quotient (RQ) as measured by indirect calorimetry (IC) may correlate with muscle mass and represent prognostic indicators in treating patients with liver cirrhosis. We aimed to assess the correlation of IC-measured REE and RQ with skeletal muscle mass (SM), mortality, and REE values as estimated by Harris–Benedict, European guidelines (EG), and Brazilian guidelines–DITEN (BG) equations in patients with liver cirrhosis.
Methods: In this prospectively designed study, REE was measured in 126 male patients with liver cirrhosis by IC and predicted by Harris–Benedict, EG (35 kcal/kg current weight), and BG (30 kcal/kg current weight) guidelines. Measurements were obtained at the time of admission to the study. Body composition was determined by whole-body dual-energy X-ray absorptiometry. The association between REE and 3-year survival was investigated.
Results: Cirrhosis etiology was classified as alcohol related (59.0%), viral (20.1%), cryptogenic (11.8%), or other (9.0%). Mean Child-Pugh and MELD indexes were 8.30 ± 2.0 and 14.38 ± 6.12, respectively. RQ showed a moderate correlation with SM ($r = 0.64$), while IC-measured REE was inversely associated with mortality (multivariate Cox Regression, HR = 0.88, 95% CI: 0.78; 1, $p = 0.04$). Among the predictive equations for REE, only Harris–Benedict yielded values close to the IC, with a positive Pearson correlation ($r = 0.77$), excellent accuracy (Cb = 0.98), and positive Lin's concordance correlation (CCC = 0.75). However, a large standard deviation was observed; HB-measured REE did not correlate with mortality.
Conclusions: RQ and REE, as measured by IC, may be valuable tools for evaluating the severity of cirrhosis, by reflecting SM and predicting mortality, respectively. The predictive equations for REE included in this study cannot replace IC for this purpose.
Registered at: www.clinicalTrials.gov (NCT02421848).

1. Background

Cardiovascular function and metabolic homeostasis are altered in patients with liver cirrhosis [1,2]. Cardiovascular dysfunction manifests as hyperdynamic syndrome, with increased heart rate and cardiac output and reduced systemic vascular resistance and arterial blood pressure. Associated metabolic changes include increased gluconeogenesis, sarcopenia, and fatty acid oxidation. These disturbances may impact resting energy expenditure (REE) and respiratory quotient (RQ), contributing to the depletion of nutritional status, even with adequate nutritional intake. By reflecting the degree of systemic distress caused by disease

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https://doi.org/10.1016/j.clnu.2018.07.001
0261-5614/

progression, REE and RQ values may have prognostic application in the treatment of patients with liver cirrhosis.

Indirect calorimetry (IC) is the reference method for REE measurements. IC also provides RQ values, which reflect the relative contributions of various substrates for energy metabolism. High REE [3] and low RQ [4] have been reported in patients with cirrhosis, even in those presenting with sarcopenia, when values are corrected to muscle mass [2]. However, these findings did not correlate with short-term outcomes. The prognostic value of IC-measured REE and RQ in patients with liver cirrhosis remains unclear.

In practice, the use of IC is limited by its high cost. Several predictive equations and formulas are therefore used to provide alternative ways of estimating REE. These include the Harris–Benedict (HB) equation, the European-ESPEN (EG), and Brazilian-DITEN (BG) guidelines [5–9]. Important deviations between IC-measured REE and estimates provided by predictive tools have been reported in different disease settings [10–12].

There is a clear need to understand the prognostic value of IC-measured REE and RQ in clinical settings, where systemic changes can impact metabolism. In this study, we test whether IC-measured REE and RQ values correlate with skeletal muscle mass and have prognostic value in predicting mortality. We also seek to determine whether IC-measured REE values may be derived from those obtained with predictive HB, EG, and BG tools.

2. Methods

2.1. Subjects

This study included 126 male patients with biopsy-diagnosed liver cirrhosis recruited prospectively from the Digestive Tract Surgery Service at the Hospital das Clínicas of the University of São Paulo Medical School (HC-FMUSP), during the period from January 2012 to December 2014. Exclusion criteria were alcohol abuse; positivity for human immunodeficiency virus; diagnosis of cancer, acute liver failure, or chronic or acute disease of the lung, kidney, or heart; previous liver transplantation; use of an orthopedic prosthesis; and dementia. All patients provided written informed consent prior to participation in the trial. A single trained technician performed all study procedures according to the ethical standards of the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Review Board (0646/11) and registered at www.clinicaltrials.gov (NCT02421848).

2.2. Demographic and clinical data collection

The following demographic and clinical data were collected: age, liver cirrhosis etiology, Child-Pugh (CP) and Model for End-Stage Liver Disease (MELD) scores, body weight, height, and body mass index (BMI). Body weight was measured with the participant standing in the center of a single electronic scale platform while barefoot and wearing only light clothes. Height was measured with a single stadiometer (Sanny, São Paulo, SP, Brazil), with the patient standing barefoot with the heels together, back upright, and arms extended next to the body. BMI was calculated as weight divided by height squared (kg/m^2). Demographic data were recorded for all subjects.

2.3. REE and RQ measurements with IC

All patients were instructed to refrain from excessive physical activity, use of diuretic agents, and alcohol consumption for 24 h prior to the assessment, which was performed with patients in a 12-h fasting state. Basal VO_2, VCO_2, RQ, and REE were measured with a calorimeter Deltatrac II metabolic monitor (Datex-Ohmeda, Helsinki, Finland) in the morning (08:00 and 10:00 am), with the patients awake and lying down. After a rest period of 5 min, a face tent was placed over the patient's mouth and nose, and gas exchange was measured for the subsequent 30 min. For data analysis, the first 5 min of testing were discarded. VO_2 and VCO_2 values were used to calculate RQ as the VCO_2/VO_2 ratio and REE (in kcal/d) with Weir's equation, where $REE = 1.44\ (3.9VO_2 + 1.1VCO_2)$.

2.4. REE estimation by predictive formula

Energy expenditure (kcal/d) was estimated with the follow predictive formulas: $HB = 66.5 + (13.75 \times \text{weight in kg}) + (5.003 \times \text{height in cm}) - (6.755 \times \text{age in years})$; $EG = 35$ kcal/kg current weight; and $BG = 30$ kcal/kg current weight.

2.5. Measurement of body composition

Body composition was assessed with a dual-energy X-ray absorptiometry (DXA) device (Discovery model; Hologic Inc., Bedford, MA) with APEX software (version 4.02; Hologic, Inc., Bedford, MA). Participants removed all metal objects and other items that might interfere with the scan and were instructed to empty their bladders. Each patient was positioned supine in the center of the scanning table with the palms down and the arms beside the body. Data related to age, height, weight, sex, and ethnicity were recorded. The device's default software was used to determine body composition indices. The DXA system was calibrated at the start of the study with the manufacturer's body composition phantom [13]. All individuals underwent whole-body DXA scans for measurement of regional lean mass (in the four limbs). Appendicular skeletal muscle mass index was calculated by dividing the sum of lean mass in all four limbs by body height, squared (kg/m^2) [14].

2.6. Survival analysis

Death events related directly to complications of cirrhosis were assessed by telephone during the 3 yr of follow-up. A longitudinal analysis of mortality was performed to assess the prognostic value of REE and RQ.

2.7. Statistical analysis

The correlation of RQ and REE with appendicular skeletal muscle mass was determined with Pearson correlation. Differences between REE values obtained by IC and predicted equations were compared by box-plot. Agreement between values was assessed by Lin's concordance correlation coefficient (CCC), the Bland–Altman graphic, and 95% confidence intervals (CIs). Survival probabilities were estimated by the Kaplan–Meier method, compared using the log-rank test, and estimated in terms of failure rate, according to an independent Cox proportional hazard model. Mortality models included REE. Data were expressed as means ± standard deviations, medians, interquartile ranges (IQRs; 25th–75th percentile), or percentages, depending on the normality of distribution and variable type. Data were analyzed with the R software package (version 3.1.3, 2015; R Core Team, Vienna, Austria). Findings with $P < 0.05$ were considered significant.

3. Results

3.1. Demographic and clinical data

In this study, all 126 male patients (median age, 54.50 years; IQR, 48–62 years) who started the study also completed the study

Table 1
Baseline characteristics and body composition of patients with liver cirrhosis.

Variable	Value (n = 126)
Age (years)	54.52 ± 9.99
Weight (kg)	73.82 ± 18.09
Height (m)	1.70 ± 0.10
Child score	8.33 ± 2.00
MELD score	14.38 ± 6.12
Absent ascites (%)	31.00
Controlled ascites (%)	42.74
Moderate ascites (%)	16.94
Refractory ascites (%)	0.81
Voluminous ascites (%)	9.68
Hepatic encephalopathy (%)	16.70
Esophagus varices (%)	30.83
BMI (kg/m^2)	21.93 ± 10.69
REE/FFM (kcal/kg)	29.23 ± 3.48
ASMI (kg/m^2)	7.53 ± 1.66

Body composition data were obtained by DXA from 126 subjects. Data are presented as mean ± standard deviation or percentage. MELD, Model for End-Stage Liver Disease [23]; BMI, body mass index; ASMI, appendicular skeletal muscle index.

protocol. Related demographic and clinical data are provided in Table 1. These patients presented liver cirrhosis of varying etiology (alcohol, 59%; viral, 20%; cryptogenic, 12%; other, 9%) and were classified according to Child-Pugh designations as follows: Child A, 20%; Child B, 52%; Child C, 28%. Mean MELD score was 14.38 (IQR, 10.53–16.18). Ascites were absent or controlled in 73.74% of patients and moderate, voluminous, or refractory in 27.43% of patients; 52 (41.20%) patients presented lower limb edema; 16 (12.90%) patients underwent liver transplantation, at an interval of 38–1001 d (median, 530 d; IQR, 226–652 d) after enrollment. Intervention with ß-blockers was performed in 122 (98.40%) of patients included in the study.

3.2. Correlation of IC-measured REE and RQ with muscle mass

Our data on appendicular skeletal muscle mass index as assessed by DXA were published previously [15]. Appendicular skeletal muscle mass was lower in cirrhotic patients than in controls ($p < 0.001$). Values were not affected by lower limb edema or ascites and predicted sarcopenia-related mortality. Mean appendicular skeletal muscle mass index, RQ, and IC-measured REE values were 7.53 ± 1.66 kg/m^2, 0.85 ± 0.06 and 1620.86 ± 264.47 kcal/d, respectively (Table 1). Appendicular skeletal muscle mass index showed poor correlation with IC-measured REE ($r = 0.03$) and moderate correlation with IC-measured RQ ($r = 0.64$).

3.3. Correlation of IC-measured REE with HB, BG, and EG-calculated REE

Mean values of HB, BG, and EG-calculated REE were 1589.06 ± 222.17 kcal/d, 2273.17 ± 418.84 kcal/d, and 2652.03 ± 488.65 kcal/d, respectively. Except for HB, all tested formula provided REE values that differed substantially from the 1620.86 ± 264.47 kcal/d value of IC-measured REE. Bland–Altman comparison of the 3 tested formulas yielded large limits of agreement between HB, BG, and EG-calculated REE values and IC-measured REE values (Figs. 1–3, respectively).

3.4. Prognostic value of REE and RQ in predicting mortality

Of the 126 patients studied, 65.08% survived, and 34.92% died due to cirrhosis, with a mean of 16 mo of follow-up until death

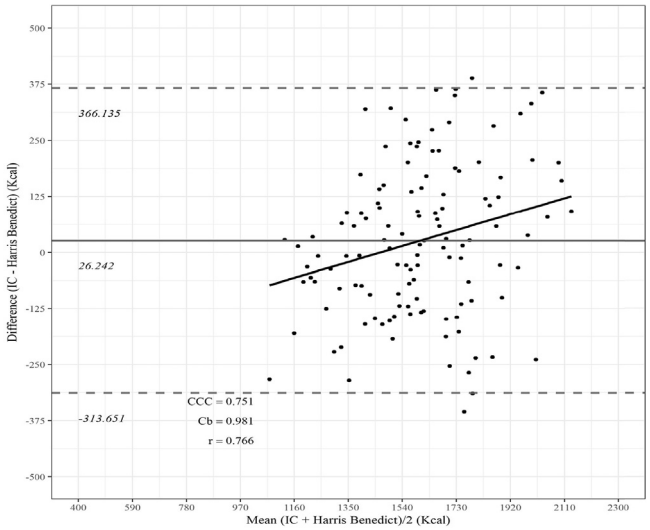

Fig. 1. Bland–Altman plot showing limits of agreement for IC vs. Harris–Benedict equation. Bold continuous line indicates observed average agreement. Continuous line indicates line of perfect average agreement. Dashed lines indicate 95% limits of agreement. Lin's concordance correlation coefficient (CCC) is shown.

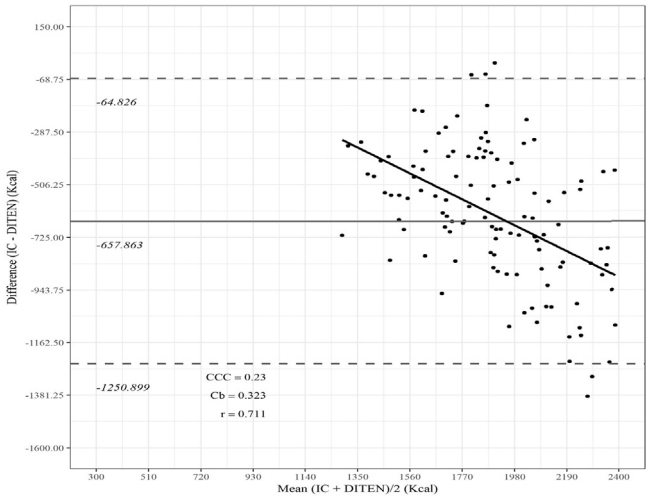

Fig. 2. Bland–Altman plot showing limits of agreement between IC and Brazilian guidelines – DITEN. Bold continuous line indicates observed average agreement. Continuous line indicates line of perfect average agreement. Dashed lines indicate 95% limits of agreement. Lin's concordance correlation coefficient (CCC) is shown.

(median, 32 months; IQR, 17.52–33.96 mo). Moreover, 12.70% of the patients who died underwent had previously undergone liver transplantation. One patient died in a car accident; this death event was not counted. High values of IC-measured REE were associated with lower mortality rates (multivariate Cox regression, HR = 0.88, 95% CI: 0.78; 1, p = 0.04) and served as independent factors in predicting death. In a mortality model adjusted by MELD, an increase in energy expenditure of 100 kcal reflected an 11% reduction in mortality risk (Table 2). Kaplan–Meier curve of cumulative survival rates showed improved survival in patients presenting IC-measured REE ≥2250 kcal/day and decreased rate of survival in patients with IC-measured REE ≤1500 kcal/day (Fig. 4). Cirrhotic patients with REE ≥1190 kcal presented greater survival than did cirrhotic patients with REE <1190 kcal (log-rank test, $p < 0.001$) (Fig. 5). IC-measured RQ values and REE-estimated by studied predicted equations (HB, BG and EG, respectively) were not

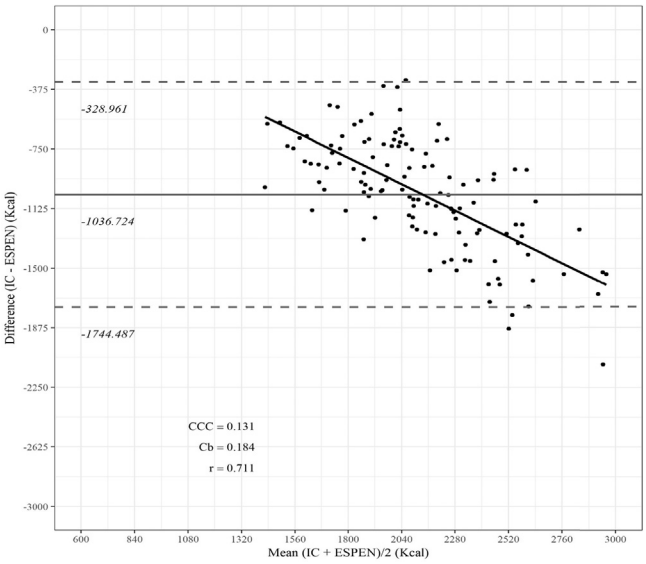

Fig. 3. Bland–Altman plot showing limits of agreement for IC vs. ESPEN guideline. Bold continuous line indicates observed average agreement. Continuous line indicates line of perfect average agreement. Dashed lines indicate 95% limits of agreement. Lin's concordance correlation coefficient (CCC) is shown.

Table 2
Mortality estimates for patients with cirrhosis from multiple Cox regression models.

Variable	Multiple model	
	HR (95% CI)	*P* value
MELD score	1.05 (1.02; 1.09)	<0.001
REE − IC	0.88 (0.78; 1)	0.003

Data were collected from 126 patients. MELD, Model for End-Stage Liver Disease; REE, Resting Energy Expenditure by Indirect Calorimetry. *P* values for independent Cox regression models refer to models explained by MELD score and REE.

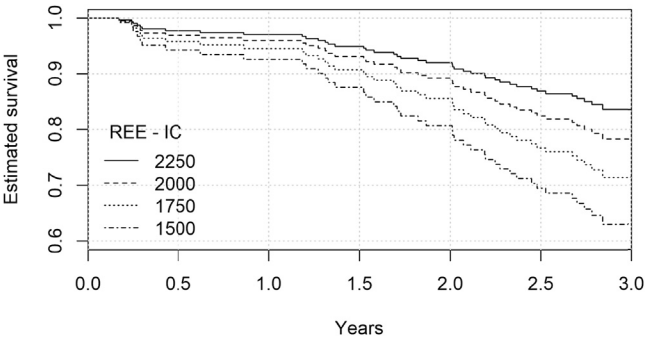

Fig. 4. Estimated Kaplan–Meier survival curve for patients with cirrhosis. REE-IC is resting energy expenditure as measured by indirect calorimetry, increasing by 250 kcal from 1500 kcal/day. Survival was followed for 3 yr.

significantly associated with changes in patient survival in a mortality model adjusted by MELD (multivariate Cox regression HB HR = 0.91, 95% CI: 0.79; 1.05, p = 0.18; BG HR = 1, 95% CI: 1; 1. p = 0.47; EG HR = 1, 95% CI: 1; 1, p = 0.47).

4. Discussion

This study assessed the potential prognostic value of IC-measured REE and RQ in reflecting muscle mass and predicting mortality in patients with liver cirrhosis. We found a correlation

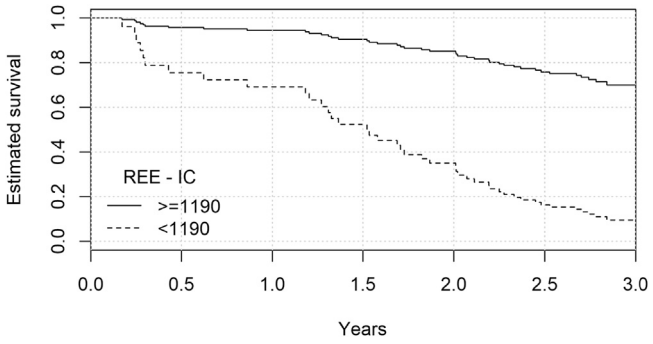

Fig. 5. Kaplan–Meier survival curves for 126 patients with cirrhosis, for obtained REE by IC. Survival was followed for 3 yr.

only between muscle mass and IC-measured RQ; a significant association with mortality was displayed only for IC-measured REE. Somewhat unexpectedly, high IC-measured REE values were associated with improved survival.

Mortality risk is the main prognostic factor in clinical practice. Child-Pugh or MELD scores are typically used to assess survival in patients with liver cirrhosis, but other parameters for this purpose have been studied. When testing the predictive value of RQ for survival of patients with liver cirrhosis, Tajika et al. [16] reported decreased overall survival when non-protein RQ (npRQ) was <0.85, in comparison to npRQ >0.85 ($p < 0.01$). Hishikawa et al. [4] confirmed this predictive value of RQ, so that npRQ for the determination of macronutrient utilization become an important prognostic tool in the treatment of liver cirrhosis and other liver-associated diseases in Japan.

In addition to VO_2 and VCO_2, npRQ uses urine urea nitrogen (UN, g/day) for calculation of npRQ ([1.44 VCO_2 − 4,89 UN]/[1.44 VO_2 − 6.04 UN]). This measurement is not routinely performed in clinical practice [17]. In our study, RQ was not a predictor of survival, and npRQ was not calculated (because urinary nitrogen was not measured). However, we found a moderate correlation of RQ values with skeletal muscle mass as a direct marker of body protein status.

McClave et al. [18] did not recognize RQ as a tool for assessment of nutritional status or prediction of survival but considered it useful for evaluating the quality of calorimetric measurements. The authors showed that REE was a good indicator for survival. When RQ values < 6.5 or >1.2 were eliminated, RQ magnitude appeared to reflect the extent of nutrient metabolism. Our patients had high mean RQ and elevated mean REE, demonstrating their ability to use carbohydrates and not mainly fatty acids, as suggested by low RQs.

In opposition to our findings, data from a previous study associated elevated REE with increased mortality before and after liver transplantation [19]. Muller et al. [20] also reported a significant association between decreased transplant-free survival and increased REE, even within the normal range of values. Hypermetabolism was proposed to be a consequence of severe inflammation; the predictive association with survival was independent of MELD and Child-Pugh scores, ascites, and clinical edema [20].

The apparent contradiction between our findings on REE and mortality with those previously reported may be associated with the specific characteristics of our enrolled patients. This group did not show extensive muscle mass depletion; 72% had Child Pugh scores of grade A or B. The ability to increase peak VO_2 has been correlated with improved outcomes [21], suggesting greater mitochondrial and energy reserves in cirrhotic patients with greater muscle mass. Furthermore, as reflected by their Child-Pugh grades, our patients generally presented low disease severity, which would lead to a relatively minimal depletion of operational

mitochondrial and energy reserves. Tajika et al. [16] found that high Child-Pugh scores were associated with decreased REE. Because this score predicts outcome in cirrhotic patients, high REE may be associated with improved survival.

Curiously, most of our patients were treated with b-blockers (>98% of our sample) and presented elevated energy expenditure. Müller et al.'s study of transplant-free survival reported that a small group of patients treated with ß-blockers were normometabolic. Another study [22] reported a decrease in REE after ß-blocker treatment in hypermetabolic patients with liver cirrhosis. Lee et al. [23] did not find any significant difference in metabolic rate when REE values of cirrhotic patients who received 3-month treatment with ß-blockers were compared to those of patients who received 3-month treatment with placebo. In the group of patients included in the present study, long-term therapy with ß-blockers did not prevent hypermetabolism. Krag et al. similarly showed that ß-blockers seem only to inhibit the thermic effect of food by decreasing splanchnic perfusion and oxygen consumption [24].

In our study, alternative predictive equations for REE estimation (except for HB) did not yield values similar to those obtained via IC-measured REE. Nevertheless, while IC-measured REE showed a direct association with survival, HB did not reflect this prognostic factor. Muller et al. [22] found that 34% of patients with liver cirrhosis had IC-measured REE >120% of that estimated by HB. In a cross-sectional study enrolling 488 Japanese in patients with cirrhosis [25], mean IC-measured REE (1256 kcal) was significantly lower than mean HB-estimated REE (1279 kcal). Average energy intake was 30.5 kcal/kg BW, which is 1.4 times greater than REE/kg BW.

In combination with previously published data, our findings suggest that using predictive equations for REE estimation may not provide accurate values with clinical relevance to patients with cirrhosis. This inaccuracy may reflect the use of weight by most available REE-predictive equations; weight measurements may be inaccurate when obtained for cirrhotic patients with ascites. We have previously shown [15] that measurements of fat free mass and REE/FFM kg are inaccurate in the presence of ascites.

Definitions of normo-, hyper- and hypometabolism are related to the relationship between REE and HB equations. However, in a study of 268 patients with liver cirrhosis, Peng et al. [26] found hypermetabolism in only 15%. The presence of hypermetabolism did not correlate with disease severity. Because of specific abnormalities in fluid retention that can affect weight, we suggest comparing REE absolute measurements to assess hypermetabolism in patients with cirrhosis rather than combining the ratio between measured REE and a predictive equation such as HB in patients with cirrhosis [22,25,26].

Notably, predictive equations for REE estimation were designed for assessment of energy requirements and rather than use as a prognostic tool. Nevertheless, our findings in adult/elderly patients with cirrhosis confirmed the inaccuracy of predictive-REE equations in assessing energy requirements reported in children with cirrhosis [27], but in our study HB provided REE values close to IC-measured REE values. In opposition to our findings, Madden and Morgan [28] showed that predictive-REE equations (including HD) performed poorly when compared with IC-measured REE in the estimation of REE. Wilkens-Knudsen et al. [29] confirmed this finding in patients with liver cirrhosis and ascites. The authors found overestimation of HB-estimated REE at baseline and after paracentesis, stressing the importance of body weight in the equation. Moreover, Teramoto et al. [30] reported differences between IC-measured REE and that estimated by HB, mainly for cirrhotic patients in the first and second quartiles for BMI. Previous studies [27–30] recommended IC-measured REE to guide the nutritional therapy of cirrhotic patients. REE-estimative equations may lead to deleterious overnutrition in patients with liver cirrhosis, because fatty liver is often related to high caloric load and may further complicate manifestations of the disease.

In conclusion, RQ and REE as measured by IC represent valuable prognostic tools for the treatment of patients with liver cirrhosis, by reflecting SM and predicting mortality, respectively. The predictive equations for REE studied may not replace IC for this purpose in this patient population, most likely due to the former's use of weight in the formulas used for calculations.

Funding

This study was supported by Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP), project no. 2011/13243-3, DD 2012/15677-3.

Authors' contributions

GB and DLW contributed to conception and design of the study. GB, MCG, WA, LADA, NM, CC, and SB were responsible for acquisition, analysis, and/or interpretation and discussion of data. GB, PS, and RSMT drafted the manuscript. GB, DLW, and RSMT participated in study design and coordination and helped to draft the manuscript. GB and LD participated in design of the study and performed statistical analysis. GB, PS, ACC, RMRP and SBH participated in analysis of the data, critical analysis of the results, and writing of the manuscript. LD performed statistical analyses. All authors read and approved the final manuscript.

Conflict of interest

None.

Acknowledgments

The authors thank the patients and nurses who participated in the study and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

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