Original Article

Contribution of hypoalbuminemia and decreased renal function to the increased mortality after newly diagnosed vertebral fracture in Japanese subjects

Tetsuo Nakano MD1, Akiko Kuwabara RD, PhD2, Hiroshi Mizuta MD, PhD3, Kiyoshi Tanaka MD, PhD4

1Department of Orthopaedic Surgery, Tamana Central Hospital, Tamana, Kumamoto, Japan
2Department of Health and Nutrition, Osaka Shoin Women’s University, Higashi-osaka, Osaka, Japan
3Department of Orthopaedic and Neuro-Musculoskeletal Surgery, Kumamoto University Graduate School of Medicine, Kumamoto, Japan
4Department of Food and Nutrition, Kyoto Women’s University, Kyoto, Japan

Background and Objectives: Reports on the mortality and its contributing factors after vertebral fracture (VFx) has been scarce, and limited to prevalent VFx. In this paper, we have studied the factors influencing mortality after freshly diagnosed VFx. Methods and Study Design: 759 subjects aged 78.8±8.5 years old with back or lumbar pain, and diagnosed as fresh VFx by MRI were studied for their age, gender, number of prevalent fracture (s), survival or the date of death, circulating concentrations of Hb, albumin, C reactive protein, and estimated glomerular filtration rate (eGFR). Cox’s proportional hazard analysis was performed to assess the significant predictors for mortality. The cut-off concentrations of the variables for mortality were analyzed using the receiver operator characteristic (ROC) curve. Results: The median observation duration was 3.8 years, and 3-year survival rate was 78.8%. Cox’s proportional hazard analysis has shown that serum albumin concentration (hazard ratio (HR) =0.355) and eGFR (HR=0.993) were significant predictors for mortality. The cut-off concentrations were 3.6 g/dL and 60 mL/min/1.73m2, respectively. Kaplan-Meier curves revealed that survival rates were significantly decreased in patients with both serum albumin concentration and eGFR below these cut-off concentrations. Conclusions: The present study has revealed that malnutrition and impaired renal function were significant predictors for mortality after VFx.

Key Words: fresh vertebral fracture, MRI mortality, hypoalbuminemia, renal function

INTRODUCTION

Of the various osteoporotic fractures, vertebral fracture (VFx) has the highest incidence. Nevertheless, compared with other osteoporosis-related fractures such as hip fracture, it has received far less attention. Recent studies have reported, however, that VFx is associated with co-morbidities or impaired quality of life (QOL). For example, patients with VFx are well-known to be at higher risk of having gastroesophageal reflux disease (GERD), chronic low back pain, impaired respiratory function, and digestive dysfunction. QOL was reported to be significantly worse in subjects with VFx than those without it. Even the morphological fracture, which is incidentally diagnosed by the X-ray examination without overt clinical signs or symptoms, was associated with QOL impairment. It is well established that the prevalence of VFx is higher, whereas that of hip fracture is lower in Japan than that in Europe or America. Thus, the clinical and societal significance of VFx would be much greater in Japan. These considerations have prompted us to perform this study with two main research questions as below.

Studies in Caucasians have shown that VFx is even associated with increased mortality. Recently, there appeared some reports also in Japan describing the higher mortality in subjects with VFx, which, however, is on the prognosis of subjects with prevalent VFx. Thus we have studied the survival rate after freshly diagnosed VFx, which has not been reported in Japan.

The post-fracture prognosis is greatly influenced by background factors including the nutritional ones. With regards to hip fracture, there have been papers to show that mortality after hip fracture is influenced by such factors as ambulatory ability, delirium, delayed surgery, comorbidities, gender, and nutritional state. Few papers have been available, however, on the factors contributing the mortality after VFx. Therefore, identifying factors contributing to mortality after fresh VFx has clinical significance.
implications, and could allow for the enhanced management of VFx patients in the clinical practice. Then we have studied factors affecting mortality following VFx in a Japanese population.

**METHODS**

**Subjects**

The entry criteria were patients visiting the orthopaedic outpatient clinic, Tamana Central Hospital because of back or lumbar pain, given the diagnosis of fresh VFx based on the MRI diagnosis, and admitted between January 1997 and April 2007.

The follow-up survey was performed between April 2008 and October 2008. In 759 subjects, information was obtained about their survival or the date of death for the deceased subjects. The study was approved by the Ethics Committee of Tamana Central Hospital, and was done conforming to the Declaration of Helsinki. Written informed consent was obtained from the subjects or proxy after explaining the purpose of this study.

**Diagnosis of fresh VFx by MRI**

The diagnosis of fresh VFx was made based on the description in the “Guideline for the prevention and treatment of osteoporosis 2011”. Based on the facts that fresh fracture in general, exhibits low signal intensity on T1-weighted image (T1WI) and high signal intensity on short-T1 invention-recovery (STIR), diagnostic features for fresh VFx described below were adopted. First, vertebral body at least partially exhibits low signal intensity image, which extends from the anterior wall to the posterior wall. Second, areas with low and normal intensity are not clearly demarked, but intermingled. Third, the low signal intensity area runs horizontally. Finally, intensity within the low signal intensity area is heterogeneous and not flow void.

**Laboratory data**

Blood was obtained at the hospital visit. After centrifugation, serum was kept frozen at −30°C until analysis. Serum concentrations of albumin, C-reactive protein (CRP), and blood concentration of Hb were measured as protein nutrition status, inflammation marker, and anemia, respectively. Renal function was evaluated by estimated glomerular filtration rate (eGFR). Biochemical data were obtained from 755 patients.

**Statistical analyses**

Statistical analyses were done with SPSS 20.0J (IBM Japan, Ltd, Tokyo, Japan). Comparison of the two independent variables was made by unpaired t-test or Mann Whitney U test. Chi-square test was employed for categorical data. Survival rate was analyzed by Kaplan-Meier curve. Multiple regression analysis for assessment of contributing factors for mortality was performed using the stepwise Cox proportional hazards model. The diagnostic value was evaluated by the area under the curve (AUC) with the larger value indicating the better diagnostic value. The appropriate cut-off value was determined using Youden’s index. Then, with the cut-off value determined, Kaplan-Meier curve was produced with a threshold concentration, and statistical significance was evaluated by the log rank test.

**RESULTS**

The follow-up data were available in 759 subjects (men 170, women 589), aged 78.8±8.5 years old. The median observation duration was 3.8 years. The survival rates of our VFx patients at diagnosis of fresh vertebral fracture year 1, 2, and 3 were 91.3%, 84.6%, and 78.8%, respectively (data not shown).

The background profiles and biochemical data are shown in Table 1. Non-survivors had significantly higher age (p<0.001), higher serum CRP concentration (p<0.001), and lower albumin (p<0.001), Hb (p=0.002), eGFR (p<0.001) compared with survivors.

Next, Cox’s proportional hazard analysis was done to determine the significant predictor (s) for mortality in

<table>
<thead>
<tr>
<th>Table 1. Characteristics of subjects</th>
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<tbody>
<tr>
<td>All (n=759)</td>
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<tr>
<td>M/F</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Age category (n)</td>
</tr>
<tr>
<td>&lt;75 y</td>
</tr>
<tr>
<td>75 to 84 y</td>
</tr>
<tr>
<td>&gt;85 y</td>
</tr>
<tr>
<td>Number of prevalence of fracture (s)</td>
</tr>
<tr>
<td>Observation duration (y)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
</tr>
</tbody>
</table>

Mean (SD), median (Q1, Q3) min-max; unpaired t-test or Mann Whitney U test depending on normality.†Chi-square test.
T Nakano, A Kuwabara, H Mizuta and K Tanaka

Table 2. Cox’s proportional hazard analysis for mortality in subjects with fresh vertebral fracture

<table>
<thead>
<tr>
<th></th>
<th>Partial regression coefficient</th>
<th>p value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (ref=men)</td>
<td>-0.679</td>
<td>&lt;0.001</td>
<td>0.507</td>
<td>(0.389-0.661)</td>
</tr>
<tr>
<td>Age</td>
<td>0.058</td>
<td>&lt;0.001</td>
<td>1.06</td>
<td>(1.04-1.08)</td>
</tr>
<tr>
<td>Albumin</td>
<td>-1.04</td>
<td>&lt;0.001</td>
<td>0.355</td>
<td>(0.270-0.467)</td>
</tr>
<tr>
<td>eGFR</td>
<td>-0.007</td>
<td>0.012</td>
<td>0.993</td>
<td>(0.987-0.998)</td>
</tr>
</tbody>
</table>

Cox’s proportional hazard analysis.
Analysis was done with multivariate Cox’s proportional hazard analysis with control for sex, age, BMI, albumin, Hb, and eGFR. Only significant predictors are shown.

Subjects with fresh VFx (Table 2), which has revealed that male gender, increased age, low serum albumin level and low eGFR were significant predictors for mortality. Based on the receiver operator characteristic (ROC) curves, the cut-off value were 3.6 g/dL for serum albumin (sensitivity, 78%; specificity, 58%), and 60 mL/min/1.73m² for eGFR (sensitivity, 73%; specificity, 49%), respectively (data not shown).

Kaplan-Meier curves with the threshold determined above, have shown that survival rates were significantly decreased in patients with both serum albumin concentration of <3.6 g/dL and eGFR of 60 mL/min/1.73m² (Figure 1).

Figure 1. Kaplan-Meier curve for the survival rate after vertebral fracture stratified by the levels of albumin and renal function. The black solid line and dotted represent normal albumin/normal renal function, and normal albumin/low renal function, respectively. The gray solid line and dotted line denote low albumin/normal renal function, and low albumin/low renal function, respectively. Normal albumin: ≥3.6 g/dL, low albumin: <3.6 g/dL; Normal renal function: eGFR ≥60 mL/min/1.73m², low renal function: <60 mL/min/1.73m².

DISCUSSION
In the present study, we have shown that subjects with newly diagnosed VFx have high risk of mortality, to which the coexistence of hypoalbuminemia and impaired renal function has significantly contributed. Increased mortality after hip fracture is well established,\textsuperscript{27,28} and the relationship between the nutritional status and post-fracture mortality has been reported. In a 4-year cohort study in a Japanese population, serum albumin concentration and BMI were significant predictors for 4-year mortality after hip fracture surgery, with the cut-off value of 3.6 g/dL for serum albumin, and 18.9 kg/m² for BMI.\textsuperscript{29} Another paper has indicated the higher mortality risk in those with decreased renal function as evaluated by eGFR in hip fractured patients after adjusting for age and sex.\textsuperscript{30}

In recently published two papers describing the mortality in subjects with prevalent VFx in Japan, determinants for post-fracture mortality are discussed. Shiraki et al have conducted a prospective, observational study enrolling 1429 postmenopausal women with the mean age of 66.5. They were followed for 4.5 years as the average. A total of 141 deaths (9.9%) were observed, for which advanced age, lower body mass index, prevalent malignancies, dementia, cardiovascular disease, serum creatinine concentration, and the severity of osteoporosis were contributing factors.\textsuperscript{18} In their paper, severe osteoporosis was defined as having the pre-existing major osteoporotic fractures. Ikeda et al have studied the prognosis of participants at the osteoporosis screening program. Of the 619 subjects with the average age of 73 years old, 131 (21%) of those had VFx as diagnosed by the lateral radiographs of the spine. The 10-year survival rate was significantly
lower (69%) in subjects with VFx than those without it (86%). According to the multiple regression analyses, advanced age, male gender, and presence of the VFx were the significant determinants for the mortality.\textsuperscript{19}

In this paper, we have revealed that both low concentration of albumin (<3.6 g/dL) and eGFR (<60 mL/min/1.73m\(^2\)) i.e. malnutrition and impaired renal function were significant predictors for mortality after freshly diagnosed VFx. Compared with the previous reports, the possible contribution of nutritional factors is not described in Shiraki’s and Ikeda’s papers on prevalent VFx. Our results are, however, compatible with the reports on hip fracture.

Of the various osteoporotic fractures, VFx requires special consideration, and two types must be discriminated. Approximately two third of the VFx patients lack overt clinical signs and symptoms, and do not visit the hospital. Such cases are incidentally found by X-ray examination (morphological fracture). Only one-third of the VFx patients visit the hospital because of their symptoms such as lumbago (clinical fracture).\textsuperscript{3,12} Thus, the information on the exact date of fracture is unavailable in patients with morphological fracture; i.e. in two-third of the VFx subjects. As described in the “Introduction”, report on the mortality associated with VFx has been scarce in Japan, and limited to the study on prevalent VFx.\textsuperscript{18,19} Thus, subjects in these studies are those who were diagnosed having VFx by X-ray examination. In other words, mortality in patients with prevalent VFx has been studied, but mortality after recently occurred VFx has not been reported in Japan. Since the participants in the present study were patients with clinical fracture, data described here refers to the mortality after newly occurred VFx. Because the prognostic variables for newly occurred VFx has not been previously reported, further studies are needed to confirm our findings.

Our study has two strengths. First, survival information could be obtained in practically all of the fractured subjects. Since low follow-up rate can yield a large bias, we considered it mandatory to keep the follow-up rate as high as possible, and asked the administrative body of the cities, towns, and villages of the subjects’ residence for information. Second, the diagnosis of VFx was made based on the MRI finding. Guideline 2011 states that the diagnosis of VFx can be made much more accurately with MRI than with the X-ray radiogram in its early stage, especially within two weeks after the fracture.\textsuperscript{23} Vertebral height loss is the basis for the X-ray diagnosis of VFx, which is often unobserved during the early phase of VFx. Since the above mentioned MRI finding is related to the altered signal intensity, MRI-based diagnosis of newly occurred VFx would be much more precise than the X-ray diagnosis. As far as we know, this is the first report describing the high mortality after newly occurred VFx.

The limitation of the current study is also related to the study design. As described above, the patients’ information was obtained from the administrative body of the cities, towns, and villages of the subjects’ residence for information. Thus, the survival information was obtainable in most subjects, but their detailed information such as the functional prognosis or the co-morbidities was not available. Due to the lack of the in-depth demographic information, further detailed analyses for the determinants for the poorer prognosis could not be done in the current study. Additionally, our study had no control. Our study, however, has shown that male gender, increased age, low nutritional status and low renal function might cause increased mortality in vertebral fracture patients.

In summary, we have shown that patients with VFx have high risk of mortality. Our data would be the basis for considering the clinical and societal significance of VFx.

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AUTHOR DISCLOSURES

None of the authors have any conflicts of interest.

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Tetsuo Nakano MD¹, Akiko Kuwabara RD, PhD², Hiroshi Mizuta MD, PhD³, Kiyoshi Tanaka MD, PhD⁴

¹Department of Orthopaedic Surgery, Tamana Central Hospital, Tamana, Kumamoto, Japan
²Department of Health and Nutrition, Osaka Shoin Women’s University, Higashi-osaka, Osaka, Japan
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⁴Department of Food and Nutrition, Kyoto Women’s University, Kyoto, Japan

Original Article

Excess mortality after vertebral fracture

Contribution of hypoalbuminemia and decreased renal function to the increased mortality after newly diagnosed vertebral fracture in Japanese subjects

Tetsuo Nakano MD¹, Akiko Kuwabara RD, PhD², Hiroshi Mizuta MD, PhD³, Kiyoshi Tanaka MD, PhD⁴

¹Department of Orthopaedic Surgery, Tamana Central Hospital, Tamana, Kumamoto, Japan
²Department of Health and Nutrition, Osaka Shoin Women’s University, Higashi-osaka, Osaka, Japan
³Department of Orthopaedic and Neuro-Musculoskeletal Surgery, Kumamoto University Graduate School of Medicine, Kumamoto, Japan
⁴Department of Food and Nutrition, Kyoto Women’s University, Kyoto, Japan

日本新诊断椎体骨折患者低蛋白血症和肾功能下降对增加死亡率的贡献

背景与目的：关于椎体骨折（VFx）的报道仅限于患病率，而死亡率和影响因素的报道却很少。本文研究了新诊断的VFx死亡率的影响因素。方法和研究设计：本研究纳入背或腰椎疼痛，经MRI新诊断为VFx的759名患者（平均年龄为78.8±8.5岁）。记录了他们的年龄、性别、骨折发生的次数、生存或死亡的日期、循环血红蛋白的浓度、白蛋白、C反应蛋白和估计的肾小球滤过率（eGFR）。进行Cox比例风险分析，以评估死亡率有意义的预测指标。使用受试者工作特征曲线（ROC）分析死亡率预测指标的截点值。结果：中位观察时间为3.8年，3年生存率为78.8%。Cox比例风险分析表明血清白蛋白（危险比HR=0.355）浓度和eGFR（HR=0.993）是死亡率的重要预测指标，截点值分别为3.6 g/dL和60 mL/min/1.73m²。Kaplan-Meier曲线显示，血清白蛋白浓度和eGFR都低于截点值的患者生存率显著降低。结论：目前的研究表明，营养不良和肾功能受损是VFx后死亡率的重要预测指标。

关键词：新发椎体骨折、MRI、死亡率、低蛋白血症、肾功能