Comparative analysis of pre- and post-dialysis albumin levels as indicators of nutritional and morbidity and mortality risk in hemodialysis patients

Cláudia Maria Costa de Oliveira
Daniela Costa de Oliveira Santos
Rosa Salani Mota
Maria Luiza Pereira

1Faculdade de Medicina Christus.
2Universidade Federal do Ceará – UFC.

Introduction: Pre-dialysis albumin is likely to be falsely low due to a dilution effect, making its usefulness in assessing protein status questionable. Objectives: The purpose of this study was to assess whether post-dialysis albumin would be a better marker of malnutrition and risk of mortality, when compared to pre-dialysis albumin. Methods: We evaluated the correlation between pre- and post-dialysis albumin and the following parameters: body mass index (BMI), adequacy of muscle arm circumference (MAC) and tricipital skinfold (TS) to the 50th percentile (P50), C-reactive protein (CRP), phase angle (PA), protein equivalent of nitrogen appearance (PNA), the Kt/V index of dialysis adequacy, and the hydration status (Pearson’s correlation coefficient). Agreement in the nutritional status according to pre- and post-dialysis (post-HD) albumin and PA was estimated according to the Kappa (K) coefficient (Bland-Altman). Results: A total of 58 haemodialysis (HD) patients were included in this study (30 female; mean age: 49 years). BMI, PA and CRP had a significant correlation with pre- and post-HD albumin, while MAC and PNA correlated only with post-HD albumin. Agreement in the diagnosis of malnutrition according to PA < 5 and pre- and post-HD albumin < 3.2 g/dL was regular (K = 0.432). When using an albumin cut-off value of 3.7 g/dL for malnutrition (mild malnutrition or risk of malnutrition), the diagnosis was concordant only in the post-HD period (K = 0.544). Conclusions: Post-dialysis albumin levels may be a better marker of protein status and mortality risk in cases of mild malnutrition or risk of malnutrition and in patients with low/medium mortality risk.

Authors
Marcos Kubrusly
Cláudia Maria Costa de Oliveira
Daniela Costa de Oliveira Santos
Rosa Salani Mota
Maria Luiza Pereira

1Faculdade de Medicina Christus.
2Universidade Federal do Ceará – UFC.

Submitted on: 06/17/2011
Approved on: 11/21/2011

Correspondence to:
Cláudia Maria Costa de Oliveira
Rua Professor Jacinto Botelho 500,
Bairro Guararapes
Fortaleza – CE – Brazil
Zip code 60810-050
E-mail: claudiadrl@gmail.com

This study was undertaken at the Ceará State University – UECE and UFC – Fortaleza – CE – Brazil.

The authors report no conflict of interest.
Pre-dialysis fluid overload may be a confounding factor when evaluating albumin levels.

**Keywords:** Serum albumin. Nutritional status. Renal dialysis.

---

**INTRODUCTION**

Protein-energy malnutrition is common in patients on hemodialysis (HD) and has several causes.

Although there is agreement on the advisability of periodically assessing the nutritional status of HD patients, there is no single method considered the gold standard for this purpose.

Albumin is the most commonly used biochemical marker, as it is easy to measure and it is associated with clinical events in this population. Several studies have shown a strong correlation between low albumin levels and increased morbidity and mortality.

Fluid overload is a non-nutritional cause of hemodilution-related hypoalbuminemia. Because blood for albumin determination is collected during the pre-dialytic period, when most patients have fluid retention, the consequent hemodilution may lead to erroneous diagnosis and management, something that has already been shown to affect hematocrit and hemoglobin determinations.

Several authors have suggested that the pre-HD albumin level be used as a marker of the hydration status, and not of the nutritional status, even questioning whether the nutritional status and mortality risk would be better assessed with the post-HD albumin level.

The purpose of this study was to analyze the interference of the fluid overload state (modifiable factor) with the albumin-based assessment of the nutritional status and mortality risk stratification.

**METHODS**

We included 58 patients with end-stage chronic kidney disease (ESCKD), on HD in a single center of Fortaleza – CE – Brazil. The following were exclusion criteria: age under 18 years; less that 3 months on HD; active neoplastic disorder; amputated limb; stroke sequelae; dependence on a wheelchair; impossibility to have weight and height measured; refusal to sign the informed consent.

In this cross-sectional study, all the patients underwent: laboratory work-up, anthropometric assessment and electrical bioimpedance.

**LABORATORY VARIABLES**

Fasting serum albumin was measured before and after HD, with bromocresol red (normal > 3.7 g/dL). Clinical interpretation of the albumin values was based on the ESRD, Clinical Performance Measures Project classification: < 3.2 g/dL – malnutrition; < 3.4 g/dL - hypoalbuminemia; < 3.7 g/dL – malnutrition risk. As for morbidity and mortality, we used Lowrie & Lew’s classification: high-risk: albumin < 3.2; medium-risk: albumin 3.2–3.7; low-risk: albumin > 3.7. In order to use serum albumin values equivalent to those of the aforementioned classification, we subtracted 0.3 g/dL from the values obtained with bromocresol red, once the method used by Lowrie and Lew was bromocresol green.

High-sensitivity C-reactive protein (hs-CRP) was measured before HD, with turbidimetry (normal < 3 mg/L).

HD adequacy was assessed with the dialysis adequacy index (Kt/V) and the protein equivalent of nitrogen appearance (PNA) was used to obtain an indirect estimate of protein intake.

**ANTHROPOMETRIC VARIABLES**

The anthropometric indices used were: height, pre- and post-HD weight, body mass index (BMI), tricipital skinfold (TS), mid-arm circumference (MAC), arm muscle circumference (AMC) and percentage of adequacy of the TS and AMC to the 50th percentile (P50)

The anthropometric measurements were obtained after the dialysis session, with the patient’s dry weight, in the contralateral limb to the one with the arteriovenous fistula, with a Lange caliper and a flexible metric tape.

The anthropometric measurements were entered into the Nutwin nutrition support software, version
1.5, for calculation of the adequacy of the TS and AMC to the P50.

**Electrical Bioimpedance**

Bioimpedance (BIA) was measured thirty minutes after the end of HD, with a monofrequency BIA analyzer (RJL Systems®, Clinton Township, Michigan, USA). Resistance and reactance were directly measured, and the phase angle (PA) was calculated from these two measurements (arc tangent of reactance/resistance x 180 degrees/π). The patients with a PA < 5 were considered to have malnutrition.

**Statistical Analysis**

While the variables with a normal distribution were compared with Student’s t test, those with an abnormal distribution were compared with Mann-Whitney’s test. Pearson’s correlation coefficient was calculated to assess the linear correlation between the parametric variables investigated, and McNemar’s test to assess the correlation between the diagnoses of malnutrition and absence of malnutrition.

Agreement between the methods was assessed through Kappa (K) coefficient, with Altman’s interpretation: K < 0.20: poor agreement; 0.21 ≤ K ≤ 0.40: regular agreement; 0.41 ≤ K ≤ 0.60: moderate agreement; 0.61 ≤ K ≤ 0.80: good agreement and K > 0.80: very good agreement.

The SPSS (Incorporation Statistical Package for the Social Science for Windows Student version) software, version 14.0, was used for the statistical analysis.

**Results**

**Characteristics of the Study Population**

58 patients were evaluated (51.7% female; mean age 49.2 years). The demographic, anthropometric, laboratory and BIA characteristics are shown in Table 1.

**Effect of the Hydration Status on the Serum Albumin Levels**

There was a significant increase of the post-HD serum albumin (3.9 ± 0.73 g/dL) in relation to pre-HD levels (3.4 ± 0.55 g/dL). This increase positively correlated with intradialytic weight loss (r = 0.44, p < 0.001) (Figure 1). This correlation was similarly observed when patients with CRP > 3 mg/L were excluded from analysis (r = 0.50, p < 0.01).

---

**Table 1**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.22</td>
<td>14.85</td>
<td>18.00</td>
<td>77.00</td>
</tr>
<tr>
<td>Time on HD</td>
<td>4.27</td>
<td>2.50</td>
<td>0.42</td>
<td>9.5</td>
</tr>
<tr>
<td>Interdialytic weight gain</td>
<td>1.93</td>
<td>1.04</td>
<td>-0.03</td>
<td>4.10</td>
</tr>
<tr>
<td>Dialysis duration (hours)</td>
<td>3.95</td>
<td>0.18</td>
<td>3.00</td>
<td>4.00</td>
</tr>
<tr>
<td>Weight</td>
<td>56.51</td>
<td>12.35</td>
<td>32.5</td>
<td>90.5</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.44</td>
<td>0.3</td>
<td>0.9</td>
<td>2.1</td>
</tr>
<tr>
<td>PNA</td>
<td>1.38</td>
<td>0.32</td>
<td>0.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Height</td>
<td>156</td>
<td>10</td>
<td>140</td>
<td>177</td>
</tr>
<tr>
<td>BMI</td>
<td>22.89</td>
<td>3.61</td>
<td>15.9</td>
<td>31.0</td>
</tr>
<tr>
<td>MAC</td>
<td>26.28</td>
<td>3.78</td>
<td>18.0</td>
<td>35.9</td>
</tr>
<tr>
<td>TS</td>
<td>10.89</td>
<td>4.92</td>
<td>2.0</td>
<td>24.4</td>
</tr>
<tr>
<td>AMC</td>
<td>22.86</td>
<td>3.52</td>
<td>16.6</td>
<td>31.3</td>
</tr>
<tr>
<td>Pre-HD albumin</td>
<td>3.45</td>
<td>0.55</td>
<td>1.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Post-HD albumin</td>
<td>3.90</td>
<td>0.73</td>
<td>1.5</td>
<td>5.1</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>0.95</td>
<td>2.0</td>
<td>0.0</td>
<td>13.50</td>
</tr>
<tr>
<td>Resistance (ohms)</td>
<td>643.28</td>
<td>110.81</td>
<td>424.00</td>
<td>937.00</td>
</tr>
<tr>
<td>Reactance (ohms)</td>
<td>68.91</td>
<td>15.11</td>
<td>19.00</td>
<td>100.00</td>
</tr>
<tr>
<td>PA (degrees)</td>
<td>6.19</td>
<td>1.33</td>
<td>1.75</td>
<td>9.11</td>
</tr>
</tbody>
</table>

SD: standard deviation; HD: hemodialysis; Kt/V: dialysis adequacy index; PNA: protein equivalent of nitrogen appearance; BMI: body mass index; MAC: mid-arm circumference; TS: tricipital skinfold; AMC: arm muscle circumference; CRP: C-reactive protein; PA: phase angle.
20 (34.5%) patients had pre-HD hypoalbuminemia (< 3.4 g/dL). After fluid status correction with HD, this number fell to 9 patients (15.5%) (Figure 2).

As for malnutrition risk (albumin < 3.7 g/dL) there was a reduction in the number of patients affected, from 55.2% pre-HD to 25.9% post-HD (Figure 3).

**Correlation between CRP and pre-HD and post-HD serum albumin**

We observed a 46.6% prevalence rate of patients with CRP > 3 mg/L, with only 17.3% of these patients with a clinically apparent infection.

CRP negatively correlated with serum albumin, both pre-HD (r = -0.40, p = 0.003) and post-HD (r = -0.30, p = 0.04).

**Correlation between pre-HD and post-HD serum albumin and the study variables**

There was a significant correlation between pre-HD and post-HD albumin and BMI, BP and reactance. There was a marginally significant correlation between pre-HD albumin and adequacy of the AMC to the P50 and the PNA, and a significant correlation between post-HD albumin and AMC adequacy to the P50 and the PNA (Table 2).

**Assessment of the nutritional status and mortality risk according to pre-HD and post-HD albumin**

In order to analyze the prevalence of high risk of mortality according to pre-HD and post-HD albumin, we compared albumin < 3.2 g/dL and PA < 5. The prevalence of high risk of morbidity and mortality according to the two parameters did not differ (McNemar’s test), there being regular to good agreement of the diagnosis of high risk of morbidity and mortality at the pre-HD and post-HD periods (κ = 0.432; p = 0.001 for pre-HD and e K = 0.473; p < 0.001 for post-HD) (Table 3).

For analysis of the prevalence of patients at risk of malnutrition according to pre-HD and post-HD albumin, we compared albumin < 3.7 g/dL and PA < 5. There was poor agreement of the diagnosis of malnutrition risk and different malnutrition prevalences, according to the two markers used (38.6% and 1.8%) (Table 4). Yet, after fluid overload correction (post-HD), there was regular to good agreement of the diagnosis of malnutrition risk, there being no different malnutrition prevalence between the two markers used (Table 4).

---

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>Pre-HD albumin</th>
<th>Post-HD albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>BMI</td>
<td>58</td>
<td>0.293</td>
</tr>
<tr>
<td>Adequacy of TS to P50</td>
<td>58</td>
<td>0.136</td>
</tr>
<tr>
<td>Adequacy of AMC to P50</td>
<td>58</td>
<td>0.242</td>
</tr>
<tr>
<td>PA</td>
<td>57</td>
<td>0.588</td>
</tr>
<tr>
<td>Reactance</td>
<td>57</td>
<td>0.403</td>
</tr>
<tr>
<td>Kt/V</td>
<td>57</td>
<td>-0.113</td>
</tr>
<tr>
<td>PNA</td>
<td>57</td>
<td>0.260</td>
</tr>
</tbody>
</table>

HD: hemodialysis; BMI: body mass index; TS: tricipital skinfold; P: percentile; AMC: arm muscle circumference; PA: phase angle; Kt/V: dialysis adequacy index; PNA: protein equivalent of nitrogen appearance.
**Table 3** Prevalence of high risk of morbidity and mortality according to the phase angle < 5 and pre-HD and post-HD albumin < 3.2 g/dL, in the study population

<table>
<thead>
<tr>
<th>Phase angle</th>
<th>Pre-HD albumin</th>
<th>Post-HD albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 5</td>
<td>n (% of total)</td>
<td>43 (75.4)</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>n (% of total)</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td>MacNemar: p = 1.000</td>
<td>K = 0.432</td>
<td>p = 0.001</td>
</tr>
</tbody>
</table>

**Table 4** Prevalence of patients at risk of malnutrition, determined by a phase angle < 5 and pre-HD and post-HD albumin < 3.7 g/dL

<table>
<thead>
<tr>
<th>Phase angle</th>
<th>Pre-HD albumin</th>
<th>Post-HD albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 5</td>
<td>n (% of total)</td>
<td>25 (43.9)</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>n (% of total)</td>
<td>01 (1.8)</td>
</tr>
<tr>
<td>MacNemar: p = 0.001</td>
<td>K = 0.236</td>
<td>p = 0.013</td>
</tr>
</tbody>
</table>

**Discussion**

Several factors, hemodilution included, contribute to the hypoalbuminemia of patients on dialysis. Correlation between the albumin levels and hydration status of HD patients has been investigated.

In this study, post-HD albumin increased in 93.1% of the patients. This increase was clearly related to intradialytic fluid loss, 1.93 kg on average, as was demonstrated through the significant correlation between the pre-HD and post-HD difference of the albumin values and weight.

Colin et al.\(^1\) also reported a significant correlation between increased serum albumin and the change of the extracellular volume (assessed with electrical BIA). Dumler\(^2\) demonstrated a significant increase of the extracellular volume in a group of patients with albumin < 3.5 g/dL, in relation to the group with higher albumin levels.

There were 18.8% and 29.3% reductions of the number of post-HD patients with hypoalbuminemia and at risk of malnutrition, respectively. Likewise, Wapensky et al.,\(^1\) demonstrated a post-HD 33.3% reduction in the number of hypoalbuminemic patients, in comparison with pre-HD. Other authors have pointed to the role of albumin as a marker of a fluid overload status.\(^2\)

Recent studies have indicated that several HD patients have a concomitant inflammatory state, associated with increased serum levels of positive acute-phase proteins (CRP among them) and decreased levels of negative acute-phase proteins (albumin, transferrin and pre-albumin).\(^2,24\) Therefore, pre-HD albumin reduction could reflect an inflammatory state, besides fluid overload.

The prevalence of increased CRP in dialysis patients or CKD patients ranges from 32 to 65%,\(^2,27\) having been detected in 46.6% of our patients. After exclusion of those with a clinically apparent infection, there remained 29.3% with an increased CRP. CRP elevation in the absence of a clinically apparent infection may be explained by several factors, such as reduced cytokine renal clearance, occult infections, atherosclerosis itself, complement activation, exposure to dialyzate endotoxins, heart failure and catheter use.\(^2,29\)

In accordance with literature data,\(^3\) we observed a significantly negative correlation between pre-HD and post-HD CRP and albumin. These data suggest that the hydration status does not interfere with the ratio of the two inflammation acute-phase proteins. The association of CRP with low albumin levels cannot be always considered a cause-effect relationship. Kaysen et al.,\(^3\) have recently demonstrated that increased CRP levels during one month did not predict reduced albumin levels in the subsequent month.

We observed that the correlation between serum albumin and intradialytic weight loss we found remained even after exclusion of the patients with increased CRP levels, pointing to an independent correlation of inflammation. This finding was previously described by Jones in an editorial on the use of albumin as a fluid overload marker.\(^12\)
The hydration status might interfere with the clinical interpretation of pre-HD albumin, leading to inadequate therapeutic decisions. The post-HD albumin level may be a better marker of clinical outcomes and nutritional status of HD patients. Although the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend pre-HD measurement of albumin levels, there is no justification for the choice of this particular moment. Therefore, hemodilution-related hypoalbuminemia is not commonly considered in clinical practice. Definition of the ideal period for albumin determination in HD patients is highly relevant in clinical practice, as albumin levels are used to predict mortality risk.\(^{8,34,35}\)

Lowrie and Lew\(^5\) showed that the low pre-HD serum albumin levels were associated with an increased likelihood of death and suggested that the established relationship between hypoalbuminemia and mortality would be mainly due to protein-energy malnutrition. However, it is almost impossible to separate the effects of poor protein intake from other non-nutritional factors, that is, interdialytic weight gain and inflammation.\(^{36}\)

We detected an important change in the rate of middle and low-risk mortality patients when post-HD albumin was used, with a 32.7% reduction in the number of medium-risk patients and a 34.4% increase in the number of low-risk patients, compared with the pre-HD assessment. Likewise, Duton et al.\(^{37}\) in a cross-sectional study of 86 HD patients, demonstrated a post-HD 28% reduction in the number of medium-risk patients and a 29% increase in the number of low-risk patients.

For the high mortality risk group (albumin < 3.2 g/dL), we detected just a 1.7% reduction on the post-HD assessment. Duton et al.\(^{37}\) also described a similar (2%) reduction in this group. These results suggest that the hydration status does not change the initial stratification (pre-HD) of high-risk patients, compared to their post-HD status. In order to test this assumption, the authors assessed whether the high mortality risk according to albumin compared with another predictor of mortality (PA), pre-HD and post-HD, through MacNemar’s test and K index.

The PA was chosen because it was proved to be an independent mortality predictor for dialysis patients.\(^{36,40}\) PA calculation suffers little operator-dependent variability, is less affected by volume alterations and does not depend on the predictive equations of BIA programs, developed in healthy individuals with stable volemia.\(^{41}\)

The prevalence of high mortality risk patients did not differ between the methods (albumin and PA) at pre-HD and post-HD (MacNemar’s test), and there was regular to good agreement in the diagnosis of high mortality risk between them (K index).

Santos et al. argued that exclusion of the hemodilution effect observed post-HD would probably result in a more accurate assessment of the nutritional status only in borderline cases of albumin-based malnutrition diagnoses.\(^{42}\) Strengthening this supposition, when we compared two nutritional markers, albumin < 3.7 g/dL (patients with mild malnutrition or at nutritional risk) and PA < 5, we observed that, exclusively post-HD, the prevalence of malnutrition did not differ between the markers, there being regular to good agreement in malnutrition diagnoses between the methods. However, when we used the albumin cut-off point < 3.2 g/dL (indicative of malnutrition), the prevalence of malnutrition did not differ between the markers, there being a regular to good agreement of malnutrition diagnoses between the methods, pre-HD and post-HD.

Albumin values indicative of high mortality risk (< 3.2 g/dL) are not exclusively secondary to hemodilution, a fact that would explain the small interference of the hydration status, as discussed above, in the risk stratification of this group. Dilution-caused albumin reduction is partly compensated by hypervolemia-stimulated increased albumin synthesis.\(^{43,44}\) Other factors, such as protein-energy malnutrition and/or inflammation, may be responsible for the hypoalbuminemia, the hydration status not being enough to mask a diagnosis of malnutrition.

Kaysen and Don\(^{44}\) reported that hypervolemia is an important factor in the pathogenesis of malnutrition, also being an independent cardiovascular risk factor in HD patients. Other authors have recently demonstrated that fluid overload is implicated in the mortality of these patients, by increasing fibrinogen synthesis, reducing protein-energy intake and directly suppressing appetite through tumor necrosis factor (TNF). Increased TNF would result from bacterial and/or endotoxin translocation caused by edema of the intestinal wall. Furthermore, hypervolemia would have a role in the pathogenesis of left ventricular overload and hypertension.\(^{43}\)

Because inadequate dialysis may lead to uremia, with consequent anorexia, nausea, vomiting and poor food intake, the Kt/V would be an important parameter for the clinical interpretation of the
nutritional status of HD patients. However, we found no significant correlation between the pre-HD and post-HD serum albumin and the Kt/V, results that were similar to those of Wapenskey et al. Laville and Fouque described the inconsistency of the Kt/V as a parameter for nutritional assessment. A French study of seven thousand dialysis patients found a 36% prevalence of malnutrition with serum albumin < 3.5 g/dL, but with Kt/V of 1.36 ± 0.36.

As for the PNA, there was a significant correlation only with post-HD albumin, which might suggest that hemodilution masks the correlation between serum albumin, albumin synthesis and protein intake, indirectly expressed by PNA. However, it should be noted that PNA is an indicator of the acute nutritional status, reflecting only recent nitrogen intake. In spite of the limitations of PNA use, the K/DOQI guidelines recommend PNA as a valid and useful method to estimate protein intake, although it should not be used in isolation for the assessment of the nutritional status.

We also analyzed the correlations between pre-and post-HD albumin and the following nutritional parameters: BMI and adequacy of AMC and TS to the P50. We observed a significant correlation between AMC adequacy to P50 and post-HD albumin, which might suggest that post-HD albumin would be a better option to assess the muscle mass of these patients. As for the BMI, there was a significant correlation with pre- and post-HD albumin. The mean 1.93 kg weight loss was not sufficient to unveil a difference in the correlation between BMI and the albumin measured at the two time-points. Limitations in the use of TS in HD patients might explain the lack of significant correlation between albumin and TS adequacy to P50. Dutton et al. showed a significant correlation between albumin and TS only at post-HD (r = 0.31, p < 0.01), and indicated post-HD albumin as the best nutritional marker.

Our results make us question whether post-HD serum albumin is indeed a better marker of the nutritional status, as previously suggested. In spite of the results discussed above, the best moment for measuring serum albumin remains undefined, as there is no gold-standard for the assessment of the nutritional status and the responses to nutritional interventions, against which serum albumin can be compared.

To date, there is not enough knowledge to affirm that an increased post-HD albumin would have a long-term positive impact on the morbidity and mortality of dialysis patients. Furthermore, there are no studies comparing patients maintained in sustained normovolemia and those on conventional dialysis, in order to determine the role of hypervolemia in the mortality of these patients. However, recent studies have pointed to lower cardiovascular risk and lower mortality of patients undergoing daily or nocturnal dialysis, compared to conventional dialysis, three times a week.

CONCLUSIONS

This study suggests that albumin-based assessment of the nutritional status and mortality risk can be different when post-HD albumin is measured, due to correction of the hydration status, chiefly when there is mild malnutrition and medium and low mortality risk. Because of the limitations of our study, cross-sectional design and limited number of patients, further longitudinal studies involving larger number of patients are necessary.

REFERENCES