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Comparison of Measured Energy Expenditure Using Indirect Calorimetry vs Predictive Equations for Liver Transplant Recipients

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Abstract

Background: To assess the appropriate energy expenditure requirement for liver transplant (LT) recipients in South Korea, 4 commonly used predictive equations were compared with indirect calorimetry (IC). *Methods:* A prospective observational study was conducted in the surgical intensive care unit (ICU) of an academic tertiary hospital between December 2017 and September 2018. The study population comprised LT recipients expected to remain in the ICU >48 hours postoperatively. Resting energy expenditure (REE) was measured 48 hours after ICU admission using open-circuit IC. Theoretical REE was estimated using 4 predictive equations (simple weight-based equation [25 kcal/kg/day], Harris-Benedict, Ireton-Jones [ventilated], and Penn State 1988). Derived and measured REE values were compared using an intraclass correlation coefficient (ICC) and Bland-Altman plots. *Results:* Of 50 patients screened, 46 were enrolled, were measured, and completed the study. The Penn State equation showed 65.0% agreement with IC (ICC, 0.65); the simple weight-based (25 kcal/kg/day), Harris-Benedict, and Ireton-Jones equations showed 62.0%, 56.0% and 39.0% agreement, respectively. Bland-Altman analysis showed that all 4 predictive equations had fixed bias, although the simple weight-based equation (25 kcal/kg/day) showed the least. *Conclusion:* Although predicted REE calculated using the Penn State method agreed with the measured REE, all 4 equations showed fixed bias and appeared to be inaccurate for predicting REE in LT recipients. Precise measurement using IC may be necessary when treating LT recipients to avoid underestimating or overestimating their metabolic needs. (*JPEN J Parenter Enteral Nutr.* 2021;45:761–767)

Keywords

energy expenditure assessment; ICU; indirect calorimetry; liver transplant; predictive equations

Clinical Relevancy Statement

Adequate nutrition support is essential for patients after liver transplantation. However, data relating to their energy expenditure are limited. Various predictive equations have been developed, but their accuracy is being questioned. We aimed to compare the expected energy expenditure calculated by predictive equations with the energy expenditure measured by indirect calorimetry.

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Introduction

Nutrition therapy is known to improve clinical outcomes in critically ill patients.[1] However, data relating to the energy expenditure of postoperative critically ill patients, particularly liver transplant (LT) recipients, are limited, and further evaluation is required. In clinical practice, the energy expenditure of critically ill patients is primarily assessed using predictive equations.[2] However, this approach has been criticized for the inaccuracy of such equations[3-5] and the fact that they were first developed based on a heterogeneous population of healthy individuals. Therefore, indirect calorimetry (IC) remains the gold standard approach to assessing energy expenditure.

Although further evaluation is warranted, many articles, including the 2019 European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on clinical nutrition in the intensive care unit (ICU), heartily recommend the use of IC as the preferred method for the assessment of energy requirements in critically ill patients.[6-8] This is particularly important for critically ill patients because underfeeding delays the healing process, and overfeeding is commonly related to hyperglycemia, hypercapnia, and infectious complications.[9,10]

The current study aimed to compare expected energy expenditure calculated by predictive equations with the energy expenditure measured by IC and to identify the appropriate requirements for LT recipients in South Korea.

Materials and Methods

Participants

This was a prospective observational study conducted in the surgical ICU of an academic tertiary hospital between December 2017 and September 2018. The study population comprised LT recipients who were expected to remain in the ICU for >48 hours postoperatively. Exclusion criteria were as follows: (1) fraction of inspired oxygen > 0.6, (2) mean arterial pressure < 50 mm Hg, (3) heart rate ≤ 50 or ≥ 140, (4) bronchopleural fistula, (5) refusal to participate, (6) do-not-resuscitate order in place, and (6) discharge from the ICU within 48 hours.

Measurements

The resting energy expenditure (REE) was measured 36 hours after ICU admission using open-circuit IC (GE Healthcare), which was conducted by a trained respiratory therapist. Measurements were conducted with strict adherence to resting condition for accurate results: (1) any intervention that could stimulate the patient was stopped, such as regular suctioning, positioning, and hemodialysis; (2) measurements should be performed in a quiet environment with individual resting for 30 minutes prior to measurement; (3) IC was calibrated for at least 10 minutes prior to each measurement. Oxygen consumption and carbon dioxide formation were measured every second for at least 10 minutes, and REE was automatically calculated using these variables. An average of the REE measurements was used in the analysis.

Predictive Equations

The REE was estimated using 4 predictive methods: the simple weight-based equation (25 kcal/kg/day, rule of thumb) and Harris-Benedict, Ireton-Jones (for ventilated patients), and Penn State 1988 equations (Table 1).

Statistical Evaluation

The REE values derived from each predictive equation were compared with the measured REE using an intraclass correlation coefficient (ICC) and the Bland-Altman method.[11,12] ICC estimates and their 95% confidence intervals (CIs) were calculated using R 3.5.3 (R core team, 2019) program for Mac OS X based on a single rater; consistency, 2-way mixed-effects model, and $P < .05$ using a 2-tailed test were taken as an indicator of significance. Statistical analysis was performed using R 3.5.3 (R core team, 2019) program for Mac OS X. The Bland-Altman method was used to calculate the mean difference between predicted and measured REE values. Proportional bias and fixed bias were evaluated for each predictive equation.

Ethical Statement

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Asan Medical Center (IRB no. 2016-1269) and registered at http://ClinicalTrials.gov (NCT03622268). Informed consent was provided by all participants at enrollment.

Results

Of 50 patients screened during the study period, 46 were enrolled, were measured, and completed the study (Figure 1). The demographic and clinical characteristics of the study participants are shown in Table 2. The study cohort comprised 26 men and 20 women, with a mean age of 56 ± 12 years, mean body weight 62.2 ± 13.8 kg, and mean height 164.1 ± 8.3 cm; 28 patients had undergone living-donor LT, and 18 underwent deceased-donor LT. The prognostic evaluation was performed by the combined application of Model for End-Stage Liver Disease score and Acute Physiology and Chronic Health Evaluation (APACHE) II score.[13]

Table 3 shows the results of the ICC analysis evaluating the degree of agreement between the 2 methods (predicted and measured REE). The Penn State 1988 equation showed 65.0% agreement (ICC 0.65) with IC (95% CI, 0.450–0.790; $P = 3.1 \times 10^{-7}$), the simple weight-based equation (25 kcal/kg/day) showed 62.0% agreement (95% CI, 0.410–0.770; $P = 1.6 \times 10^{-6}$), the Harris-Benedict

Table 1. Predictive Equations for REE.

Predictive equations	Gender	
Rule of thumb (25 kcal/kg/day)		REE = 25*W
Harris-Benedict method	Male	REE = 66.47 + 13.75*W + 5*H − 6.755*A
	Female	REE = 665.1 + 9.563*W + 1.85*H − 4.676*A
Ireton-Jones ventilated[a]	Male	REE = 2028 − 11(A) + 5(W) + 239(T) + 804(B)
	Female	REE = 1784 − 11(A) + 5(W) + 239(T) + 804(B)
Penn State 1988		REE = (1.1 × value of HBE) + (140 × Tmax) + (32 × VE) − 5340

A, ages (y); B, burn; H, height (cm); HBE, REE calculated by Harris-Benedict method (kcal/day); REE, resting energy expenditure (kcal/day); T, trauma; Tmax, maximum body temperature in the past 24 h (°C); VE, expired minute volume (L/min); W, actual body weight (kg).
[a]The original formula checks trauma or burn but was relevant for none of our patients.

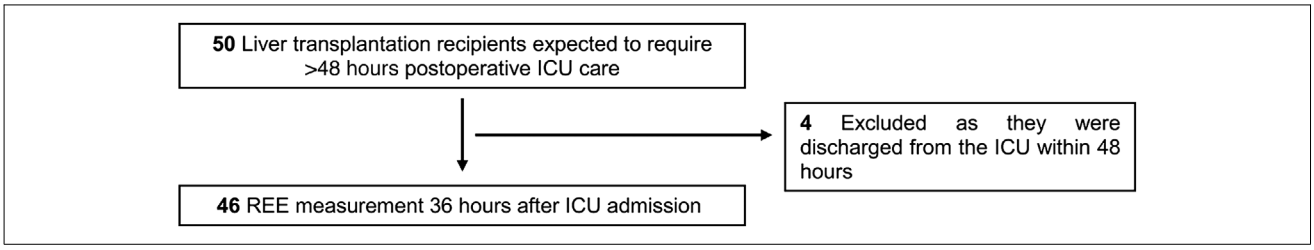

Figure 1. Patient screening, exclusions, and final measurements. ICU, intensive care unit; REE, resting energy expenditure.

Table 2. Characteristics of the LT Patients (n = 46).

Characteristcs	Mean ± SD or Number (%)
Age, years	56 ± 12
Male	26 (56.5%)
Weight, kg	62.2 ± 13.8
Height, cm	164.1 ± 8.3
BMI, kg/m^2	23.1 ± 4.7
Etiology	
HBV	17 (37.0%)
HCC	10 (21.7%)
Alcoholic LC	9 (19.6%)
FHF	5 (10.9%)
Others	15 (32.6%)
Living-donor LT	28 (60.9%)
MELD score	18.3 ± 6.6
APACHE II score	26.5 ± 12.0

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; FHF, fulminant hepatic failure; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LC, liver cirrhosis; LT, liver transplantation; MELD, Model for End-Stage Liver Disease.

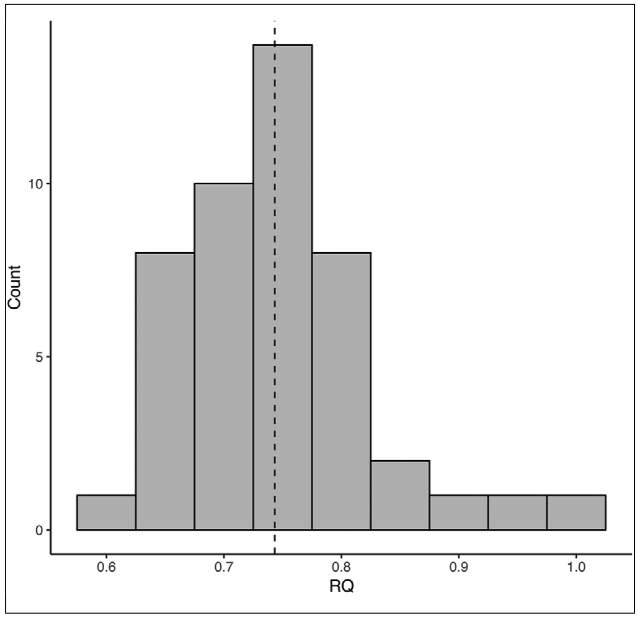

Figure 2. Histogram of respiratory quotient (RQ) measured by indirect calorimetry.

method showed 56.0% agreement (95% CI, 0.320−0.730; $P = 2.3 \times 10^{-5}$), and the Ireton-Jones showed 39.0% agreement (95% CI, 0.110−0.610; $P = .0037$).

REE values from IC and predictive equations are described in Table 4 with mean and standard deviation. Measured REE values from IC were 1513.83 ± 295.57 kcal and were 24.89 ± 4.58 kcal/kg when expressed on a per-kg weight basis. According to gender, REE/kg weight of male patients was 24.80 ± 4.61 kcal/kg, and REE/kg weight of female patients was 25.01 ± 4.65 kcal/kg. There was no significant difference in REE/kg according to gender ($P = .88$). Moreover, Pearson correlation coefficient of REE values and age was 0.08; thus, there was nearly no difference between age and gender.

Figure 2 shows the distribution of respiratory quotient (RQ) of patients. The dashed line shows the mean value. The value of RQ shows that most of the patients are under

Table 3. Intraclass Correlation Coefficients Between Measured and Predicted REE.

Predictive equation	Intraclass correlation coefficient between predicted and measured REE	*P*-value	Mean difference between measured and predicted REE, kcal
Rule of thumb	0.62	1.6×10^{-6}	−41.47 ± 280.05
Harris-Benedict method	0.56	2.3×10^{-5}	148.50 ± 247.67
Ireton-Jones (ventilated)	0.39	3.7×10^{-3}	−105.30 ± 284.72
Penn State 1988	0.65	3.1×10^{-7}	−52.49 ± 249.86

REE, resting energy expenditure.

Table 4. REE Values From Indirect Calorimetry and Predictive Equations.

Equations	
REE (kcal)	1513.83 ± 295.57
REE/kg (kcal/kg)	24.89 ± 4.58
Respiratory quotient	0.74 ± 0.08
Rule of thumb	1555.30 ± 345.63
Harris-Benedict method	1365.33 ± 226.79
Ireton-Jones (ventilated)	1619.12 ± 210.99
Penn State 1988	1566.31 ± 305.10

REE, resting energy expenditure.

metabolic perturbations in the immediate postoperative phase.

Figure 3 shows the Bland-Altman plot for the 4 predictive equations and the IC data. The mean difference between measured and predicted REE for each method was as follows: rule of thumb, −41.47 ± 280.05 kcal; Harris-Benedict method, 148.50 ± 247.67 kcal; Ireton-Jones ventilated, −105.30 ± 284.72 kcal; and Penn State 1988, −52.49 ± 249.86 kcal. In the Bland-Altman plot, all 4 predictive equations showed fixed bias, although the simple weight-based equation (25 kcal/kg/day) had the least. The Harris-Benedict method tended to underestimate REE, whereas simple weight-based equation (25 kcal/kg/day), Ireton-Jones ventilated, and Penn State 1988 tended to overestimate REE.

Discussion

Since the first human orthotopic LT in 1963, transplant surgery has rapidly evolved from an experimental procedure to a standard therapeutic modality for certain end-stage liver diseases. In South Korea, 10,581 LTs were performed at 40 centers from 1988 to 2013.[14] The liver is recognized as the most crucial metabolic organ, and the modification in nutrition status after LT has been the subject of extensive investigation.[15]

The liver plays a central role in the regulation of whole-body metabolism, primarily glucose,[16] and metabolic alterations pretransplantation and posttransplantation are well described in patients with end-stage chronic cirrhosis.[17] Plasma glucose concentrations are usually elevated in these patients because of hyperglycemia and hyperinsulinemia resulting from insulin resistance, which is caused by impaired peripheral glucose disposal.[18,19] Even after transplantation, glucose intolerance may persist for ≈5 months because of the hyperglycemic stress response to surgery and the use of immunosuppressive drugs, such as prednisone, cyclosporine, or tacrolimus.[20] Therefore, patients who are diabetic prior to transplantation will also require insulin treatment following transplantation,[21] and nutrition therapy posttransplantation must be carefully considered, particularly in critically ill patients.

Malnutrition, excessive weight gain, and metabolic disturbances are an ongoing challenge in posttransplantation management.[2] More than half of recipients experience malnutrition after LT, which is associated with increased length of stay in the ICU and the total number of days spent in the hospital.[22] However, the instability of the metabolic state and the metabolic requirements are poorly understood, and calculated energy expenditure is routinely assessed by predictive equations. As seen in the current study, predictive equations are inaccurate and biased when applied to LT recipients. Therefore, precise nutrition management after LT using IC will benefit patients by avoiding nutrition deficits and excess nutrition.

It is well established that parenteral nutrition results in deterioration of liver function, potentially leading to parenteral nutrition–associated liver disease (PNALD).[23-25] Liver grafts require time to stabilize and establish normal functioning, and LT recipients are exposed to the hazards of unnecessary parenteral nutrition during this period.[26] The pathophysiology of PNALD is not yet fully understood, but excess nutrition has been identified as 1 etiology.[27,28] Clinical studies suggest that the development of steatosis during parenteral nutrition is primarily due to excessive energy intake.[29] Overfeeding of either carbohydrate or

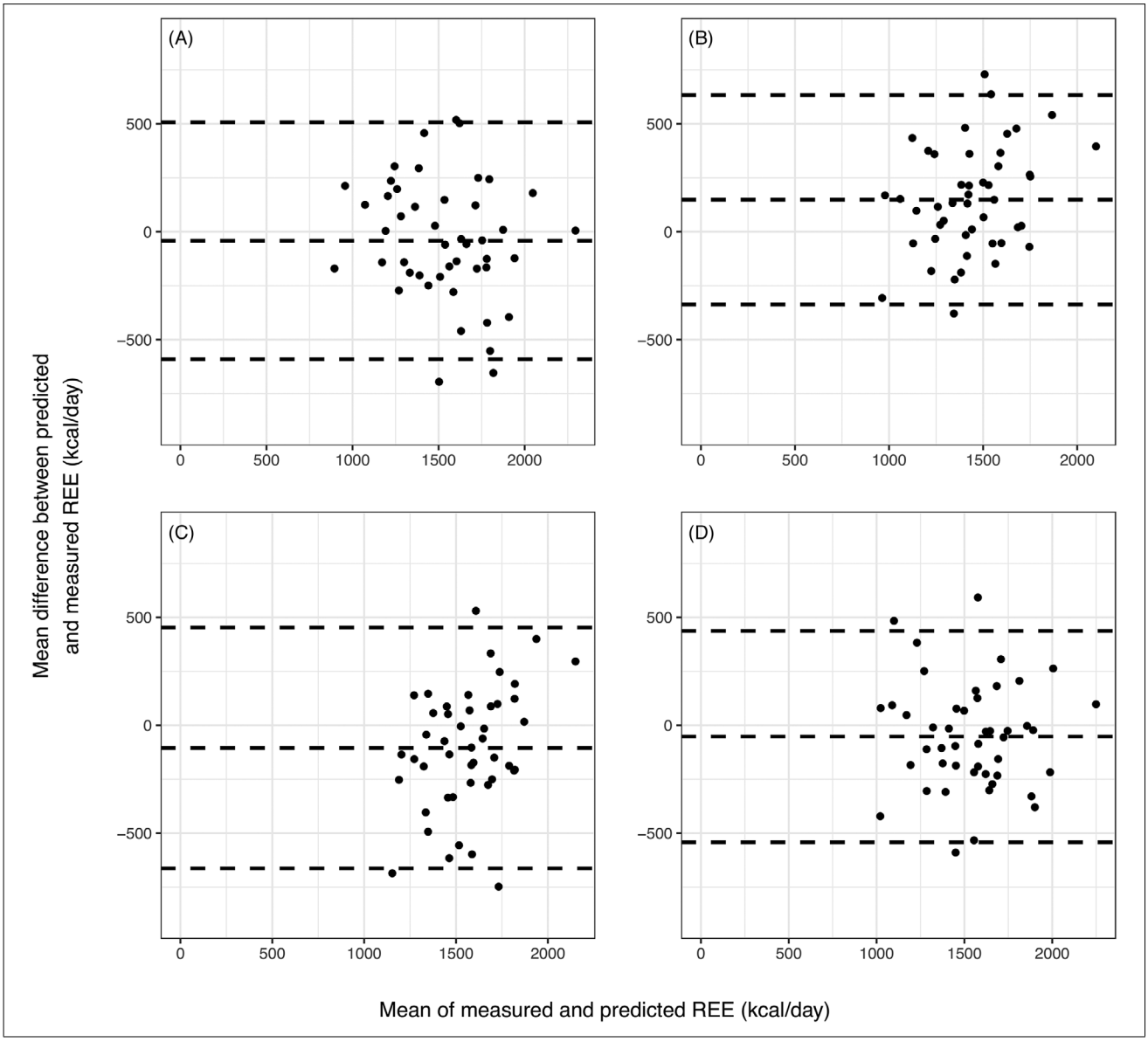

Figure 3. Bland-Altman plots comparing predictive equations and measured energy expenditure by indirect calorimetry: (A) rule of thumb (simple weight-based equation, 25 kcal/kg/day); (B) Harris-Benedict method; (C) Ireton-Jones (ventilated); (D) Penn State 1988. The middle dashed horizontal line represents absolute bias (mean difference between the 2 methods in kcal/day). The upper and lower dashed lines depict the 95% limits of agreement (mean difference ± 1.96 SD) in kcal/day. REE, resting energy expenditure.

lipid may be associated with the development of hepatic steatosis and/or cholestasis by increasing insulin concentration and the concentration of hepatic acetyl-coenzyme A.[30-33] Other studies suggest that high levels of amino acids may be directly hepatotoxic, as they affect the canalicular membrane of the hepatocyte.[34,35] An association between parenteral energy intake > 70% of the calculated energy requirement and an increased propensity for PNALD has been demonstrated; therefore, parenteral energy intake consistently greater than metabolic expenditure may also be deleterious to the liver.[36,37] The current study population is unique because the patients not only were critically ill but also received parenteral nutrition during the period in which the graft is establishing normal function. The results of our study show that nutrition support using predictive equations is associated with a high possibility of providing excess energy and, therefore, exposing LT recipients to the risk of PNALD.

In the absence of IC, a prediction equation is the best alternative. Predictive equations are used to calculate the

energy expenditure of patients in the ICU because of the simplicity of this approach and the lack of alternatives. However, each equation has limitations to replace measured REE, especially in critically ill patients who are unstable metabolically. Harris-Benedict equation was derived from IC on a healthy population adjusted for weight, height, age, and sex. Harris-Benedict equation is unreliable when applied to critically ill patients. Ireton-Jones and Penn State are worthy of consideration for critically ill patients undergoing mechanical ventilation. Penn State equation utilized the Harris-Benedict equation with minute ventilation and maximum temperature over 24 hours. It was the first equation to consider energy requirements over time in critically ill patients. However, these equations still cannot be used in specific populations.[3,38,39] Therefore, clinicians are reluctant to use predictive equations in the ICU, where complex scenarios may introduce variables that will influence the results, such as daily changes in body weight, body temperature, level of nutrition, presence of sepsis, level of sedation, and differing therapeutic agents.[40]

However, avoiding nutrition deficits or overnutrition is particularly crucial during acute illness, and targeted energy prescription in critically ill, dynamic, complicated patients by IC has shown improvements in morbidity and mortality.[41,42] IC is currently the gold standard used to measure REE, but this approach is not available in most clinical settings.[9] However, as many articles (including the 2019 ESPEN guideline on clinical nutrition in the ICU and 2016 American Society for Parenteral and Enteral Nutrition [ASPEN] guidelines) recommend the use of IC in ICU practice,[6-8,43] optimal nutrition support directed by IC will soon be an integral part of ICU care. The current study has demonstrated that the current practice of using predictive equations in LT recipients lacks sufficient accuracy, and therefore, further evaluation of IC is warranted in this patient group.

The main limitation in the present study was that measurement using IC did not change the energy prescription given to the patient and there was also a lack of data regarding clinical outcomes. Nonetheless, this study suggests that using IC rather than predictive equations, which are limited by inherent bias, will improve the clinical outcomes of LT recipients whose metabolic state is not stable.

Conclusions

Although predicted REE calculated using the Penn State 1988 method agreed with the measured REE, all 4 predictive equations showed a fixed bias and appeared to be inaccurate for predicting REE in this cohort of LT recipients. Therefore, precise measurements using IC may be helpful when treating critically ill patients to avoid underestimating or overestimating their metabolic needs.

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Statement of Authorship

S. J. Lee drafted the manuscript and contributed to the analysis of data; H.-J. Lee contributed to the acquisition and the interpretation of the data; Y.-J. Jung contributed to the acquisition of the data; M. Han contributed to the interpretation of the data; S.-G. Lee contributed to the acquisition of the data; S.-K. Hong contributed to the conception and design of the research. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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