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Coefficient of Determination between Estimated and Measured Renal Function in Japanese Patients with Sarcopenia May Be Improved by Adjusting for Muscle Mass and Sex: A Prospective Study

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Creatinine (Cr) levels are strongly affected by muscle mass, and the estimated glomerular filtration rate (eGFR), a measure based on serum creatinine (SCr), is often overestimated in patients with sarcopenia. To evaluate the coefficient of determination ($R^2$) between eGFR and the actual measured value, we performed a linear regression analysis of a modified GFR (mGFR: measured Cr clearance $\times$ 0.715) and various renal function estimates adjusted for muscle mass in 19 patients with sarcopenia. The eGFR values based on SCr (eGFRcr) were higher than those based on mGFR, although a high $R^2$ (0.704; $p<0.001$) was found between these values. There was no deviation between eGFR based on serum cystatin C (eGFRcys) and mGFR, although the $R^2$ value 0.691 was equivalent to that of eGFRcr. In the equation used to calculate eGFRcr not adjusted for body surface area (mL/min), muscle mass parameters obtained from bioelectrical impedance analysis were used instead of actual body weight to recalculate the eGFRcr. The $R^2$ between this eGFRcr and mGFR did not improve, although there was less deviation. However, assuming that all patients were female by using female coefficients for all patients, the $R^2$ between eGFRcr-fcc (eGFRcr with female coefficient correction) and mGFR improved and was the highest (0.808) on substitution of appendicular skeletal muscle mass. The correlation between eGFRcr-fcc and mGFR improved over eGFRcys when muscle mass was substituted for body weight in the equation used to estimate eGFR in patients with sarcopenia and sex differences were removed.

Key words estimated glomerular filtration rate formula; sarcopenia; muscle mass; serum creatinine; serum cystatin C

INTRODUCTION

To devise a safe and effective drug administration plan, it is important to have an accurate knowledge of both the urinary excretion rate of the drug and the patient's renal function. Inulin clearance is the gold standard for measuring glomerular filtration rate (GFR) and calculates renal function accurately. However, this protocol is cumbersome for both patients and doctors, so it is not realistic for use in routine clinical practice. Instead, renal function is usually estimated using serum creatinine (SCr) values obtained from blood tests when planning medical therapy. However, there is a problem in that the SCr value is affected not only by renal function but also by muscle mass.

Creatinine (Cr) is the final metabolite of creatine and is found mainly in skeletal muscle. SCr decreases with decreasing muscle mass. According to Levy et al., several SCr-based equations for deriving the estimated GFR (eGFR) have been developed, including the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) methods and the equation for determining the eGFR from serum creatinine (eGFRcr) developed by the Japanese Society of Nephrology. However, in elderly patients, who have lost a considerable amount of muscle mass, estimates of renal function based on SCr tend to be greater than the actual values. Inaccurate estimates of renal function increase the risk of overdose.

Serum cystatin C (SCysC) is a useful marker for estimating renal function in patients who have lost muscle mass. However, the cost of measuring SCysC is high and it can only be performed once every 3 months under the Japanese health insurance system. Furthermore, there are several conditions that affect SCysC, such as end-stage kidney disease, thyroid dysfunction, and steroid administration. When one of these situations occurs in patients with sarcopenia, estimation of renal function on the basis of SCysC alone can be problematic, so other methods are needed. This can also be a problem because frequent measurements become necessary in patients with acute kidney injury, which elderly patients are prone to because of conditions such as dehydration. If the issue...
of the effect of muscle mass can be addressed, SCr would become a useful marker of renal function because it is more cost-effective, thus, allowing measurements to be taken more frequently in situations when the SCysC value cannot be used for whatever reason.

In obese patients, use of muscle mass instead of body weight (BW) to estimate creatinine clearance (CCr) has been reported to improve the estimation by yielding values closer to the actual measured values. Similarly, in patients with reduced muscle mass, it may be possible to improve the coefficient of determination \( R^2 \) between the estimated and actual values by using muscle mass in the equation. However, there are few reports of significant improvement in estimates of renal function obtained by this method. Sarcopenia, that is, the decline in skeletal muscle mass that occurs with aging, is likely to progress more rapidly and cause more morbidity in elderly patients if they have chronic kidney disease. Therefore, we hypothesized that there would be a discrepancy between the measured and predicted indicators of kidney function in patients with sarcopenia.

In this study, we investigated the effect of muscle mass on the \( R^2 \) value between eGFRcr, a method used widely to estimate renal function in the clinical setting, and the actual measured values of renal function indices in urine samples collected from elderly patients with sarcopenia. Also, in this study, we did not aim to devise a clinically adaptable equation for estimation of renal function.

MATERIALS AND METHODS

Study Design/Subjects
This prospective pilot study was approved by the ethics committees of Tamana Regional Health Medical Center (Kumamoto, Japan) and the epidemiology/general section of the Department of Public Health, Faculty of Life Sciences, Kumamoto University. All experiments were carried out in accordance with the guidelines stated in the 1964 Declaration of Helsinki. Patients who were admitted to the Tamana Regional Health Medical Center between May 2017 and August 2017 were enrolled in the study if they had a Barthel Index <50, were aged >65 years, had an indwelling catheter, and provided written informed consent. The exclusion criteria were as follows: ineligible for bioelectrical impedance analysis (BIA; i.e., patients with a pacemaker, defibrillator, or artificial joints; eGFR <30 mL/min/1.73 m²; acute kidney injury; progressive cancer; terminal cancer; myopathy (e.g., muscular dystrophy); and dialysis. One of 20 patients identified was excluded because of terminal cancer, leaving 19 patients for inclusion in the study (Table 1).

At the beginning and end of the 24-h urine collection period, blood was sampled, body composition was analyzed by the direct segmental multi-frequency BIA method with the InBody S10 body water analyzer (InBody, Seoul, Korea), and subjective global assessment (SGA) parameters were measured.

Measurement of SCr and SCysC Concentrations
SCr and urinary Cr were measured by the enzymatic method using a Cygnus auto CRE device (Shino-Test Corporation, Tokyo, Japan) and measurements were obtained with the Labospect 008 automatic analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan). CysC was measured by the colloidal gold agglutination method using Nescote GC Cystatin C (Alfresa Pharma Corporation, Osaka, Japan) and measurements were obtained using the JCA-BM-8000 series photometer (Jeol Ltd., Tokyo, Japan).

Actual Measurement of CCr and Calculation of Modified GFR
Urine collected in the bag was disposed of at the beginning of the 24-h collection period. Measured CCr (mCCr) was calculated from urine Cr concentration, urine volume, and SCr concentration measured on the same day (1). Modified GFR (mGFR) was calculated by multiplying mCCr by 0.715 (2). For convenience, this value was used as the GFR in this study.

\[
mCCr(\text{mL/min}) = \frac{Ucr(\text{mg/dL}) \times V(\text{mL/d})}{SCr(\text{mg/dL}) \times 24 \times 60}
\]  

Table 1. Characteristics of the Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (year)</th>
<th>Height (cm)</th>
<th>Body weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>Barthel index</th>
<th>Reason for administration</th>
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</thead>
<tbody>
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<td>82</td>
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<td>0</td>
<td>Aspiration pneumonia</td>
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<td>0</td>
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<td>0</td>
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<td>35</td>
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<td>142.0</td>
<td>32.4</td>
<td>16.1</td>
<td>5</td>
<td>Urinary tract infection</td>
</tr>
</tbody>
</table>

BMI, body mass index.
Estimation of Muscle Mass Using the BIA Method and SGA  Body composition was measured by the direct segmental multi-frequency BIA method using the InBody® S10 either at the beginning or the end of the 24-h urine collection period in the recumbent position. Fat free mass (FFM), skeletal muscle mass (SM), and appendicular skeletal muscle mass (ASM) were measured.

Next, the SGA parameters, namely, arm circumference (AC), triceps skinfold thickness (TSF), and calf circumference (CC), were measured. Using AC and TSF, arm muscle circumference (AMC) and arm muscle area (AMA) were calculated using the following Eqs. 3 and 4. Linear regression analysis was performed on each parameter of AC, AMC, AMA, and CC with FFM, SM, and ASM from BIA. SGA measurements (cm) were then converted to muscle mass parameters (kg):

\[
AMC(cm) = AC(cm) - TSF(cm) \times \pi 
\]  

\[
AMA(cm^2) = AMC^2/4\pi 
\]  

Calculation of Renal Function Estimates  For renal function estimates, eGFRcr was obtained using Eq. 5, and the eGFR based on SCysC (eGFRcys) was obtained using Eq. 6:

\[
eGFRcr (mL/min/1.73m^2) = 194 \times SCr^{-1.094} \times \text{Age}^{-0.287} \times \text{if female } 0.739 
\]  

\[
eGFRcys (mL/min/1.73m^2) = \{104 \times SCysC^{-1.019} \times 0.996^{\text{kg}} \times \text{if female } 0.929\} - 8 
\]  

GFR is presented in mL/min/1.73 m², and the body surface area (BSA) of each patient was calculated using the Du Bois Eq. 7 to remove the BSA correction (8):

\[
BSA(m^2) = BW^{0.425} \times \text{Height}^{0.725} \times 0.007184 
\]  

\[
eGFR(mL/min) = eGFR (mL/min/1.73m^2) \times BSA/1.73 
\]  

From here onwards, mL/min, representing individual renal function, is used in place of mL/min/1.73 m² as the units for eGFRcr and eGFRcys.

Linear regression analysis was carried out on eGFRcr (mL/min) and eGFRcr (mL/min). BSA correction was removed in eGFRcr by applying BSA values obtained by substituting FFM, SM, and ASM measured using the BIA method in the Du Bois Eq. 7 in place of BW. Linear regression analysis was also performed on the eGFRcr and mGFR, where all patients were assumed to be male (i.e., female coefficients were not applied). Similarly, linear regression analysis was performed on eGFRcr and mGFR where eGFRcr was modified by muscle mass parameters estimated from AC, AMC, AMA, and CC obtained from SGA, as in the BIA method. Next, the correlation coefficients were tested by assuming that all patients were female (eGFRcr female corrected coefficient: eGFRcr-fcc). That meant not taking into account a sex difference by using a female coefficient for all patients. Also, the correlation coefficients were tested by assuming that all patients were male (eGFRcr not using coefficient: eGFRcr-nuc). R² was equal in value upon calculation whatever coefficients were applied uniformly to all patients.

Metrics for comparison of methods were mean error (ME) (9), mean absolute error (MAE) (10), root mean squared error (RMSE) (11), percentage of patients within 15% of mGFR (within 15% of mGFR) (12), and percentage of patients within 30% of mGFR (within 30% of mGFR) (13). These were calculated as follows:

\[
a_i = \text{estimated GFRcr}, \quad b_i = \text{mGFRcr} 
\]  

\[
ME = \frac{1}{n} \sum_{i=1}^{n} (a_i - b_i) 
\]  

\[
MAE = \frac{1}{n} \sum_{i=1}^{n} |a_i - b_i| 
\]  

\[
RMSE = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (a_i - b_i)^2} 
\]

Count of patients within 15% of mGFR

\[
= \text{if } |a_i - b_i| < b_i \times 0.15 
\]

Count of patients within 30% of mGFR

\[
= |a_i - b_i| < b_i \times 0.3 
\]

Statistical Analysis  The data are shown as the mean ± standard deviation (S.D.). Estimated and actual measured values were subjected to linear regression analysis using Excel 2016 software (Microsoft Corp., Redmond, WA, U.S.A.). The correlation was evaluated based on the Pearson correlation coefficient (R), and the effect of the explanatory variable was evaluated based on the coefficient of determination (R²). Welch’s t-test was used to examine differences in means. The significance level was 5% on both sides. Sample size was determined based on the number of cases in the study center within the research institution that met the eligibility criteria.

RESULTS  Mean age was 82.5 ± 8.1 years, mean body mass index was 17.5 ± 8.1 kg/m², and mean Barthel Index was 10.3 ± 12.0 (Table 1). Eighteen of the 19 patients had sarcopenia according to the Asian Working Group for Sarcopenia criteria. The skeletal muscle index of one woman (case #19) who did not have sarcopenia was 6.0 kg/m² and the Barthel Index was 5. In clinical terms, this case was regarded as being almost equivalent to sarcopenia. The test values and measurements for 19 of the 20 patients whose data were collected were available for analysis (Table 2). Mean SCr was 0.6 ± 0.3 mg/dL and mean CysC was 1.35 ± 0.4 mg/L.

Accuracy of Each Renal Function Estimate Equation in Patients with Sarcopenia  In the regression analysis between eGFRcr and mGFR (mL/min), the R² value was 0.704 (p < 0.001, Fig. 1a); the values for eGFRcys and mGFR (mL/min) were 0.691 (p < 0.001, Fig. 1b). In all patients, the
renal function estimates using parameters with reflected muscle mass

as parameters that directly reflect decreases in muscle mass, FFM, SM, and ASM (skeletal muscle parameters obtained by the BIA method) were substituted for actual BW in the eGFRcr estimate equation. the coefficient of determination was investigated between this eGFRcr and mGFR (mL/min). upon substitution, the $R^2$ value was 0.711 for eGFRcr (FFM; $p < 0.001$), 0.708 for eGFRcr (SM; $p < 0.001$), and 0.678 for eGFRcr (ASM; $p < 0.001$) (Figs. 2b–d). by substituting FFM or SM with BW, the $R^2$ value increased and the deviation was minimized. the ME, MAE and RMSE were ASM < SM < FFM < BW and these metrics were minimized by ASM (Table 3).

next, eGFRcr-fcc was calculated by using female coefficients for all patients, that is, by assuming that all patients were female (not taking a sex difference into account), and correlation analysis was performed between eGFRcr vs. mGFR (mL/min). upon substitution with BW, FFM, SM, and ASM respectively, the $R^2$ value was 0.741 ($p < 0.001$) for eGFRcr-fcc (BW), 0.784 ($p < 0.001$) for eGFRcr-fcc (FFM), 0.799 ($p < 0.001$) for eGFRcr-fcc (SM), and 0.808 ($p < 0.001$) for eGFRcr-fcc (ASM). the highest $R^2$ value was for eGFRcr-fcc (ASM) (Figs. 3a–d). as with the previous result, the ME, MAE and RMSE were minimized by ASM (Table 3). instead of calculating estimates by taking sex differences into account, the $R^2$ value increased for both eGFR vs. mGFR when female coefficients were applied to all patients.

renal function estimates using SGA-reflected muscle mass parameters

correlations between FFM, SM, and ASM obtained by the BIA method, and AC, TSF, AMA, and CC, which are indices of muscle mass, are shown in Table 4. the $R^2$ value was highest for CC. by using the regression formula, estimated SM (kg) was calculated from CC (cm), and the determination coefficient between eGFRcr (CC) and

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Table 2. Measurements of Renal Function and Muscle Mass Parameters Using Bio-electrical Impedance Analysis and Subjective Global Assessment

<table>
<thead>
<tr>
<th>Case</th>
<th>SCr (mg/dL)</th>
<th>SCysC (mg/L)</th>
<th>Cr excretion (mg/d)</th>
<th>mCCr (mL/min)</th>
<th>mGFR (mL/min)</th>
<th>BIA</th>
<th>SGA</th>
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<td>SM</td>
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<td>AC</td>
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AC, arm circumference; ASM, appendicular skeletal muscle mass; BIA, bio-electrical impedance analysis; CC, calf circumference; FFM, fat free mass; SCr, serum creatinine; SCysC, serum cystatin C; SM, skeletal muscle mass; SGA, subjective global assessment; TSF, triceps skinfold thickness.
mGFR (mL/min) was investigated. As in the normal case, the $R^2$ value for eGFRcr (CC) was 0.725 ($p < 0.001$) when the sex coefficients were changed (Fig. 4a), but when considering there to be no sex difference (i.e., using female coefficients for all patients), the $R^2$ value for eGFRcr-fcc (CC) increased to 0.753 ($p < 0.001$, Fig. 4b). Also, ME, MAE, RMSE were the smaller when eGFRcr-fcc (CC) was calculated than eGFRcr (CC) and eGFRcr-nuc (CC). Estimated eGFRcr-fcc (CC) increased when all patients were assumed to be female and differed markedly from mGFR.

**DISCUSSION**

In this study, eGFRcys was the best estimation method in patients with sarcopenia, considering both the $R^2$ value and deviation from mGFR, which is consistent with conventional reports. However, eGFRcys is rarely used clinically in Japan. Therefore, we investigated the effect of muscle mass on the $R^2$ value between eGFRcr and modified GFR determined using samples from elderly patients with sarcopenia. By using FFM, SM, and ASM measured with the BIA method instead...
of using BW, there was less deviation in renal function estimation. However, this simple substitution was not sufficient to improve the correlation between eGFRcr and mGFR when compared to the case where BW was used for estimation (Figs. 2a–d). Interestingly, the correlation became greater than that between eGFRcys vs. mGFR when sex differences were eliminated by using female coefficients for all patients (Figs. 3a–d). These results may suggest that an eGFRcr equation in which muscle mass was accounted for directly would reduce the influence of sex difference. A previous study of the relationship between inulin clearance and variables commonly used to predict GFR found that the relationship between patient sex and inulin clearance was decreased when ASM was accounted for.\(^{20}\) The same effect may occur when the eGFRcr developed by the Japanese Society of Nephrology is used. Furthermore, the SGA method used to assess gain in muscle mass was evaluated from the aspect of popularization of the BIA. Use of estimated SM (kg) calculated from the CC, which is a surrogate marker of sarcopenia,\(^ {21}\) led to an increased \(R^2\) for eGFRcr, and this was further increased when female coefficients were not used (Figs. 4a, b). These findings suggest that renal function in patients with sarcopenia may be estimated more accurately even in medical institutions that do not use the dual-energy X-ray absorptiometry or BIA method for obtaining body composition data.

The values of ME, MAE and RMSE became small in order of BW, FFM, SM, ASM. These muscle parameters also became small in order of BW, FFM, SM, ASM. So, it was possible overestimation of kidney function got balanced out by small muscle values. Therefore, effective range of muscle mass and SCr need to be investigated in other background patients such as non-sarcopenic elderly people.

Also, we investigated several coefficients other than 0.739 (female coefficient). When eGFRcr-fcc (ASM) was calculated using coefficient 0.7 on all patients, the regression equation was the closeted to \(y = x\) (no data was shown). Ratios of ASM between our study group and non-sarcopenia elderly Japanese groups reported by Kitamura \textit{et al.} were 0.64–0.72 (60 and 70s groups).\(^ {22}\) These trends suggest possibility that smaller coefficient than 0.739 (female coefficient) would be suitable for patients with low muscle mass such as sarcopenia.

In this study, significant sex-related differences were not found when the Welch’s t-test was applied using FFM, SM, ASM, and FM of BW, or between SCr and SCysC (mean

<table>
<thead>
<tr>
<th>BIA</th>
<th>AC (cm) (R^2)</th>
<th>AC (cm) p</th>
<th>AMC (cm) (R^2)</th>
<th>AMC (cm) p</th>
<th>AMA (cm(^2)) (R^2)</th>
<th>AMA (cm(^2)) p</th>
<th>CC (cm) (R^2)</th>
<th>CC (cm) p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFM</td>
<td>0.182</td>
<td>0.0682</td>
<td>0.258</td>
<td>0.0264</td>
<td>0.233</td>
<td>0.0364</td>
<td>0.460</td>
<td>0.0014</td>
</tr>
<tr>
<td>SM</td>
<td>0.211</td>
<td>0.0481</td>
<td>0.291</td>
<td>0.0171</td>
<td>0.264</td>
<td>0.0246</td>
<td>0.477</td>
<td>0.0011</td>
</tr>
<tr>
<td>ASM</td>
<td>0.249</td>
<td>0.0295</td>
<td>0.300</td>
<td>0.0151</td>
<td>0.284</td>
<td>0.0187</td>
<td>0.450</td>
<td>0.0017</td>
</tr>
</tbody>
</table>

AC, arm circumference; AMC, arm muscle circumference; AMC, arm muscle circumference; ASM, appendicular skeletal muscle mass; BIA, bio-electrical impedance analysis; CC, calf circumference; FFM, fat free mass; SGA, subjective global assessment; SM, skeletal muscle mass.
Scr was 0.70 ± 0.33 mg/dL in men and 0.52 ± 0.14 mg/dL in women, \( p = 0.22 \), and mean SCysC was 1.42 ± 0.51 mg/L in men and 1.31 ± 0.36 mg/L in women, \( p = 0.62 \). It is generally assumed that there is a sex-related difference in muscle mass in elderly people, although such differences in body composition were likely to have diminished in the patients with sarcopenia recruited for this study. When female coefficients were used for all patients, the \( R^2 \) value between mGFR was the highest for eGFRr-fcc (ASM), and this is consistent with the report by Macdonald et al. in which ASM derived using the BIA method improved the estimation of GFR.\(^\text{22} \) The value of ME, MAE and RMSE of eGFRr-fcc trend to become small with sarcopenia.\(^\text{25} \) Moreover, sarcopenia is more prevalent in elderly people, although such differences in body composition may have diminished in elderly patients with sarcopenia who are bedridden, sarcopenic obesity, that is, a parallel reduction in muscle mass and an increase in body fat percentage, could occur when patients receive tube feeding or total parenteral nutrition, which could reduce the sex-related difference in body composition.

Only 19 subjects were enrolled in this study. Therefore, a further study in a larger number of patients and application of appropriate coefficient corrections is needed to improve the practicability of this method. As noted in Materials and Methods, there was no change in the \( R^2 \) value whatever coefficient used for all patients. eGFRr-fcc (ASM) with using coefficient 0.7 was the similar to \( y = x \) (\( R^2 \) was not change), but that coefficient is not generally. Therefore, so we need to investigate the coefficient values from patients who have more widely background to know more practical coefficient. This study had some limitations. We assessed mGFR (＝mCcr × 0.715), not inulin clearance, as a measure of renal function. Therefore, the effect of renal tubular secretion of Cr as a result of hypoalbuminemia\(^\text{29} \) or the presence of end-stage kidney disease\(^\text{30} \) may have become more significant. Furthermore, the number of subjects was limited, so the possibility that sex-related differences in body composition may have diminished by chance in this study cannot be excluded.

### CONCLUSION

By substituting muscle mass parameters obtained using the BIA method or SGA in place of BW when estimating renal function and by removing sex-related differences in GFR estimates, the \( R^2 \) value between eGFRr and mGFR became greater than that between eGFRcys and mGFR. The \( R^2 \) value was greatest and the deviation was smallest between eGFRr-fcc and mGFR when applying the ASM substitution in the BIA method. Similarly, eGFRr modified by CC of SGA was strongly correlated with mGFR, which may make this method practically useful. The results of our study suggest that measuring muscle mass in elderly patients with sarcopenia is possibly useful because it increases the correlation with the actual measured kidney function. However, it would be necessary to include patients of various backgrounds when applying this regression model in the clinical setting when using muscle mass.
parameters obtained by the BIA method or SGA for estimation of renal function.

Further study that includes multiple correlation analysis, correction of deviation from measured values, and a larger number of subjects is required.

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Conflict of Interest The authors declare no conflict of interest.

REFERENCES


