



Incidence and Mortal Risk Factors of Vertebral Osteomyelitis: A Retrospective Analysis Using the Japanese Diagnosis Procedure Combination Database

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7 **Incidence and Mortal Risk Factors of Vertebral Osteomyelitis: A Retrospective Analysis Using the Japanese**

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10 **Diagnosis Procedure Combination Database**

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16 Incidence and Mortal Risk Factors of Vertebral Osteomyelitis

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27 vertebral tuberculosis, in-hospital mortality
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Abstract

Objective: To examine the incidence of vertebral osteomyelitis (VO) and clinical features of VO focusing on risk factors for death using a Japanese nationwide administrative database.

Design: Retrospective observational study.

Setting and Participants: We identified 7,454 patients who were diagnosed with VO and hospitalized between July and December, 2007-2010, using the Japanese Diagnosis Procedure Combination database.

Main Outcome Measures: The annual incidence of VO was estimated. Logistic regression analysis was performed to analyse factors affecting in-hospital mortality in the VO patients. Dependent variables included patient backgrounds (age, sex and comorbidities), procedures (hemodialysis and surgery) and hospital factors (type of hospital and hospital volume).

Results: Overall, 58.7% of eligible patients were male and the average age was 69.2 years. The estimated incidence of VO increased from 5.6 per 100,000 population per year in 2007 to 7.7 per 100,000 population per year in 2010.

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7 In-hospital mortality was 5.7%. There was a linear trend between higher in-hospital mortality and greater age.
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10 Higher in-hospital mortality was significantly associated with hemodialysis use (odds ratios, 10.62 [95% confidence
11 interval, 8.21–13.73]), diabetes (2.34 [1.87–2.92]), liver cirrhosis (2.63 [1.50–4.61]), malignancy (2.66, [2.09–3.39]),
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13 infective endocarditis (3.22 [1.82–5.70]) and treatment in non-academic hospital (1.36 [1.00–1.86]).
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18 **Conclusions:** Our study is the first to demonstrate the increasing incidence of VO, its mortality and risk factors for
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20 death with a nationwide database. Several comorbidities were significantly associated with higher rates of in-hospital
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22 death in VO patients. We believe these novel findings are important for improving the clinical management of VO.
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Article summary

Article focus

- Vertebral osteomyelitis (VO) remains a life-threatening disease.
- Previous epidemiological studies on VO patients were limited because of small sample size.
- The present study examined the incidence of VO and clinical features of VO focusing on risk factors for death, using a nationwide database.

Key messages

- Using the Japanese Diagnosis Procedure Combination database, we analysed 7,454 VO patients.
- The estimated incidence of VO increased from 5.6 per 100,000 population per year in 2007 to 7.7 per 100,000 population per year in 2010.
- In-hospital mortality was 5.7%, which was significantly associated with greater age, hemodialysis use, diabetes,

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7 liver cirrhosis, malignancy, and infective endocarditis.
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10 11 12 **Strengths and limitations of this study'** 13

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15 - This study is the first to report significant risk factors for death in VO patients.
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19 - The database does not include information on causative microorganisms or post-discharge status.
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Introduction

Vertebral osteomyelitis (VO) is a rare, but life-threatening disease and its incidence appears to be on the rise [1-9].

Reportedly, VO represented 3–5% of cases of osteomyelitis[10]. In developed countries, the estimated incidence ranged from 1 case per 40,000 population per year to 1 case per 250,000 population per year [1 2 5 11-17]. However, these data were based on limited-scale epidemiological studies[15], covering small areas with fewer than 200 cases[1 7 9 16]. Published data on the incidence of VO are thus of low validity and reliability[3].

Mortality in VO has been reported to be less than 11%[1 3-6], but these figures were also based on relatively small studies. Furthermore, factors associated with mortality in VO have not yet been fully investigated.

Understanding the current epidemiology and clinical features of VO is an urgent requirement for effective management of this condition. The aims of the present study were (i) to estimate the incidence of VO, and (ii) to examine clinical features of VO focusing on risk factors for mortality in VO, using a Japanese nationwide administrative database. Additionally, the following details were examined. First, data have also been lacking on

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7 mortality following surgical procedures for VO. Indications for surgical treatment are decided by the following factors;
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10 prevention for spinal cord or major neural compression, stabilization or correction of spinal construction, reduction of
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12 intractable pain and failure of conservative management.[10 18-22][23] The present study verified mortality of VO
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14 patients following conservative or surgical treatments. Second, VO consists of vertebral tuberculosis (VT) and
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16 pyogenic vertebral osteomyelitis (PVO), but clinical details in these two conditions have not been fully described [5 17
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19 24]. We examined the difference in patient backgrounds and mortality between these two diseases.
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27 **Materials and Methods**

28 *Data source*

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33 For this study, we utilized the Japanese Diagnosis Procedure Combination (DPC) database. Details of the database
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35 are described elsewhere[25]. Briefly, discharge abstract and administrative claim data are collected from the
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37 participating hospitals between July 1 and December 31 each year by the DPC Study Group funded by the Japanese
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7 Ministry of Health, Labour and Welfare. The numbers of inpatients in the DPC database were 2.99 million from 926
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10 hospitals in 2007, 2.86 million from 855 hospitals in 2008, 2.57 million from 818 hospitals in 2009 and 3.19 million
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12 from 952 hospitals in 2010, which covered approximately 43% of all the acute-care inpatients in Japan. The database
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14 includes the following data: unique identifier of hospital and type of hospital (academic or non-academic); patient age
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16 and sex; diagnoses, comorbidities at admission and complications after admission recorded according to the
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18 International Classification of Diseases, Tenth Revision (ICD-10) codes and text data in Japanese language;
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20 procedures according to the original Japanese codes; drugs used; length of stay (LOS); and in-hospital deaths. The
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22 anonymous nature of the data allowed the requirement for informed consent to be waived. This study was approved
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24 by the Institutional Review Board at The University of Tokyo.
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36 *Patient selection*

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38 We included all patients who were diagnosed with VO according to the following ICD-10-based codes: vertebral
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7 osteomyelitis (M46.2), pyogenic infection of intervertebral disk (M46.3), unspecified discitis (M46.4), other infective
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10 spondylopathy (M46.5), other specified inflammatory spondylopathy (M46.8), unspecified inflammatory
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12 spondylopathy (M46.9), unspecified spondylopathy (M48.9), vertebral tuberculosis (M49.0), *Brucella* spondylitis
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14 (M49.1), enterobacterial spondylitis (M49.2), spondylopathy in other infectious or parasitic diseases (M49.3), and
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16 acute osteomyelitis located within the spinal column, head, neck, cranium or trunk (M86.0.8, M86.1.8). VO was
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19 categorized into PVO and VT.
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27 ***Estimation of the incidence of VO***

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30 We estimated the annual incidence of VO per population per year, based on the annual number of patients discharged
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32 from all acute-care hospitals in Japan (A_i), the annual number of patients discharged from all DPC hospitals in Japan
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34 (B_i), the number of VO patients in the DPC hospitals (N_i), the observation period (O_i) and the population of Japan (P_i).
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39 The coverage of the DPC hospitals (R_i) was defined as B_i divided by A_i . Values of B_i were calculated from the DPC
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7 database and data for A_i were obtained from the Survey of Medical Institutions and Hospital Report, 2010[26]. P_i was
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10 obtained from Japanese Population Census data (<http://www.stat.go.jp/english/data/kokusei/index.htm>). The
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12 estimated incidence of VO per population per year (Y_i) was calculated using the following equation: $Y_i = N_i / R_i / O_i / P_i$.
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19 ***Patient background***

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21 The following variables were abstracted from the DPC database: patient age and sex; comorbidities that could
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23 potentially affect mortality in VO including diabetes, liver cirrhosis, rheumatoid arthritis, malignancy, infective
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25 endocarditis (IE) and aortic aneurysm; use of hemodialysis; spinal surgery performed during hospitalization; and type
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27 of hospital and hospital volume. We also examined use of anticoagulants for each patient, including aspirin, warfarin,
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Hospital volume was categorized into tertiles: low-volume hospitals (<7 cases/year), medium-volume hospitals (7–10 cases/year) and high-volume hospitals (>10 cases/year). These categories were based on cutoffs that yielded equivalent

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7 numbers of patients in each volume category.
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10 11 12 13 *Outcome measurements* 14

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16 The primary outcome measured was in-hospital mortality. The secondary outcome was LOS.
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19 20 21 22 *Statistical analysis* 23

24 We used the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables to
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26 perform univariate comparisons of patient characteristics and outcomes between subgroups. Logistic regression
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28 analysis was performed to analyze the concurrent effects of various factors on the occurrence of in-hospital death,
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30 while adjusting for clustering of patients within hospitals using a generalized estimating equation[27]. The threshold
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32 for significance was a p value <0.05 . All statistical analyses were conducted using IBM SPSS version 19.0 (IBM SPSS,
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34 Armonk, NY, USA).
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RESULTS

Estimated incidence of VO in Japan

We identified 7,454 eligible patients. Table 1 shows the estimated incidence of VO in Japan. The overall incidence of VO between 2007 and 2010 was 6.8 per 100,000 population per year. The estimated incidence increased from 5.6 per 100,000 population per year in 2007 to 7.7 per 100,000 population per year in 2010. The incidence was lower in the population aged ≤ 59 years (1.9 per 100,000 population per year) than in those aged 60–69 years (11.2), 70–79 years (22.4) or ≥ 80 years (26.5).

Patient background

The patients' backgrounds are shown in Table 2. Overall, 58.7% were male and the average age (\pm standard deviation) was 69.2 ± 14.0 years. There were 7,143 cases of PVO and 311 of VT. The proportion of male PVO patients (59.0%) was higher than that of male VT patients (50.2%, $p=0.002$). No significant difference in age was observed between the

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7 PVO and VT groups. PVO patients were more likely to have a comorbid condition than VT patients.
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9 10 **In-hospital mortality**

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12 In-hospital mortality for each category is shown in Table 3. The overall in-hospital mortality was 5.8%. Higher
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14 in-hospital mortality was associated with greater age ($p<0.001$), hemodialysis use (27.5%, $p<0.001$), diabetes (10.1%,
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16 $p<0.001$), liver cirrhosis (12.9%, $p<0.001$), malignancy (10.0%, $p<0.001$), IE (12.4%, $p=0.001$) and treatment in a
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18 non-academic hospital (6.2%, $p=0.003$). Higher hospital volume was significantly associated with lower mortality
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($p=0.005$).

30 **Logistic regression analysis for in-hospital mortality**

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32 Table 4 shows the results of the logistic regression analysis for in-hospital mortality. Higher mortality was
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34 significantly associated with greater age (odds ratio [OR]), 2.75, 3.97 and 6.89; $p<0.001$ for patients aged 60–69, 70–79
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36 and ≥ 80 years compared with those aged ≤ 59), hemodialysis use (OR, 10.62; $p<0.001$), diabetes (OR, 2.34; $p<0.001$),
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38 liver cirrhosis (OR, 2.63; $p=0.001$), malignancy (OR, 2.66; $p<0.001$), IE (OR, 3.22; $p<0.001$) and treatment in a
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7 non-academic hospital (OR, 1.36; $p=0.049$). Patients treated in high-volume hospitals were significantly less likely to
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9 die compared with those at low-volume hospitals (OR, 0.75; $p=0.033$).

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12 Overall, the median LOS (interquartile range) was 47 (24–77) days. The median LOS was longer in PVO patients (47
13 [24–77] days) than that in VT patients (56 [25.5–85.5] days, $p=0.027$). No significant difference in LOS was observed
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15 between academic and non-academic hospitals (47 [24–75] days vs. 47 [24–78] days, $p=0.511$) or between
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17 hospital-volume groups (47 [24–80] days, 48 [24–79] days and 47 [24–74] days in low-, medium- and high-volume
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19 hospitals, respectively, $p=0.145$).

20 21 22 23 24 25 26 27 28 29 30 **DISCUSSION**

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33 The present study examined the annual trends in the VO occurrence and risk factors for death from VO using a
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35 Japanese nationwide inpatient database. Our study had two major findings. First, the incidence of VO was
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37 significantly higher in the elderly and increased year by year. Second, higher in-hospital mortality in VO was
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7 significantly associated with various factors.
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10 Our data demonstrated that the incidence of VO in Japan increased during the study period, from 5.6 to 7.7 per
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12 100,000 population per year. Yoshimoto et al. reported that the increase in the VO incidence could be related to the
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14 increasing ratio of aged people (65 years of age or older) in Japan[9]. A recent report of demographic shift in Japan
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16 demonstrated the rapid increase in aged population; the increasing percentage compared to 2007 was 3.2 % in 2008,
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18 6.1% in 2009 and 7.1% in 2010, respectively[28]. Based on the relationship between higher age and the higher
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20 frequency of VO occurrence, as was demonstrated in this study, we believe that this increase is partly attributable to
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22 aging population in Japan.
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30 Previous limited data suggested that factors affecting the occurrence of VO included antecedent infection, diabetes
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32 mellitus, rheumatic diseases, immunosuppression, drug abuse, alcoholism, vertebral compression due to malignant
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34 metastasis, trauma, disc herniation, IE and prior surgery (gastrointestinal and urogenital tract)[1]. However, risk
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36 factors affecting death from VO have not been well investigated. The present study indicated that significant risk
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7 factors for death from VO were greater age, hemodialysis, diabetes, liver cirrhosis, malignancy and IE. Mortal risks of
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10 PVO were not different from those of VT.

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13 Recently, two small-scale studies of fewer than 100 cases reported that IE appeared to increase the incidence of VO,
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16 but did not increase its mortality [29 30]. Conversely, our large-scale data showed that IE was a significant factor that
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19 increased mortality of VO. The other factors have never previously been analysed as risk factors for death in VO.

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22 Hemodialysis use was reported to be a risk factor for hematogenous complications of intravascular catheter use
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25 associated with *S. aureus* bacteremia[31]. A case report suggested the possibility of VO in hemodialysis patients [32].

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28 Our study is the first to demonstrate a significant relationship between hemodialysis use and death from VO.

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31 Previous reports indicated that VO patients were more likely to have diabetes mellitus (11–19%)[1 7 33-35], but the
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34 present study further demonstrated that diabetes mellitus was a significant predictor of mortality in VO. Although
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37 not surprising, that our study first demonstrated that age, liver cirrhosis and malignancy were all related to death
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7 As shown in table 4, spinal surgery did not reach statistical significance. Randomized controlled trial is essential to
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10 verify the efficacy of spinal surgery, because confounding factor by surgical indication affect the surgical
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13 result. However several papers suggested the impossibility of randomized controlled trials to decide the treatment
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16 strategy of VO, not limited in spinal surgery [36 37]. Thus, our DPC data could not reveal the efficacy of spinal
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19 surgery of VO.

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21 The high mortality suggests that VO remains a life-threatening disease despite advances in medical practice and
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24 should be regarded as a fatal systemic disorder rather than just a localized vertebral disorder.
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30 We acknowledge several limitations of the present study. First, the DPC database does not provide important clinical
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33 data such as causative microorganisms and information on post-discharge outpatient services. Second, although the
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36 sample size was large, the population representativeness was limited because the participating hospitals were
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39 skewed toward large hospitals. Third, the diagnoses recorded in the administrative database are less well validated
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7 than those made in planned prospective surveys. Lastly, the mortality of VO may be underestimated because of
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10 transferring to other hospitals. Despite these limitations, our study made several new findings regarding VO,
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13 including risk factors for death.
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19 **CONCLUSION**

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21 The present study confirmed the increasing incidence of VO using a nationwide database. Greater age, use of
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24 hemodialysis, diabetes, liver cirrhosis, malignancy and IE were significantly associated with higher rates of
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27 in-hospital death in patients with VO. Based on the high mortality, we believe that VO remains a life-threatening,
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30 systemic disease. These novel findings will be important for improving the clinical management of VO.
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36 **Contributors**

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39 HY, HH and KF collected the data. TA, HC, HY and KS designed the study, analysed and interpreted the data and
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7 drafted the manuscript. All authors had full access to all data (including statistical reports and tables) in the study
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10 and take responsibility for the integrity of the data and the accuracy of the data analysis.
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20
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27
28 Technology Policy, Japan (grant number: 0301002001001).
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33 **Competing Interests**

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36 We declare that there are no competing interests for publication.
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Data Sharing

No additional data are available.

Contributorship

HY, HH and KF collected the data. TA, HC, HY and KS designed the study, analysed and interpreted the data and drafted the manuscript. All authors had full access to all data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Beronius M, Bergman B, Andersson R. Vertebral osteomyelitis in Goteborg, Sweden: a retrospective study of patients during 1990-95. *Scandinavian journal of infectious diseases* 2001;**33**(7):527-32
2. Krogsgaard MR, Wagn P, Bengtsson J. Epidemiology of acute vertebral osteomyelitis in Denmark: 137 cases in Denmark 1978-1982, compared to cases reported to the National Patient Register 1991-1993. *Acta orthopaedica Scandinavica* 1998;**69**(5):513-7
3. Gouliouris T, Aliyu SH, Brown NM. Spondylodiscitis: update on diagnosis and management. *The Journal of antimicrobial chemotherapy* 2010;**65** Suppl 3:iii11-24 doi: 10.1093/jac/dkq303[published Online First: Epub Date] | .
4. Legrand E, Flipo RM, Guggenbuhl P, et al. Management of nontuberculous infectious discitis. treatments used in 110 patients admitted to 12 teaching hospitals in France. *Joint, bone, spine : revue du rhumatisme* 2001;**68**(6):504-9
5. Colmenero JD, Jimenez-Mejias ME, Sanchez-Lora FJ, et al. Pyogenic, tuberculous, and brucellar vertebral osteomyelitis: a descriptive and

- comparative study of 219 cases. *Annals of the rheumatic diseases* 1997;**56**(12):709-15
6. Bauman GI, Stifel RE. Osteomyelitis of the Spine. *Annals of surgery* 1923;**78**(1):119-21
7. Jensen AG, Espersen F, Skinhoj P, Rosdahl VT, Frimodt-Moller N. Increasing frequency of vertebral osteomyelitis following *Staphylococcus aureus* bacteraemia in Denmark 1980-1990. *The Journal of infection* 1997;**34**(2):113-8
8. Sapico FL, Montgomerie JZ. Pyogenic vertebral osteomyelitis: report of nine cases and review of the literature. *Reviews of infectious diseases* 1979;**1**(5):754-76
9. Yoshimoto M, Takebayashi T, Kawaguchi S, et al. Pyogenic spondylitis in the elderly: a report from Japan with the most aging society. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2011;**20**(4):649-54 doi: 10.1007/s00586-010-1659-4[published Online First: Epub Date] | .
10. Sobottke R, Seifert H, Fatkenheuer G, Schmidt M, Gossmann A, Eysel P. Current diagnosis and treatment of spondylodiscitis. *Deutsches Arzteblatt international* 2008;**105**(10):181-7 doi: 10.3238/arztebl.2008.0181[published Online First: Epub Date] | .
11. Chelsom J, Solberg CO. Vertebral osteomyelitis at a Norwegian university hospital 1987-97: clinical features, laboratory findings and outcome. *Scandinavian journal of infectious diseases* 1998;**30**(2):147-51
12. Shousha M, Boehm H. Surgical treatment of cervical spondylodiscitis: a review of 30 consecutive patients. *Spine* 2012;**37**(1):E30-6 doi: 10.1097/BRS.0b013e31821bfbdb2[published Online First: Epub Date] | .
13. D'Agostino C, Scorzolini L, Massetti AP, et al. A seven-year prospective study on spondylodiscitis: epidemiological and microbiological features. *Infection* 2010;**38**(2):102-7 doi: 10.1007/s15010-009-9340-8[published Online First: Epub Date] | .
14. Digby JM, Kersley JB. Pyogenic non-tuberculous spinal infection: an analysis of thirty cases. *The Journal of bone and joint surgery. British volume* 1979;**61**(1):47-55
15. Grammatico L, Baron S, Rusch E, et al. Epidemiology of vertebral osteomyelitis (VO) in France: analysis of hospital-discharge data 2002-2003. *Epidemiology and infection* 2008;**136**(5):653-60 doi: 10.1017/S0950268807008850[published Online First: Epub Date] | .
16. Hopkinson N, Stevenson J, Benjamin S. A case ascertainment study of septic discitis: clinical, microbiological and radiological features.

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7 QJM : monthly journal of the Association of Physicians 2001;**94**(9):465-70
- 8 17. Joughin E, McDougall C, Parfitt C, Yong-Hing K, Kirkaldy-Willis WH. Causes and clinical management of vertebral osteomyelitis in
9 Saskatchewan. *Spine* 1991;**16**(3):261-4
- 10 18. Hsieh PC, Wienecke RJ, O'Shaughnessy BA, Koski TR, Ondra SL. Surgical strategies for vertebral osteomyelitis and epidural abscess.
11 *Neurosurgical focus* 2004;**17**(6):E4
- 12 19. Quinones-Hinojosa A, Jun P, Jacobs R, Rosenberg WS, Weinstein PR. General principles in the medical and surgical management of
13 spinal infections: a multidisciplinary approach. *Neurosurgical focus* 2004;**17**(6):E1 doi: 10.3171/foc.2004.17.6.1[published Online
14 First: Epub Date] | .
- 15 20. Chen WH, Jiang LS, Dai LY. Surgical treatment of pyogenic vertebral osteomyelitis with spinal instrumentation. *European spine*
16 *journal* : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the
17 Cervical Spine Research Society 2007;**16**(9):1307-16 doi: 10.1007/s00586-006-0251-4[published Online First: Epub Date] | .
- 18 21. Lehovsky J. Pyogenic vertebral osteomyelitis/disc infection. *Bailliere's best practice & research. Clinical rheumatology* 1999;**13**(1):59-75
19 doi: 10.1053/berh.1999.0006[published Online First: Epub Date] | .
- 20 22. Rezaei AR, Woo HH, Errico TJ, Cooper PR. Contemporary management of spinal osteomyelitis. *Neurosurgery* 1999;**44**(5):1018-25;
21 discussion 25-6
- 22 23. Hee HT, Majd ME, Holt RT, Pienkowski D. Better treatment of vertebral osteomyelitis using posterior stabilization and titanium mesh
23 cages. *Journal of spinal disorders & techniques* 2002;**15**(2):149-56; discussion 56
- 24 24. Yoon SH, Chung SK, Kim KJ, Kim HJ, Jin YJ, Kim HB. Pyogenic vertebral osteomyelitis: identification of microorganism and laboratory
25 markers used to predict clinical outcome. *European spine journal* : official publication of the European Spine Society, the European
26 Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 2010;**19**(4):575-82 doi:
27 10.1007/s00586-009-1216-1[published Online First: Epub Date] | .
- 28 25. Chikuda H, Yasunaga H, Horiguchi H, et al. Mortality and morbidity in dialysis-dependent patients undergoing spinal surgery: analysis
29 of a national administrative database in Japan. *The Journal of bone and joint surgery. American volume* 2012;**94**(5):433-8 doi:
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- 10.2106/JBJS.K.00183[published Online First: Epub Date] | .
26. Ministry of Health LaW, Japan. Survey of Medical Institutions and Hospital Report, 2010, 2010.
27. Hubbard AE, Ahern J, Fleischer NL, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. *Epidemiology* 2010;**21**(4):467-74 doi: 10.1097/EDE.0b013e3181caeb90[published Online First: Epub Date] | .
28. Ministry of Internal Affairs and Communications J. *The Demographic Shift*, 2012, 2012.
29. Pigrau C, Almirante B, Flores X, et al. Spontaneous pyogenic vertebral osteomyelitis and endocarditis: incidence, risk factors, and outcome. *The American journal of medicine* 2005;**118**(11):1287 doi: 10.1016/j.amjmed.2005.02.027[published Online First: Epub Date] | .
30. Tamura K. Clinical characteristics of infective endocarditis with vertebral osteomyelitis. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy* 2010;**16**(4):260-5 doi: 10.1007/s10156-010-0046-8[published Online First: Epub Date] | .
31. Fowler VG, Jr., Justice A, Moore C, et al. Risk factors for hematogenous complications of intravascular catheter-associated *Staphylococcus aureus* bacteremia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2005;**40**(5):695-703 doi: 10.1086/427806[published Online First: Epub Date] | .
32. Korzets A, Weinstein T, Ori Y, et al. Back pain and Staphylococcal bacteraemia in haemodialysed patients--beware! *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 1999;**14**(2):483-6
33. Belzunegui J, Del Val N, Intxausti JJ, et al. Vertebral osteomyelitis in northern Spain. Report of 62 cases. *Clinical and experimental rheumatology* 1999;**17**(4):447-52
34. Sapico FL, Montgomerie JZ. Vertebral osteomyelitis. *Infectious disease clinics of North America* 1990;**4**(3):539-50
35. Harris LF, Haws FP. Disc space infection. *Alabama medicine : journal of the Medical Association of the State of Alabama* 1994;**63**(7):12-4

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Table 1. Estimates of the incidence of VO

	No. of VO patients in the DPC hospitals (<i>N_i</i>)	Coverage rate (%) (<i>R_i</i>)	Sum of observation period (year) (<i>O_i</i>)	Population (×100,000) (<i>P_i</i>)	Incidence of VO (per 100,000 population per year) (<i>Y_i</i>)
Total	7,454	42.7%	2	1,278	6.8
Year					
2007 (July–Dec.)	1,599	44.5%	0.5	1,278	5.6
2008 (July–Dec.)	1,818	42.6%	0.5	1,277	6.7
2009 (July–Dec.)	1,789	38.0%	0.5	1,275	7.4
2010 (July–Dec.)	2,248	45.8%	0.5	1,281	7.7

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Sex

Male	4,373	42.7%	2	623	8.2
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Female	3,081	42.7%	2	657	5.5
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Age (years)

≤59	1,396	42.7%	2	878	1.9
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60–69	1,751	42.7%	2	182	11.2
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70–79	2,467	42.7%	2	129	22.4
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≥80	1,840	42.7%	2	81	26.5
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VO: vertebral osteomyelitis; DPC: Diagnosis Procedure Combination database

Yi=Nil Ril Oi Pi

Table 2. Patient backgrounds

	All		PVO		VT		<i>p</i>
	<i>N</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	
Total	7,454		7,143		311		
Age (years)							
≤59	1,396	(18.7)	1,329	(18.6)	67	(21.5)	0.462
60–69	1,751	(23.5)	1,674	(23.4)	77	(24.8)	
70–79	2,467	(33.1)	2,370	(33.2)	97	(31.2)	
≥80	1,840	(24.7)	1,770	(24.8)	70	(22.5)	
Sex							
Male	4,373	(58.7)	4,217	(59.0)	156	(50.2)	0.002
Female	3,081	(41.3)	2,926	(41.0)	155	(49.8)	
Hemodialysis	553	(7.4)	541	(7.6)	12	(3.9)	0.014
Diabetes	2,042	(27.4)	1,983	(27.8)	59	(19.0)	0.001
Liver cirrhosis	140	(1.9)	135	(1.9)	5	(1.6)	0.720
Rheumatoid arthritis	110	(1.5)	106	(1.5)	4	(1.3)	
Anticoagulant use	1,493	(20.0)	1,448	(20.3)	45	(14.5)	0.012
Malignancy	1,170	(15.7)	1,120	(15.7)	50	(16.1)	0.850

IE	145	(1.9)	145	(2.0)	0	(0.0)	0.011
Aortic aneurysm	66	(0.9)	65	(0.9)	1	(0.3)	<0.001
Spinal surgery	1,543	(20.7)	1,448	(20.3)	125	(40.2)	0.278
Type of hospital							
Academic	1,332	(17.9)	1,258	(17.6)	74	(23.8)	0.005
Non-academic	6,122	(82.1)	5,885	(82.4)	237	(76.2)	
Hospital volume							
(cases/year)							
≤6	2,766	(37.1)	2,660	(37.2)	106	(34.1)	0.254
7–10	2,290	(30.7)	2,192	(30.7)	98	(31.5)	
≥11	2,398	(32.2)	2,291	(32.1)	107	(34.4)	

PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE:

infective endocarditis

Table 3. In-hospital mortality

		In-hospital mortality			
		<i>N</i>	<i>n</i>	(%)	<i>p</i>
All		7,454	433	(5.8)	
Diagnosis	PVO	7,143	417	(5.8)	0.609
	VT	311	16	(5.1)	
Age (years)	≤59	1,396	23	(1.6)	<0.001
	60–69	1,751	94	(5.4)	
	70–79	2,467	154	(6.2)	
	≥80	1,840	162	(8.8)	
Sex	Male	4,373	265	(6.1)	0.270
	Female	3,081	168	(5.5)	
Hemodialysis	No	6,901	281	(4.1)	<0.001
	Yes	553	152	(27.5)	
Diabetes	No	5,412	226	(4.2)	<0.001
	Yes	2,042	207	(10.1)	
Liver cirrhosis	No	7,314	415	(5.7)	<0.001
	Yes	140	18	(12.9)	

Rheumatoid arthritis	No	7,344	427	(5.8)	0.873
	Yes	110	6	(5.5)	
Anticoagulants	No	5,961	333	(5.6)	0.101
	Yes	1,493	100	(6.7)	
Malignancy	No	6,284	316	(5.0)	<0.001
	Yes	1,170	117	(10.0)	
IE	No	7,309	415	(5.7)	0.001
	Yes	145	18	(12.4)	
Aortic aneurysm	No	7,388	426	(5.8)	0.106
	Yes	66	7	(10.6)	
Spinal surgery	No	5,881	368	(6.3)	0.001
	Yes	1,573	65	(4.1)	
Type of hospital	Academic	1,332	54	(4.1)	0.003
	Non-academic	6,122	379	(6.2)	
Hospital volume	≤6	2,766	186	(6.7)	0.005
(cases/year)	7–10	2,290	130	(5.7)	
	≥11	2,398	117	(4.9)	

PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE:

infective endocarditis

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Table 4. Logistic regression analysis for in-hospital mortality

		OR	95% CI	<i>P</i>
Diagnosis	PVO	Reference		
	VT	1.31	0.78–2.18	0.304
Age (years)	≤59	Reference		
	60–69	2.75	1.73–4.38	<0.001
	70–79	3.97	2.50–6.28	<0.001
	≥80	6.89	4.33–10.96	<0.001
Sex	Male	Reference		
	Female	0.89	0.72–1.11	0.308
Hemodialysis	No	Reference		
	Yes	10.62	8.21–13.73	<0.001
Diabetes	No	Reference		
	Yes	2.34	1.87–2.92	<0.001
Liver cirrhosis	No	Reference		
	Yes	2.63	1.50–4.61	0.001
Malignancy	No	Reference		
	Yes	2.66	2.09–3.39	<0.001

IE	No	Reference		
	Yes	3.22	1.82–5.70	<0.001
Spinal surgery	No	Reference		
	Yes	0.76	0.56–1.02	0.066
Type of hospitals	Academic	Reference		
	Non-academic	1.36	1.00–1.86	0.049
Hospital volume	≤6	Reference		
(/year)	7-10	0.82	0.64–1.05	0.122
	≥11	0.75	0.58–0.98	0.033

OR: odds ratio, CI: confidence interval, PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE: infective endocarditis



Incidence and Risk Factors for Mortality of Vertebral Osteomyelitis: A Retrospective Analysis Using the Japanese Diagnosis Procedure Combination Database

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5 **Incidence and Risk Factors for Mortality of Vertebral Osteomyelitis: A**
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8 **Retrospective Analysis Using the Japanese Diagnosis Procedure**
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10 **Combination Database**
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17 Incidence and Mortal Risk Factors of Vertebral Osteomyelitis
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Keywords: vertebral osteomyelitis, Diagnosis Procedure Combination

Database, pyogenic vertebral osteomyelitis, vertebral tuberculosis,

in-hospital mortality

(2,116 words for text only, excluding title page, abstract, references, figures

and tables)

Abstract

Objective: To examine the incidence of vertebral osteomyelitis (VO) and the clinical features of VO focusing on risk factors for death using a Japanese nationwide administrative database.

Design: Retrospective observational study.

Setting and Participants: We identified 7,454 patients who were diagnosed with VO and hospitalized between July and December, 2007-2010, using the Japanese Diagnosis Procedure Combination database.

Main Outcome Measures: The annual incidence of VO was estimated. Logistic regression analysis was performed to analyse factors affecting in-hospital mortality in the VO patients. Dependent variables included patient characteristics (age, sex and comorbidities), procedures (hemodialysis and surgery) and hospital factors (type of hospital and hospital volume).

Results: Overall, 58.7% of eligible patients were male and the average age was 69.2 years. The estimated incidence of VO increased from 5.6 per 100,000 population per year in 2007 to 7.7 per 100,000 population per year in 2010. In-hospital mortality was 5.7%. There was a linear trend between

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5 higher rates of in-hospital mortality and greater age. A higher rate of
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8 in-hospital mortality was significantly associated with hemodialysis use
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11 (odds ratios, 10.62 [95% confidence interval, 8.21–13.73]), diabetes (2.34
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13 [1.87–2.92]), liver cirrhosis (2.63 [1.50–4.61]), malignancy (2.66, [2.09–3.39]),
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16 infective endocarditis (3.22 [1.82–5.70]) and treatment in non-academic
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18 hospital (1.36 [1.00–1.86]).
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22 **Conclusions:** Our study demonstrates an increasing incidence of VO, and
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24 defines risk factors for death with a nationwide database. Several
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26 comorbidities were significantly associated with higher rates of in-hospital
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28 death in VO patients.
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Article summary

Article focus

- Vertebral osteomyelitis (VO) remains a life-threatening disease.
- Previous epidemiological studies on VO patients were limited because of small sample size.
- The present study examined the incidence of VO and clinical features of VO focusing on risk factors for death, using a nationwide database.

Key messages

- Using the Japanese Diagnosis Procedure Combination database, we analysed 7,454 VO patients.
- The estimated incidence of VO increased from 5.6 per 100,000 population per year in 2007 to 7.7 per 100,000 population per year in 2010.
- In-hospital mortality was 5.7%, which was significantly associated with greater age, hemodialysis use, diabetes, liver cirrhosis, malignancy, and infective endocarditis.

Strengths and limitations of this study'

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5 - This study is the largest study on risk factors for in-hospital mortality in
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8 VO patient.
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11 - The database does not include information on causative microorganisms or
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14 post-discharge status.
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Introduction

Vertebral osteomyelitis (VO) is a rare but life-threatening disease. [1-8] Its incidence appears to be on the rise. [9-11] In developed countries, the estimated incidence ranged from 1 case per 40,000 population per year to 1 case per 250,000 population per year. [6, 7, 11-16] However, these data were based on limited-scale epidemiological studies, [11] covering small areas with fewer than 200 cases. [6, 7, 12-16] Published data on the incidence of VO are thus of low validity and reliability.

Mortality in VO has been reported to be less than 11% [2-7] but these figures were also based on relatively small studies. A recent large scale study demonstrated adverse (death or qualified recovery) risk factors of VO, but did not focus specifically on the mortality of VO. [17] Thus, factors associated with mortality in VO have not yet been fully investigated.

Understanding the current epidemiology and clinical features of VO is an urgent requirement for effective management of this condition. The aims of the present study were (i) to estimate the incidence of VO, and (ii) to examine the clinical features of VO focusing on risk factors for mortality in VO, using a Japanese nationwide administrative database. In addition, the

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5 following details were examined as relevant clinical features of VO. First,
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8 data have also been lacking on mortality following surgical procedures for
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11 VO. Indications for surgical treatment are the following: prevention of
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14 spinal cord or major neural compression, stabilization or correction of spinal
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17 destruction, reduction of intractable pain, and failure of conservative
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20 management. [18-24] The present study ascertained the mortality of VO
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23 patients following conservative or surgical treatment. Second, VO consists
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26 of vertebral tuberculosis (VT) and pyogenic vertebral osteomyelitis (PVO),
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29 but clinical details in these two conditions have not been fully described. [3,
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32 6, 11, 25] We examined the differences in patient backgrounds and
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35 mortality between these two diseases.
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40 **Materials and Methods**

41 ***Data source***

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44 For this study, we utilized the Japanese Diagnosis Procedure Combination
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47 (DPC) database. Details of the database are described elsewhere. [26]
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52 Briefly, discharge abstract and administrative claim data are collected from
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55 the participating hospitals between July 1 and December 31 of each year by
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5 the DPC Study Group funded by the Japanese Ministry of Health, Labour
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8 and Welfare. The numbers of inpatients in the DPC database were 2.99
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11 million from 926 hospitals in 2007, 2.86 million from 855 hospitals in 2008,
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14 2.57 million from 818 hospitals in 2009, and 3.19 million from 952 hospitals
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17 in 2010, which covered approximately 43% of all the acute-care inpatients
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20 in Japan. The database includes the following data: unique identifier of
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23 hospital and type of hospital (academic or non-academic); patient age and
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26 sex; diagnoses, comorbidities at admission and complications after
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29 admission recorded according to the International Classification of Diseases,
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32 Tenth Revision (ICD-10) codes and text data in Japanese language;
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35 procedures according to the original Japanese codes; drugs used; length of
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38 stay (LOS); and in-hospital deaths. The anonymous nature of the data
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41 allowed the requirement for informed consent to be waived. This study was
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44 approved by the Institutional Review Board at The University of Tokyo.
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48 *Patient selection*

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51 We included all patients who were diagnosed with VO according to the
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54 following ICD-10-based codes: vertebral osteomyelitis (M46.2), pyogenic
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5 infection of intervertebral disk (M46.3), unspecified discitis (M46.4), other
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8 infective spondylopathy (M46.5), other specified inflammatory
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11 spondylopathy (M46.8), unspecified inflammatory spondylopathy (M46.9),
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14 unspecified spondylopathy (M48.9), vertebral tuberculosis (M49.0), *Bruceella*
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17 spondylitis (M49.1), enterobacterial spondylitis (M49.2), spondylopathy in
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20 other infectious or parasitic diseases (M49.3), and acute osteomyelitis
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23 located within the spinal column, head, neck, cranium or trunk (M86.0.8,
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26 M86.1.8). VO was categorized into PVO (other codes than M49.0) and VT
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29 (M49.0).
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34 ***Estimation of the incidence of VO***

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37 We estimated the annual incidence of VO per population per year, based on
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40 the annual number of patients discharged from all acute-care hospitals in
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43 Japan (A_i), the annual number of patients discharged from all DPC
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46 hospitals in Japan (B_i), the number of VO patients in the DPC hospitals
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49 (N_i), the observation period (O_i) and the population of Japan (P_i). The
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52 coverage of the DPC hospitals (R_i) was defined as B_i divided by A_i . Values of
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55 B_i were calculated from the DPC database and data for A_i were obtained
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5 from the Survey of Medical Institutions and Hospital Report, 2010. [27] P_i
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8 was obtained from Japanese Population Census data
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11 (<http://www.stat.go.jp/english/data/kokusei/index.htm>). The estimated
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14 incidence of VO per population per year (Y_i) was calculated using the
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17 following equation: $Y_i = N_i / R_i / O_i / P_i$.
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23 **Patient characteristics**

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25 The following variables were abstracted from the DPC database: patient
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28 age and sex; comorbidities that could potentially affect mortality in VO
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31 including diabetes, liver cirrhosis, rheumatoid arthritis, malignancy,
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34 infective endocarditis (IE) and aortic aneurysm; use of hemodialysis; spinal
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37 surgery performed during hospitalization; and type of hospital and hospital
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40 volume. We also examined use of anticoagulants for each patient, including
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43 aspirin, warfarin, clopidogrel and ticlopidine.
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46 Hospital volume was categorized into tertiles: low-volume hospitals (<7
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48 cases/year), medium-volume hospitals (7–10 cases/year) and high-volume
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51 hospitals (>10 cases/year). These categories were based on cutoffs that
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54 yielded equivalent numbers of patients in each volume category.
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Outcome measurements

The primary outcome measured was in-hospital mortality. The secondary outcome was LOS.

Statistical analysis

We used the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables to perform univariate comparisons of patient characteristics and outcomes between subgroups. Logistic regression analysis was performed to analyze the concurrent effects of various factors on the occurrence of in-hospital death, while adjusting for clustering of patients within hospitals using a generalized estimating equation. [28] The threshold for significance was a p value <0.05 . All statistical analyses were conducted using IBM SPSS version 19.0 (IBM SPSS, Armonk, NY, USA).

RESULTS

Estimated incidence of VO in Japan

We identified 7,454 eligible patients. Table 1 shows the estimated incidence of VO in Japan. The overall incidence of VO between 2007 and 2010 was 6.8 per 100,000 population per year. The estimated incidence increased from 5.6 per 100,000 population per year in 2007 to 7.7 per 100,000 population per year in 2010 ($p<0.001$). The incidence was lower in the population aged ≤ 59 years (1.9 per 100,000 population per year) than in those aged 60–69 years (11.2), 70–79 years (22.4) or ≥ 80 years (26.5) ($p<0.001$).

Patient background

The patients' backgrounds are shown in Table 2. Overall, 58.7% were male and the average age (\pm standard deviation) was 69.2 ± 14.0 years. There were 7,143 cases of PVO and 311 of VT. The proportion of male PVO patients (59.0%) was higher than that of male VT patients (50.2%, $p=0.002$). No significant difference in age was observed between the PVO and VT groups. PVO patients were more likely to have a comorbid condition than VT patients.

In-hospital mortality

In-hospital mortality for each category is shown in Table 3. The overall in-hospital mortality was 5.8%. Higher in-hospital mortality was associated

with greater age ($p<0.001$), hemodialysis use (27.5%, $p<0.001$), diabetes (10.1%, $p<0.001$), liver cirrhosis (12.9%, $p<0.001$), malignancy (10.0%, $p<0.001$), IE (12.4%, $p=0.001$) and treatment in a non-academic hospital (6.2%, $p=0.003$). Higher hospital volume was significantly associated with lower mortality ($p=0.005$).

Logistic regression analysis for in-hospital mortality

Table 4 shows the results of the logistic regression analysis for in-hospital mortality. Higher mortality was significantly associated with greater age (odds ratios [ORs] of 2.75, 3.97, and 6.89 for patients aged 60–69, 70–79, and ≥ 80 years compared with those aged ≤ 59 , respectively $p<0.001$), hemodialysis use (OR 10.62; $p<0.001$), diabetes (OR 2.34; $p<0.001$), liver cirrhosis (OR 2.63; $p=0.001$), malignancy (OR 2.66; $p<0.001$), IE (OR 3.22; $p<0.001$) and treatment in a non-academic hospital (OR 1.36; $p=0.049$).

Patients treated in high-volume hospitals were significantly less likely to die compared with those at low-volume hospitals (OR 0.75; $p=0.033$).

Overall, the median LOS (interquartile range) was 47 (24–77) days. The median LOS was shorter in PVO patients (47 [24–77] days) than that in VT patients (56 [25.5–85.5] days, $p=0.027$). No significant difference in LOS

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5 was observed between academic and non-academic hospitals (47 [24–75]
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8 days vs. 47 [24–78] days, $p=0.511$) or between hospital-volume groups (47
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10 [24–80] days, 48 [24–79] days, and 47 [24–74] days in low-, medium-, and
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12 high-volume hospitals, respectively, $p=0.145$).
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20 DISCUSSION

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22 The present study examined the annual trends in the occurrence of VO and
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24 risk factors for death from VO using a Japanese nationwide inpatient
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26 database. Our study had two major findings. First, the incidence of VO was
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28 significantly higher in the elderly and increased year by year. Second,
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30 higher in-hospital mortality in VO was significantly associated with various
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32 factors.
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40 Our data demonstrated that the incidence of VO in Japan increased during
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42 the study period, from 5.6 to 7.7 per 100,000 population per year. Yoshimoto
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44 et al. reported that the increase in the VO incidence could be related to the
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46 increasing ratio of aged people (65 years of age or older) in Japan. [9] A
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48 recent report of demographic shifts in Japan demonstrated the rapid
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50 increase in aged population: the percentage increase compared with 2007
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5 was 3.2 % in 2008, 6.1% in 2009, and 7.1% in 2010. [29] Based on the
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8 relationship between higher age and higher frequency of VO occurrence, as
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11 was demonstrated in this study, we believe that this increase is partly
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14 attributable to the aging population in Japan.

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17 Previous limited data have suggested that factors affecting the occurrence
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20 of VO include antecedent infection, diabetes mellitus, rheumatic diseases,
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23 immunosuppression, drug abuse, alcoholism, vertebral compression due to
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26 malignant metastasis, trauma, disc herniation, IE, and prior surgery
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29 (gastrointestinal and urogenital tract).[6] However, risk factors affecting
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32 death from VO have not been well investigated. The present study indicated
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35 that significant risk factors for death from VO were greater age,
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38 hemodialysis, diabetes, liver cirrhosis, malignancy and IE. Mortality risks
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41 of PVO were not different from those of VT.

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43 Recently, two small-scale studies of fewer than 100 cases reported that IE
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46 appeared to increase the incidence of VO, but did not increase its mortality.
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49 [5,30] Conversely, our large-scale data showed that IE was a significant
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52 factor that increased mortality associated with VO. The other factors have
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55 never previously been analysed as risk factors for death with VO.
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5 Hemodialysis use was reported to be a risk factor for hematogenous
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8 complications of intravascular catheter use associated with *S. aureus*
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11 bacteremia. [31] A case report suggested the possibility of VO in
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14 hemodialysis patients. [32] Our study is the first to demonstrate a
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17 significant relationship between hemodialysis use and death from VO.
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20 Previous reports indicated that VO patients were more likely to have
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23 diabetes mellitus (11–19%), [12, 25, 33, 34] but the present study further
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26 demonstrated that diabetes mellitus was a significant predictor for
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29 mortality in VO. Although not surprising, our study has demonstrated that
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32 age, liver cirrhosis, and malignancy were all related to death with VO.
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35 As shown in Table 4, the association of VO mortality with spinal surgery did
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38 not reach statistical significance. Randomized controlled trials are essential
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41 to verify the efficacy of spinal surgery because confounding by surgical
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44 indication affects the surgical result. However, several papers have
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47 suggested the impossibility of randomized controlled trials to decide the
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50 treatment strategy for VO, even apart from spinal surgery. [35, 36] Thus,
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53 our DPC data could not reveal the efficacy of spinal surgery for VO.
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56 The high mortality suggests that VO remains a life-threatening disease
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5 despite advances in medical practice and should be regarded as a fatal
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8 systemic disorder rather than just a localized vertebral disorder.
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10 Our data revealed that several systemic diseases increased the mortality
11 risk of VO, underscoring the need to keep VO in mind and to catch such
12 signs of VO as unidentified fever or back pain as soon as possible during the
13 treatment of these background diseases.
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22 We acknowledge several limitations of the present study. First, the DPC
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24 database does not provide important clinical data such as causative
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26 microorganisms and information on post-discharge outpatient services.
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29 Second, although the sample size was large, the population
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31 representativeness was limited because the participating hospitals were
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33 skewed toward large hospitals. Third, the diagnoses recorded in the
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35 administrative database are less well validated than those made in planned
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37 prospective surveys. Fourth, the period of observation was short for showing
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39 the long term trend of VO incidence. Fifth, the increased rate of VO may be
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41 an overestimation because of several artifacts including the improvement
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43 and increased prevalence of surveillance machines. Last, the mortality of
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55 VO may be underestimated because of transfers to other hospitals. Despite
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5 these limitations, our study has resulted in several new findings regarding
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8 VO, including risk factors for death.
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14 CONCLUSION

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17 The present study confirmed the increasing incidence of VO using a
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19 nationwide database. Greater age, use of hemodialysis, diabetes, liver
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21 cirrhosis, malignancy, and IE were significantly associated with higher
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23 rates of in-hospital death in patients with VO. Based on the high mortality,
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26 VO remains a life-threatening, systemic disease. These novel findings will
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29 be important for improving the clinical management of VO.
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37 Contributors

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40 HY, HH and KF collected the data. TA, HC, HY and KS designed the study,
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42 analysed and interpreted the data, and drafted the manuscript. All authors
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44 had full access to all data (including statistical reports and tables) in the
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46
47 study and take responsibility for the integrity of the data and the accuracy
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50 of the data analysis.
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References

1. Kulowski J. Pyogenic osteomyelitis of the spine: an analysis and discussion of 102 cases. *J Bone Joint Surg* 1936;**18**(2):22.
2. Sapico FL, Montgomerie JZ. Pyogenic vertebral osteomyelitis: report of nine cases and review of the literature. *Rev Infect Dis* 1979;**1**(5):754-76.
3. Colmenero JD, Jimenez-Mejias ME, Sanchez-Lora FJ, et al. Pyogenic, tuberculous, and brucellar vertebral osteomyelitis: a descriptive and comparative study of 219 cases. *Ann Rheum Dis* 1997;**56**(12):709-15.
4. Carragee EJ. Pyogenic vertebral osteomyelitis. *J Bone Joint Surg Am* 1997;**79**(6):874-80.
5. Pigrau C, Almirante B, Flores X, et al. Spontaneous pyogenic vertebral osteomyelitis and endocarditis: incidence, risk factors, and outcome. *Am J Med* 2005;**118**(11):1287.
6. Beronius M, Bergman B, Andersson R. Vertebral osteomyelitis in Goteborg, Sweden: a retrospective study of patients during 1990-95. *Scand J Infect Dis* 2001;**33**(7):527-32.
7. Chelsom J, Solberg CO. Vertebral osteomyelitis at a Norwegian university hospital 1987-97: clinical features, laboratory findings and outcome. *Scand J Infect Dis* 1998;**30**(2):147-51.
8. Legrand E, Flipo RM, Guggenbuhl P, et al. Management of nontuberculous infectious discitis. treatments used in 110 patients admitted to 12 teaching hospitals in France. *Joint, bone, spine : revue du rhumatisme* 2001;**68**(6):504-9.
9. Yoshimoto M, Takebayashi T, Kawaguchi S, et al. Pyogenic spondylitis in the elderly: a report from Japan with the most aging society. *Eur Spine J* 2011;**20**(4):649-54.
10. Gouliouris T, Aliyu SH, Brown NM. Spondylodiscitis: update on diagnosis and management. *J Antimicrob Chemother* 2010;**65 Suppl 3**:iii11-24.
11. Grammatico L, Baron S, Rusch E, et al. Epidemiology of vertebral osteomyelitis (VO) in France: analysis of hospital-discharge data 2002-2003. *Epidemiol Infect* 2008;**136**(5):653-60.
12. Krogsgaard MR, Wagn P, Bengtsson J. Epidemiology of acute vertebral osteomyelitis in Denmark: 137 cases in Denmark 1978-1982, compared to cases reported to the National Patient Register 1991-1993. *Acta Orthop Scand* 1998;**69**(5):513-7.
13. Kapeller P, Fazekas F, Krametter D, et al. Pyogenic infectious spondylitis: clinical, laboratory and MRI features. *Eur Neurol* 1997;**38**(2):94-8.
14. Hopkinson N, Stevenson J, Benjamin S. A case ascertainment study of septic discitis: clinical, microbiological and radiological features. *QJM* 2001;**94**(9):465-70.
15. Digby JM, Kersley JB. Pyogenic non-tuberculous spinal infection: an analysis of thirty

- cases. *J Bone Joint Surg Br* 1979;**61**(1):47-55.
16. Jensen AG, Espersen F, Skinhoj P, et al. Increasing frequency of vertebral osteomyelitis following *Staphylococcus aureus* bacteraemia in Denmark 1980-1990. *J Infect* 1997;**34**(2):113-8.
17. McHenry MC, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. *Clin Infect Dis* 2002;**34**(10):1342-50.
18. Hsieh PC, Wienecke RJ, O'Shaughnessy BA, et al. Surgical strategies for vertebral osteomyelitis and epidural abscess. *Neurosurg Focus* 2004;**17**(6):E4.
19. Quinones-Hinojosa A, Jun P, Jacobs R, et al. General principles in the medical and surgical management of spinal infections: a multidisciplinary approach. *Neurosurg focus* 2004;**17**(6):E1.
20. Chen WH, Jiang LS, Dai LY. Surgical treatment of pyogenic vertebral osteomyelitis with spinal instrumentation. *Eur Spine J* 2007;**16**(9):1307-16.
21. Lehovskiy J. Pyogenic vertebral osteomyelitis/disc infection. *Baillieres Best Pract Res Clin Rheumatol* 1999;**13**(1):59-75.
22. Rezai AR, Woo HH, Errico TJ, et al. Contemporary management of spinal osteomyelitis. *Neurosurgery* 1999;**44**(5):1018-25; discussion 25-6.
23. Hee HT, Majd ME, Holt RT, et al. Better treatment of vertebral osteomyelitis using posterior stabilization and titanium mesh cages. *J Spinal Disord Tech* 2002;**15**(2):149-56; discussion 56.
24. Shousha M, Boehm H. Surgical treatment of cervical spondylodiscitis: a review of 30 consecutive patients. *Spine* 2012;**37**(1):E30-6.
25. Joughin E, McDougall C, Parfitt C, et al. Causes and clinical management of vertebral osteomyelitis in Saskatchewan. *Spine* 1991;**16**(3):261-4.
26. Chikuda H, Yasunaga H, Horiguchi H, et al. Mortality and morbidity in dialysis-dependent patients undergoing spinal surgery: analysis of a national administrative database in Japan. *J Bone Joint Surg Am* 2012;**94**(5):433-8.
27. Ministry of Health LaW, Japan. Survey of Medical Institutions and Hospital Report, 2010, 2010.
28. Hubbard AE, Ahern J, Fleischer NL, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. *Epidemiology* 2010;**21**(4):467-74.
29. Ministry of Internal Affairs and Communications J. The Demographic Shift, 2012, 2012.
30. Tamura K. Clinical characteristics of infective endocarditis with vertebral osteomyelitis. *J Infect Chemother* 2010;**16**(4):260-5.

- 1
2
3
4
5 31. Fowler VG, Jr., Justice A, Moore C, et al. Risk factors for hematogenous complications
6 of intravascular catheter-associated Staphylococcus aureus bacteremia. Clin Infect
7 Dis 2005;**40**(5):695-703.
8
9 32. Korzets A, Weinstein T, Ori Y, et al. Back pain and Staphylococcal bacteraemia in
10 haemodialysed patients--beware! Nephrol Dial Transplant 1999;**14**(2):483-6.
11
12 33. Belzunegui J, Del Val N, Intxausti JJ, et al. Vertebral osteomyelitis in northern Spain.
13 Report of 62 cases. Clin Exp Rheumatol 1999;**17**(4):447-52.
14
15 34. Harris LF, Haws FP. Disc space infection. Ala med 1994;**63**(7):12-4.
16
17 35. Darouiche RO. Spinal epidural abscess. N Engl J Med 2006;**355**(19):2012-20.
18
19 36. Zimmerli W. Clinical practice. Vertebral osteomyelitis. N Engl J Med
20 2010;**362**(11):1022-9.
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Table 1. Estimates of the incidence of VO

	No. of VO patients in the DPC hospitals (<i>N_i</i>)	Coverage rate (%) (<i>R_i</i>)	Sum of observation period (year) (<i>O_i</i>)	Population (×100,000) (<i>P_i</i>)	Incidence of VO (per 100,000 population per year) (<i>Y_i</i>)	<i>p</i>
Total	7,454	42.7%	2	1,278	6.8	
Year						
2007 (July–Dec.)	1,599	44.5%	0.5	1,278	5.6	<u><0.001</u>
2008 (July–Dec.)	1,818	42.6%	0.5	1,277	6.7	
2009 (July–Dec.)	1,789	38.0%	0.5	1,275	7.4	
2010 (July–Dec.)	2,248	45.8%	0.5	1,281	7.7	

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Sex

Male 4,373 42.7% 2 623 8.2 <0.001

Female 3,081 42.7% 2 657 5.5

Age (years)

≤59 1,396 42.7% 2 878 1.9 <0.001

60–69 1,751 42.7% 2 182 11.2

70–79 2,467 42.7% 2 129 22.4

≥80 1,840 42.7% 2 81 26.5

VO: vertebral osteomyelitis; DPC: Diagnosis Procedure Combination database

Yi=Nil Ril Oil Pi

Table 2. Patient backgrounds

	All		PVO		VT		<i>p</i>
	<i>N</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	
Total	7,454		7,143		311		
Age (years)							
≤59	1,396	(18.7)	1,329	(18.6)	67	(21.5)	0.462
60–69	1,751	(23.5)	1,674	(23.4)	77	(24.8)	
70–79	2,467	(33.1)	2,370	(33.2)	97	(31.2)	
≥80	1,840	(24.7)	1,770	(24.8)	70	(22.5)	
Sex							
Male	4,373	(58.7)	4,217	(59.0)	156	(50.2)	0.002
Female	3,081	(41.3)	2,926	(41.0)	155	(49.8)	
Hemodialysis	553	(7.4)	541	(7.6)	12	(3.9)	0.014
Diabetes	2,042	(27.4)	1,983	(27.8)	59	(19.0)	0.001
Liver cirrhosis	140	(1.9)	135	(1.9)	5	(1.6)	0.720
Rheumatoid arthritis	110	(1.5)	106	(1.5)	4	(1.3)	
Anticoagulant use	1,493	(20.0)	1,448	(20.3)	45	(14.5)	0.012
Malignancy	1,170	(15.7)	1,120	(15.7)	50	(16.1)	0.850

IE	145	(1.9)	145	(2.0)	0	(0.0)	0.011
Aortic aneurysm	66	(0.9)	65	(0.9)	1	(0.3)	<0.001
Spinal surgery	1,543	(20.7)	1,448	(20.3)	125	(40.2)	0.278
Type of hospital							
Academic	1,332	(17.9)	1,258	(17.6)	74	(23.8)	0.005
Non-academic	6,122	(82.1)	5,885	(82.4)	237	(76.2)	
Hospital volume							
(cases/year)							
≤6	2,766	(37.1)	2,660	(37.2)	106	(34.1)	0.254
7–10	2,290	(30.7)	2,192	(30.7)	98	(31.5)	
≥11	2,398	(32.2)	2,291	(32.1)	107	(34.4)	

PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE:

infective endocarditis

Table 3. In-hospital mortality

		<i>N</i>	In-hospital mortality		
			<i>n</i>	(%)	<i>p</i>
All		7,454	433	(5.8)	
Diagnosis	PVO	7,143	417	(5.8)	0.609
	VT	311	16	(5.1)	
Age (years)	≤59	1,396	23	(1.6)	<0.001
	60–69	1,751	94	(5.4)	
	70–79	2,467	154	(6.2)	
	≥80	1,840	162	(8.8)	
Sex	Male	4,373	265	(6.1)	0.270
	Female	3,081	168	(5.5)	
Hemodialysis	No	6,901	281	(4.1)	<0.001
	Yes	553	152	(27.5)	
Diabetes	No	5,412	226	(4.2)	<0.001
	Yes	2,042	207	(10.1)	
Liver cirrhosis	No	7,314	415	(5.7)	<0.001
	Yes	140	18	(12.9)	

Rheumatoid arthritis	No	7,344	427	(5.8)	0.873
	Yes	110	6	(5.5)	
Anticoagulants	No	5,961	333	(5.6)	0.101
	Yes	1,493	100	(6.7)	
Malignancy	No	6,284	316	(5.0)	<0.001
	Yes	1,170	117	(10.0)	
IE	No	7,309	415	(5.7)	0.001
	Yes	145	18	(12.4)	
Aortic aneurysm	No	7,388	426	(5.8)	0.106
	Yes	66	7	(10.6)	
Spinal surgery	No	5,881	368	(6.3)	0.001
	Yes	1,573	65	(4.1)	
Type of hospital	Academic	1,332	54	(4.1)	0.003
	Non-academic	6,122	379	(6.2)	
Hospital volume	≤6	2,766	186	(6.7)	0.005
(cases/year)	7–10	2,290	130	(5.7)	
	≥11	2,398	117	(4.9)	

PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE:

infective endocarditis

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Table 4. Logistic regression analysis for in-hospital mortality

		OR	95% CI	<i>P</i>
Diagnosis	PVO	Reference		
	VT	1.31	0.78–2.18	0.304
Age (years)	≤59	Reference		
	60–69	2.75	1.73–4.38	<0.001
	70–79	3.97	2.50–6.28	<0.001
	≥80	6.89	4.33–10.96	<0.001
Sex	Male	Reference		
	Female	0.89	0.72–1.11	0.308
Hemodialysis	No	Reference		
	Yes	10.62	8.21–13.73	<0.001
Diabetes	No	Reference		
	Yes	2.34	1.87–2.92	<0.001
Liver cirrhosis	No	Reference		
	Yes	2.63	1.50–4.61	0.001
Malignancy	No	Reference		
	Yes	2.66	2.09–3.39	<0.001

IE	No	Reference		
	Yes	3.22	1.82–5.70	<0.001
Spinal surgery	No	Reference		
	Yes	0.76	0.56–1.02	0.066
Type of hospitals	Academic	Reference		
	Non-academic	1.36	1.00–1.86	0.049
Hospital volume	≤6	Reference		
(/year)	7-10	0.82	0.64–1.05	0.122
	≥11	0.75	0.58–0.98	0.033

OR: odds ratio, CI: confidence interval, PVO: pyogenic vertebral

osteomyelitis, VT: vertebral tuberculosis, IE: infective endocarditis

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~~Incidence and Risk Factors for Mortality of Incidence and Mortal Risk~~

~~Factors of~~ Vertebral Osteomyelitis: A Retrospective Analysis Using the

Japanese Diagnosis Procedure Combination Database

Incidence and Mortal Risk Factors of Vertebral Osteomyelitis

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23 Keywords: vertebral osteomyelitis, Diagnosis Procedure Combination

24 Database, pyogenic vertebral osteomyelitis, vertebral tuberculosis,

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27 in-hospital mortality
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34 (2,135 words for text only, excluding title page, abstract, references, figures

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Abstract

Objective: To examine the incidence of vertebral osteomyelitis (VO) and the clinical features of VO focusing on risk factors for death using a Japanese nationwide administrative database.

Design: Retrospective observational study.

Setting and Participants: We identified 7,454 patients who were diagnosed with VO and hospitalized between July and December, 2007-2010, using the Japanese Diagnosis Procedure Combination database.

Main Outcome Measures: The annual incidence of VO was estimated. Logistic regression analysis was performed to analyse factors affecting in-hospital mortality in the VO patients. Dependent variables included patient characteristics~~patient backgrounds~~ (age, sex and comorbidities), procedures (hemodialysis and surgery) and hospital factors (type of hospital and hospital volume).

Results: Overall, 58.7% of eligible patients were male and the average age was 69.2 years. The estimated incidence of VO increased from 5.6 per 100,000 population per year in 2007 to 7.7 per 100,000 population per year in 2010. In-hospital mortality was 5.7%. There was a linear trend between

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5 higher rates in-hospital mortality and greater age. ~~Higher~~ A higher rate of
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8 in-hospital mortality was significantly associated with hemodialysis use
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11 (odds ratios, 10.62 [95% confidence interval, 8.21–13.73]), diabetes (2.34
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13 [1.87–2.92]), liver cirrhosis (2.63 [1.50–4.61]), malignancy (2.66, [2.09–3.39]),
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15 infective endocarditis (3.22 [1.82–5.70]) and treatment in non-academic
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17 hospital (1.36 [1.00–1.86]).
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23 **Conclusions:** Our study demonstrates an increasing incidence of VO, and
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25 defines risk factors ~~Our study is the first to demonstrate the increasing~~
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27 ~~incidence of VO, its mortality and risk factors~~ for death with a nationwide
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29 database. Several comorbidities were significantly associated with higher
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31 rates of in-hospital death in VO patients. ~~We believe these novel findings~~
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37 ~~are important for improving the clinical management of VO.~~
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Article summary

Article focus

- Vertebral osteomyelitis (VO) remains a life-threatening disease.
- Previous epidemiological studies on VO patients were limited because of small sample size.
- The present study examined the incidence of VO and clinical features of VO focusing on risk factors for death, using a nationwide database.

Key messages

- Using the Japanese Diagnosis Procedure Combination database, we analysed 7,454 VO patients.
- The estimated incidence of VO increased from 5.6 per 100,000 population per year in 2007 to 7.7 per 100,000 population per year in 2010.
- In-hospital mortality was 5.7%, which was significantly associated with greater age, hemodialysis use, diabetes, liver cirrhosis, malignancy, and infective endocarditis.

Strengths and limitations of this study'

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5 - This study is the largest study on risk factors for in-hospital mortality in
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8 VO patient.~~This study is the first to report significant risk factors for death~~
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11 ~~in VO patients.~~

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14 - The database does not include information on causative microorganisms or
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17 post-discharge status.
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Introduction

Vertebral osteomyelitis (VO) is a rare but life-threatening disease. [1-8] Its incidence appears to be on the rise. [9-11] Vertebral osteomyelitis (VO) is a rare, but life-threatening disease and its incidence appears to be on the rise [1-9]. Reportedly, VO represented 3–5% of cases of osteomyelitis[10]. In developed countries, the estimated incidence ranged from 1 case per 40,000 population per year to 1 case per 250,000 population per year . [3 6 7 11-17]. [6, 7, 11-16] However, these data were based on limited-scale epidemiological studies, [11], covering small areas with fewer than 200 cases. [6, 7, 12-16][6 9 14 16]. Published data on the incidence of VO are thus of low validity and reliability[10].

Mortality in VO has been reported to be less than 11%[3 6 8 10 17], [2-7] but these figures were also based on relatively small studies. Furthermore, A recent large scale study demonstrated adverse (death or qualified recovery) risk factors of VO, but did not focus specifically on the mortality of VO. [17]

Thus, factors associated with mortality in VO have not yet been fully investigated.–

Understanding the current epidemiology and clinical features of VO is an

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5 urgent requirement for effective management of this condition. The aims of
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8 the present study were (i) to estimate the incidence of VO, and (ii) to
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11 examine clinical features of VO focusing on risk factors for mortality in VO,
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14 using a Japanese nationwide administrative database. In addition, the
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16 following details were examined as relevant clinical features of VO.
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20 ~~Additionally, the following details were examined.~~ First, data have also
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22 been lacking on mortality following surgical procedures for VO. Indications
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24 for surgical treatment are ~~the following: decided by the following factors;~~
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26 prevention of spinal cord or major neural compression, stabilization or
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28 correction of spinal destruction, reduction of intractable pain, and failure of
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30 conservative management. [18-24] ~~prevention for spinal cord or major~~
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32 ~~neural compression, stabilization or correction of spinal construction,~~
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34 ~~reduction of intractable pain and failure of conservative~~
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36 ~~management.~~ [17-22][23] The present study ascertained the verified
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38 mortality of VO patients following conservative or surgical treatments.
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49 Second, VO consists of vertebral tuberculosis (VT) and pyogenic vertebral
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51 osteomyelitis (PVO), but clinical details in these two conditions have not
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55 been fully described ~~[3-17-18].~~ [3, 6, 11, 25] We examined the difference in
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5 patient backgrounds and mortality between these two diseases.
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10 **Materials and Methods**

11 *Data source*

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14 For this study, we utilized the Japanese Diagnosis Procedure Combination
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17 (DPC) database. Details of the database are described elsewhere^{[19][26]}.
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22 Briefly, discharge abstract and administrative claim data are collected from
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24 the participating hospitals between July 1 and December 31 each year by
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26 the DPC Study Group funded by the Japanese Ministry of Health, Labour
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28 and Welfare. The numbers of inpatients in the DPC database were 2.99
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30 million from 926 hospitals in 2007, 2.86 million from 855 hospitals in 2008,
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32 2.57 million from 818 hospitals in 2009 and 3.19 million from 952 hospitals
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34 in 2010, which covered approximately 43% of all the acute-care inpatients
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36 in Japan. The database includes the following data: unique identifier of
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38 hospital and type of hospital (academic or non-academic); patient age and
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40 sex; diagnoses, comorbidities at admission and complications after
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42 admission recorded according to the International Classification of Diseases,
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44 Tenth Revision (ICD-10) codes and text data in Japanese language;
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5 procedures according to the original Japanese codes; drugs used; length of
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8 stay (LOS); and in-hospital deaths. The anonymous nature of the data
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11 allowed the requirement for informed consent to be waived. This study was
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14 approved by the Institutional Review Board at The University of Tokyo.
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16 17 18 19 20 *Patient selection*

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22 We included all patients who were diagnosed with VO according to the
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24 following ICD-10-based codes: vertebral osteomyelitis (M46.2), pyogenic
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26 infection of intervertebral disk (M46.3), unspecified discitis (M46.4), other
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28 infective spondylopathy (M46.5), other specified inflammatory
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30 spondylopathy (M46.8), unspecified inflammatory spondylopathy (M46.9),
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32 unspecified spondylopathy (M48.9), vertebral tuberculosis (M49.0), *Brucella*
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34 spondylitis (M49.1), enterobacterial spondylitis (M49.2), spondylopathy in
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36 other infectious or parasitic diseases (M49.3), and acute osteomyelitis
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38 located within the spinal column, head, neck, cranium or trunk (M86.0.8,
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40 M86.1.8). ~~VO was categorized into PVO and VT. VO was categorized into~~
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42 PVO (other codes than M49.0) and VT (M49.0).
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Estimation of the incidence of VO

We estimated the annual incidence of VO per population per year, based on the annual number of patients discharged from all acute-care hospitals in Japan (A_i), the annual number of patients discharged from all DPC hospitals in Japan (B_i), the number of VO patients in the DPC hospitals (N_i), the observation period (O_i) and the population of Japan (P_i). The coverage of the DPC hospitals (R_i) was defined as B_i divided by A_i . Values of B_i were calculated from the DPC database and data for A_i were obtained from the Survey of Medical Institutions and Hospital Report, 2010^[20]. ^[27] P_i was obtained from Japanese Population Census data (<http://www.stat.go.jp/english/data/kokusei/index.htm>). The estimated incidence of VO per population per year (Y_i) was calculated using the following equation: $Y_i = N_i / R_i / O_i / P_i$.

Patient background Patient characteristics

The following variables were abstracted from the DPC database: patient age and sex; comorbidities that could potentially affect mortality in VO including diabetes, liver cirrhosis, rheumatoid arthritis, malignancy,

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5 infective endocarditis (IE) and aortic aneurysm; use of hemodialysis; spinal
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8 surgery performed during hospitalization; and type of hospital and hospital
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11 volume. We also examined use of anticoagulants for each patient, including
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14 aspirin, warfarin, clopidogrel and ticlopidine.

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17 Hospital volume was categorized into tertiles: low-volume hospitals (<7
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19 cases/year), medium-volume hospitals (7–10 cases/year) and high-volume
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21 hospitals (>10 cases/year). These categories were based on cutoffs that
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23 yielded equivalent numbers of patients in each volume category.
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31 ***Outcome measurements***

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34 The primary outcome measured was in-hospital mortality. The secondary
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36 outcome was LOS.
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43 ***Statistical analysis***

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46 We used the chi-square test for categorical variables and the Wilcoxon
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48 rank-sum test for continuous variables to perform univariate comparisons
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50 of patient characteristics and outcomes between subgroups. Logistic
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52 regression analysis was performed to analyze the concurrent effects of
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various factors on the occurrence of in-hospital death, while adjusting for clustering of patients within hospitals using a generalized estimating equation^{[21]. [28]} The threshold for significance was a p value <0.05 . All statistical analyses were conducted using IBM SPSS version 19.0 (IBM SPSS, Armonk, NY, USA).

RESULTS

Estimated incidence of VO in Japan

We identified 7,454 eligible patients. Table 1 shows the estimated incidence of VO in Japan. The overall incidence of VO between 2007 and 2010 was 6.8 per 100,000 population per year. The estimated incidence increased from 5.6 per 100,000 population per year in 2007 to 7.7 per 100,000 population per year in 2010 ($p<0.001$). The incidence was lower in the population aged ≤ 59 years (1.9 per 100,000 population per year) than in those aged 60–69 years (11.2), 70–79 years (22.4) or ≥ 80 years (26.5) ($p<0.001$).

Patient ~~background characteristics~~

The patients' ~~backgrounds characteristics~~ are shown in Table 2. Overall, 58.7% were male and the average age (\pm standard deviation) was 69.2 ± 14.0

years. There were 7,143 cases of PVO and 311 of VT. The proportion of male PVO patients (59.0%) was higher than that of male VT patients (50.2%, $p=0.002$). No significant difference in age was observed between the PVO and VT groups. PVO patients were more likely to have a comorbid condition than VT patients.

In-hospital mortality

In-hospital mortality for each category is shown in Table 3. The overall in-hospital mortality was 5.8%. Higher in-hospital mortality was associated with greater age ($p<0.001$), hemodialysis use (27.5%, $p<0.001$), diabetes (10.1%, $p<0.001$), liver cirrhosis (12.9%, $p<0.001$), malignancy (10.0%, $p<0.001$), IE (12.4%, $p=0.001$) and treatment in a non-academic hospital (6.2%, $p=0.003$). Higher hospital volume was significantly associated with lower mortality ($p=0.005$).

Logistic regression analysis for in-hospital mortality

Table 4 shows the results of the logistic regression analysis for in-hospital mortality. Higher mortality was significantly associated with greater age (odds ratio [OR]), 2.75, 3.97 and 6.89; $p<0.001$ for patients aged 60–69, 70–79 and ≥ 80 years compared with those aged ≤ 59), hemodialysis use (OR,

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5 10.62; $p<0.001$), diabetes (OR, 2.34; $p<0.001$), liver cirrhosis (OR, 2.63;
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8 $p=0.001$), malignancy (OR, 2.66; $p<0.001$), IE (OR, 3.22; $p<0.001$) and
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11 treatment in a non-academic hospital (OR, 1.36; $p=0.049$). Patients treated
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14 in high-volume hospitals were significantly less likely to die compared with
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17 those at low-volume hospitals (OR, 0.75; $p=0.033$).

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20 Overall, the median LOS (interquartile range) was 47 (24–77) days. The
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23 median LOS was longer in PVO patients (47 [24–77] days) than that in VT
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26 patients (56 [25.5–85.5] days, $p=0.027$). No significant difference in LOS
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29 was observed between academic and non-academic hospitals (47 [24–75]
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32 days vs. 47 [24–78] days, $p=0.511$) or between hospital-volume groups (47
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35 [24–80] days, 48 [24–79] days and 47 [24–74] days in low-, medium- and
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38 high-volume hospitals, respectively, $p=0.145$).

39 40 41 42 43 **DISCUSSION**

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46 The present study examined the annual trends in the VO occurrence and
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49 risk factors for death from VO using a Japanese nationwide inpatient
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52 database. Our study had two major findings. First, the incidence of VO was
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55 significantly higher in the elderly and increased year by year. Second,
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5 higher in-hospital mortality in VO was significantly associated with various
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8 factors.
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11 Our data demonstrated that the incidence of VO in Japan increased during
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14 the study period, from 5.6 to 7.7 per 100,000 population per year. Yoshimoto
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17 et al. reported that the increase in the VO incidence could be related to the
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20 increasing ratio of aged people (65 years of age or older) in Japan^[9]. ^[9] A
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22 recent report of demographic shift in Japan demonstrated the rapid
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25 increase in aged population; the increasing percentage compared to 2007
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28 was 3.2 % in 2008, 6.1% in 2009 and 7.1% in 2010, respectively^[22]. ^[29]
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31 Based on the relationship between higher age and the higher frequency of
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34 VO occurrence, as was demonstrated in this study, we believe that this
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37 increase is partly attributable to aging population in Japan.
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40 Previous limited data suggested that factors affecting the occurrence of VO
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43 included antecedent infection, diabetes mellitus, rheumatic diseases,
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46 immunosuppression, drug abuse, alcoholism, vertebral compression due to
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49 malignant metastasis, trauma, disc herniation, IE and prior surgery
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52 (gastrointestinal and urogenital tract)^[6]. ^[6] However, risk factors affecting
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55 death from VO have not been well investigated. The present study indicated
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5 that significant risk factors for death from VO were greater age,
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8 hemodialysis, diabetes, liver cirrhosis, malignancy and IE. Mortal risks of
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11 PVO were not different from those of VT.

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14 Recently, two small-scale studies of fewer than 100 cases reported that IE
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17 appeared to increase the incidence of VO, but did not increase its mortality

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20 ~~[5-23].~~ [\[5, 30\]](#) Conversely, our large-scale data showed that IE was a
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23 significant factor that increased mortality of VO. The other factors have
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26 never previously been analysed as risk factors for death in VO.

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29 Hemodialysis use was reported to be a risk factor for hematogenous
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32 complications of intravascular catheter use associated with *S. aureus*

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35 bacteremia [\[24\]. \[31\]](#) A case report suggested the possibility of VO in
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38 hemodialysis patients [\[25\]. \[32\]](#) Our study is the first to demonstrate a
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41 significant relationship between hemodialysis use and death from VO.

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44 Previous reports indicated that VO patients were more likely to have
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47 diabetes mellitus (11–19%) [\[6-16-26-28\], \[12, 25, 33, 34\]](#) but the present

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50 study further demonstrated that diabetes mellitus was a significant
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53 predictor of mortality in VO. Although not surprising, ~~that~~ our study
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56 ~~first~~ [has](#) demonstrated that age, liver cirrhosis and malignancy were all

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5 related to death ~~from~~with VO.
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8 As shown in table 4, the association of VO mortality with spinal surgery
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10 did not reach statistical significance. Randomized controlled trials s are~~is~~
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12 essential to verify the efficacy of spinal surgery, because confounding ~~factor~~
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14 by surgical indication affects the surgical result. However several papers
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16 have suggested the impossibility of randomized controlled trials to decide
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18 the treatment strategy of VO, not limited in spinal surgery ~~[36-37]~~. [35, 36]
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20 Thus, our DPC data could not reveal the efficacy of spinal surgery ~~for~~ VO.
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28 The high mortality suggests that VO remains a life-threatening disease
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30 despite advances in medical practice and should be regarded as a fatal
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32 systemic disorder rather than just a localized vertebral disorder.
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37 Our data revealed that several systemic diseases increased the mortality
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39 risk of VO, underscoring the need to keep VO in mind and to catch such
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41 signs of VO as unidentified fever or back pain as soon as possible during the
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43 treatment of these background diseases.
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48 We acknowledge several limitations of the present study. First, the DPC
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50 database does not provide important clinical data such as causative
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52 microorganisms and information on post-discharge outpatient services.
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5 Second, although the sample size was large, the population
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8 representativeness was limited because the participating hospitals were
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11 skewed toward large hospitals. Third, the diagnoses recorded in the
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14 administrative database are less well validated than those made in planned
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17 prospective surveys. Fourth, the period of observation was short for showing
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20 the long term trend of VO incidence. Fifth, the increased rate of VO may be
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23 an overestimation because of several artifacts including the improvement
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26 and increased prevalence of surveillance machines. Lastly, the mortality of
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29 VO may be underestimated because of transferring to other hospitals.
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32 Despite these limitations, our study made several new findings regarding
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35 VO, including risk factors for death.
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41 CONCLUSION

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43 The present study confirmed the increasing incidence of VO using a
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46 nationwide database. Greater age, use of hemodialysis, diabetes, liver
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49 cirrhosis, malignancy and IE were significantly associated with higher rates
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52 of in-hospital death in patients with VO. Based on the high mortality, we
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55 believe that VO remains a life-threatening, systemic disease. These novel
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5 findings will be important for improving the clinical management of VO.
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10 11 **Contributors**

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14 HY, HH and KF collected the data. TA, HC, HY and KS designed the study,
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16 analysed and interpreted the data and drafted the manuscript. All authors
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18 had full access to all data (including statistical reports and tables) in the
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20 study and take responsibility for the integrity of the data and the accuracy
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22 of the data analysis.
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59
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0301002001001).

References

1. [Kulowski J. Pyogenic osteomyelitis of the spine: an analysis and discussion of 102 cases. J Bone Joint Surg 1936;18\(2\):22.](#)
2. [Sapico FL, Montgomerie JZ. Pyogenic vertebral osteomyelitis: report of nine cases and review of the literature. Rev Infect Dis 1979;1\(5\):754-76.](#)
3. [Colmenero JD, Jimenez-Mejias ME, Sanchez-Lora FJ, et al. Pyogenic, tuberculous, and brucellar vertebral osteomyelitis: a descriptive and comparative study of 219 cases. Ann Rheum Dis 1997;56\(12\):709-15.](#)
4. [Carragee EJ. Pyogenic vertebral osteomyelitis. J Bone Joint Surg Am 1997;79\(6\):874-80.](#)
5. [Pigrau C, Almirante B, Flores X, et al. Spontaneous pyogenic vertebral osteomyelitis and endocarditis: incidence, risk factors, and outcome. Am J Med 2005;118\(11\):1287.](#)
6. [Beronius M, Bergman B, Andersson R. Vertebral osteomyelitis in Goteborg, Sweden: a retrospective study of patients during 1990-95. Scand J Infect Dis 2001;33\(7\):527-32.](#)
7. [Chelsom J, Solberg CO. Vertebral osteomyelitis at a Norwegian](#)

1
2
3
4
5 [university hospital 1987-97: clinical features, laboratory findings and](#)
6
7
8 [outcome. Scand J Infect Dis 1998;30\(2\):147-51.](#)
9

10
11 [8. Legrand E, Flipo RM, Guggenbuhl P, et al. Management of](#)
12
13 [nontuberculous infectious discitis. treatments used in 110 patients](#)
14
15 [admitted to 12 teaching hospitals in France. Joint, bone, spine : revue du](#)
16
17 [rhumatisme 2001;68\(6\):504-9.](#)
18
19

20
21 [9. Yoshimoto M, Takebayashi T, Kawaguchi S, et al. Pyogenic spondylitis in](#)
22
23 [the elderly: a report from Japan with the most aging society. Eur Spine J](#)
24
25 [2011;20\(4\):649-54.](#)
26
27

28
29 [10. Gouliouris T, Aliyu SH, Brown NM. Spondylodiscitis: update on](#)
30
31 [diagnosis and management. J Antimicrob Chemother 2010;65 Suppl](#)
32
33 [3:iii11-24.](#)
34
35

36
37 [11. Grammatico L, Baron S, Rusch E, et al. Epidemiology of vertebral](#)
38
39 [osteomyelitis \(VO\) in France: analysis of hospital-discharge data 2002-2003.](#)
40
41 [Epidemiol Infect 2008;136\(5\):653-60.](#)
42
43

44
45 [12. Krogsgaard MR, Wagn P, Bengtsson J. Epidemiology of acute vertebral](#)
46
47 [osteomyelitis in Denmark: 137 cases in Denmark 1978-1982, compared to](#)
48
49 [cases reported to the National Patient Register 1991-1993. Acta Orthop](#)
50
51
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47
48
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[Scand 1998;69\(5\):513-7.](#)

13. [Kapeller P, Fazekas F, Krametter D, et al. Pyogenic infectious spondylitis: clinical, laboratory and MRI features. Eur Neurol 1997;38\(2\):94-8.](#)

14. [Hopkinson N, Stevenson J, Benjamin S. A case ascertainment study of septic discitis: clinical, microbiological and radiological features. QJM 2001;94\(9\):465-70.](#)

15. [Digby JM, Kersley JB. Pyogenic non-tuberculous spinal infection: an analysis of thirty cases. J Bone Joint Surg Br 1979;61\(1\):47-55.](#)

16. [Jensen AG, Espersen F, Skinhoj P, et al. Increasing frequency of vertebral osteomyelitis following Staphylococcus aureus bacteraemia in Denmark 1980-1990. J Infect 1997;34\(2\):113-8.](#)

17. [McHenry MC, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. Clin Infect Dis 2002;34\(10\):1342-50.](#)

18. [Hsieh PC, Wienecke RJ, O'Shaughnessy BA, et al. Surgical strategies for vertebral osteomyelitis and epidural abscess. Neurosurg Focus](#)

2004;17(6):E4.

19. Quinones-Hinojosa A, Jun P, Jacobs R, et al. General principles in the medical and surgical management of spinal infections: a multidisciplinary approach. Neurosurg focus 2004;17(6):E1.

20. Chen WH, Jiang LS, Dai LY. Surgical treatment of pyogenic vertebral osteomyelitis with spinal instrumentation. Eur Spine J 2007;16(9):1307-16.

21. Lehovskiy J. Pyogenic vertebral osteomyelitis/disc infection. Baillieres Best Pract Res Clin Rheumatol 1999;13(1):59-75.

22. Rezai AR, Woo HH, Errico TJ, et al. Contemporary management of spinal osteomyelitis. Neurosurgery 1999;44(5):1018-25; discussion 25-6.

23. Hee HT, Majd ME, Holt RT, et al. Better treatment of vertebral osteomyelitis using posterior stabilization and titanium mesh cages. J Spinal Disord Tech 2002;15(2):149-56; discussion 56.

24. Shousha M, Boehm H. Surgical treatment of cervical spondylodiscitis: a review of 30 consecutive patients. Spine 2012;37(1):E30-6.

25. Joughin E, McDougall C, Parfitt C, et al. Causes and clinical management of vertebral osteomyelitis in Saskatchewan. Spine 1991;16(3):261-4.

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- [26. Chikuda H, Yasunaga H, Horiguchi H, et al. Mortality and morbidity in dialysis-dependent patients undergoing spinal surgery: analysis of a national administrative database in Japan. J Bone Joint Surg Am 2012;94\(5\):433-8.](#)
- [27. Ministry of Health LaW, Japan. Survey of Medical Institutions and Hospital Report, 2010, 2010.](#)
- [28. Hubbard AE, Ahern J, Fleischer NL, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. Epidemiology 2010;21\(4\):467-74.](#)
- [29. Ministry of Internal Affairs and Communications J. The Demographic Shift, 2012, 2012.](#)
- [30. Tamura K. Clinical characteristics of infective endocarditis with vertebral osteomyelitis. J Infect Chemother 2010;16\(4\):260-5.](#)
- [31. Fowler VG, Jr., Justice A, Moore C, et al. Risk factors for hematogenous complications of intravascular catheter-associated Staphylococcus aureus bacteremia. Clin Infect Dis 2005;40\(5\):695-703.](#)
- [32. Korzets A, Weinstein T, Ori Y, et al. Back pain and Staphylococcal](#)

[bacteraemia in haemodialysed patients--beware! Nephrol Dial Transplant](#)

[1999;14\(2\):483-6.](#)

[33. Belzunegui J, Del Val N, Intxausti JJ, et al. Vertebral osteomyelitis in](#)

[northern Spain. Report of 62 cases. Clin Exp Rheumatol 1999;17\(4\):447-52.](#)

[34. Harris LF, Haws FP. Disc space infection. Ala med 1994;63\(7\):12-4.](#)

[35. Darouiche RO. Spinal epidural abscess. N Engl J Med](#)

[2006;355\(19\):2012-20.](#)

[36. Zimmerli W. Clinical practice. Vertebral osteomyelitis. N Engl J Med](#)

[2010;362\(11\):1022-9.](#)

Table 1. Estimates of the incidence of VO

	No. of VO patients in the DPC hospitals (<i>N_i</i>)	Coverage rate (%) (<i>R_i</i>)	Sum of observation period (year) (<i>O_i</i>)	Population (×100,000) (<i>P_i</i>)	Incidence of VO (per 100,000 population per year) (<i>Y_i</i>)	<i>p</i>
Total	7,454	42.7%	2	1,278	6.8	
Year						
2007 (July–Dec.)	1,599	44.5%	0.5	1,278	5.6	<u><0.001</u>
2008 (July–Dec.)	1,818	42.6%	0.5	1,277	6.7	
2009 (July–Dec.)	1,789	38.0%	0.5	1,275	7.4	
2010 (July–Dec.)	2,248	45.8%	0.5	1,281	7.7	

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Sex

Male 4,373 42.7% 2 623 8.2 <0.001

Female 3,081 42.7% 2 657 5.5

Age (years)

≤59 1,396 42.7% 2 878 1.9 <0.001

60–69 1,751 42.7% 2 182 11.2

70–79 2,467 42.7% 2 129 22.4

≥80 1,840 42.7% 2 81 26.5

VO: vertebral osteomyelitis; DPC: Diagnosis Procedure Combination database

Yi=Nil Ril Oi Pi

Table 2. Patient backgrounds

	All		PVO		VT		<i>p</i>
	<i>N</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	
Total	7,454		7,143		311		
Age (years)							
≤59	1,396	(18.7)	1,329	(18.6)	67	(21.5)	0.462
60–69	1,751	(23.5)	1,674	(23.4)	77	(24.8)	
70–79	2,467	(33.1)	2,370	(33.2)	97	(31.2)	
≥80	1,840	(24.7)	1,770	(24.8)	70	(22.5)	
Sex							
Male	4,373	(58.7)	4,217	(59.0)	156	(50.2)	0.002

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Female	3,081	(41.3)	2,926	(41.0)	155	(49.8)	
Hemodialysis	553	(7.4)	541	(7.6)	12	(3.9)	0.014
Diabetes	2,042	(27.4)	1,983	(27.8)	59	(19.0)	0.001
Liver cirrhosis	140	(1.9)	135	(1.9)	5	(1.6)	0.720
Rheumatoid arthritis	110	(1.5)	106	(1.5)	4	(1.3)	
Anticoagulant use	1,493	(20.0)	1,448	(20.3)	45	(14.5)	0.012
Malignancy	1,170	(15.7)	1,120	(15.7)	50	(16.1)	0.850
IE	145	(1.9)	145	(2.0)	0	(0.0)	0.011
Aortic aneurysm	66	(0.9)	65	(0.9)	1	(0.3)	<0.001
Spinal surgery	1,543	(20.7)	1,448	(20.3)	125	(40.2)	0.278
Type of hospital							

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Academic	1,332	(17.9)	1,258	(17.6)	74	(23.8)	0.005
Non-academic	6,122	(82.1)	5,885	(82.4)	237	(76.2)	
Hospital volume							
(cases/year)							
≤6	2,766	(37.1)	2,660	(37.2)	106	(34.1)	0.254
7–10	2,290	(30.7)	2,192	(30.7)	98	(31.5)	
≥11	2,398	(32.2)	2,291	(32.1)	107	(34.4)	

PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE: infective endocarditis

Table 3. In-hospital mortality

		<i>N</i>	In-hospital mortality		
			<i>n</i>	(%)	<i>p</i>
All		7,454	433	(5.8)	
Diagnosis	PVO	7,143	417	(5.8)	0.609
	VT	311	16	(5.1)	
Age (years)	≤59	1,396	23	(1.6)	<0.001
	60–69	1,751	94	(5.4)	
	70–79	2,467	154	(6.2)	
	≥80	1,840	162	(8.8)	
Sex	Male	4,373	265	(6.1)	0.270

	Female	3,081	168	(5.5)	
Hemodialysis	No	6,901	281	(4.1)	<0.001
	Yes	553	152	(27.5)	
Diabetes	No	5,412	226	(4.2)	<0.001
	Yes	2,042	207	(10.1)	
Liver cirrhosis	No	7,314	415	(5.7)	<0.001
	Yes	140	18	(12.9)	
Rheumatoid arthritis	No	7,344	427	(5.8)	0.873
	Yes	110	6	(5.5)	
Anticoagulants	No	5,961	333	(5.6)	0.101
	Yes	1,493	100	(6.7)	

Malignancy	No	6,284	316	(5.0)	<0.001
	Yes	1,170	117	(10.0)	
IE	No	7,309	415	(5.7)	0.001
	Yes	145	18	(12.4)	
Aortic aneurysm	No	7,388	426	(5.8)	0.106
	Yes	66	7	(10.6)	
Spinal surgery	No	5,881	368	(6.3)	0.001
	Yes	1,573	65	(4.1)	
Type of hospital	Academic	1,332	54	(4.1)	0.003
	Non-academic	6,122	379	(6.2)	
Hospital volume	≤6	2,766	186	(6.7)	0.005

(cases/year)	7–10	2,290	130	(5.7)
	≥11	2,398	117	(4.9)

PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE: infective endocarditis

Table 4. Logistic regression analysis for in-hospital mortality

		OR	95% CI	<i>P</i>
Diagnosis	PVO	Reference		
	VT	1.31	0.78–2.18	0.304
Age (years)	≤59	Reference		
	60–69	2.75	1.73–4.38	<0.001
	70–79	3.97	2.50–6.28	<0.001
	≥80	6.89	4.33–10.96	<0.001
Sex	Male	Reference		
	Female	0.89	0.72–1.11	0.308
Hemodialysis	No	Reference		

	Yes	10.62	8.21–13.73	<0.001
Diabetes	No	Reference		
	Yes	2.34	1.87–2.92	<0.001
Liver cirrhosis	No	Reference		
	Yes	2.63	1.50–4.61	0.001
Malignancy	No	Reference		
	Yes	2.66	2.09–3.39	<0.001
IE	No	Reference		
	Yes	3.22	1.82–5.70	<0.001
Spinal surgery	No	Reference		
	Yes	0.76	0.56–1.02	0.066

Type of hospitals	Academic	Reference		
	Non-academic	1.36	1.00–1.86	0.049
Hospital volume (/year)	≤6	Reference		
	7-10	0.82	0.64–1.05	0.122
	≥11	0.75	0.58–0.98	0.033

OR: odds ratio, CI: confidence interval, PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE: infective

endocarditis

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Incidence and Risk Factors for Mortality of Vertebral Osteomyelitis: A Retrospective Analysis Using the Japanese Diagnosis Procedure Combination Database

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5 **Incidence and Risk Factors for Mortality of Vertebral Osteomyelitis: A**
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7 **Retrospective Analysis Using the Japanese Diagnosis Procedure**
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9 **Combination Database**
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17 Incidence and Mortal Risk Factors of Vertebral Osteomyelitis
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Keywords: vertebral osteomyelitis, Diagnosis Procedure Combination

Database, pyogenic vertebral osteomyelitis, vertebral tuberculosis,

in-hospital mortality

(2,181 words for text only, excluding title page, abstract, references, figures

and tables)

Abstract

Objective: To examine the incidence of vertebral osteomyelitis (VO) and the clinical features of VO focusing on risk factors for death using a Japanese nationwide administrative database.

Design: Retrospective observational study.

Setting and Participants: We identified 7,118 patients who were diagnosed with VO and hospitalized between July and December, 2007-2010, using the Japanese Diagnosis Procedure Combination database.

Main Outcome Measures: The annual incidence of VO was estimated. Logistic regression analysis was performed to analyse factors affecting in-hospital mortality in the VO patients. Dependent variables included patient characteristics (age, sex and comorbidities), procedures (hemodialysis and surgery) and hospital factors (type of hospital and hospital volume).

Results: Overall, 58.9% of eligible patients were male and the average age was 69.2 years. The estimated incidence of VO increased from 5.3 per 100,000 population per year in 2007 to 7.4 per 100,000 population per year in 2010. In-hospital mortality was 6.0%. There was a linear trend between

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5 higher rates of in-hospital mortality and greater age. A higher rate of
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8 in-hospital mortality was significantly associated with hemodialysis use
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10 (odds ratios, 10.56 [95% confidence interval, 8.12–13.74]), diabetes (2.37
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12 [1.89–2.98]), liver cirrhosis (2.63 [1.49–4.63]), malignancy (2.68, [2.10–3.42])
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14 and infective endocarditis (3.19 [1.80–5.65]).
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19 **Conclusions:** Our study demonstrates an increasing incidence of VO, and
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21 defines risk factors for death with a nationwide database. Several
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23 comorbidities were significantly associated with higher rates of in-hospital
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25 death in VO patients.
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Article summary

Article focus

- Vertebral osteomyelitis (VO) remains a life-threatening disease.
- Previous epidemiological studies on VO patients were limited because of small sample size.
- The present study examined the incidence of VO and clinical features of VO focusing on risk factors for death, using a nationwide database.

Key messages

- Using the Japanese Diagnosis Procedure Combination database, we analysed 7,118 VO patients.
- The estimated incidence of VO increased from 5.3 per 100,000 population per year in 2007 to 7.4 per 100,000 population per year in 2010.
- In-hospital mortality was 6.0%, which was significantly associated with greater age, hemodialysis use, diabetes, liver cirrhosis, malignancy, and infective endocarditis.

Strengths and limitations of this study

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5 - This study is the largest study on risk factors for in-hospital mortality in
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8 VO patient.

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Introduction

Vertebral osteomyelitis (VO) is a rare but life-threatening disease. [1-8] Its incidence appears to be on the rise. [9-11] In developed countries, the estimated incidence ranged from 1 case per 40,000 population per year to 1 case per 250,000 population per year. [6, 7, 11-16] However, these data were based on limited-scale epidemiological studies, [11] covering small areas with fewer than 200 cases. [6, 7, 12-16] Published data on the incidence of VO are thus of low validity and reliability.

Mortality in VO has been reported to be less than 11% [2-7] but these figures were also based on relatively small studies. A recent large scale study demonstrated adverse (death or qualified recovery) risk factors of VO, but did not focus specifically on the mortality of VO. [17] Thus, factors associated with mortality in VO have not yet been fully investigated.

Understanding the current epidemiology and clinical features of VO is an urgent requirement for effective management of this condition. The aims of the present study were (i) to estimate the incidence of VO, and (ii) to examine the clinical features of VO focusing on risk factors for mortality in VO, using a Japanese nationwide administrative database. In addition, the

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5 following details were examined as relevant clinical features of VO. First,
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8 data have also been lacking on mortality following surgical procedures for
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11 VO. Indications for surgical treatment are the following: prevention of
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14 spinal cord or major neural compression, stabilization or correction of spinal
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17 destruction, reduction of intractable pain, and failure of conservative
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20 management. [18-24] The present study ascertained the mortality of VO
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23 patients following conservative or surgical treatment. Second, VO consists
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26 of vertebral tuberculosis (VT) and pyogenic vertebral osteomyelitis (PVO),
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29 but clinical details in these two conditions have not been fully described. [3,
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32 6, 11, 25] We examined the differences in patient backgrounds and
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35 mortality between these two diseases.
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40 **Materials and Methods**

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45 For this study, we utilized the Japanese Diagnosis Procedure Combination
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48 (DPC) database. Details of the database are described elsewhere. [26]

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51 Briefly, discharge abstract and administrative claim data are collected from
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54 the participating hospitals between July 1 and December 31 of each year by
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5 the DPC Study Group funded by the Japanese Ministry of Health, Labour
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8 and Welfare. The numbers of inpatients in the DPC database were 2.99
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10 million from 926 hospitals in 2007, 2.86 million from 855 hospitals in 2008,
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12 2.57 million from 818 hospitals in 2009, and 3.19 million from 952 hospitals
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14 in 2010, which covered approximately 43% of all the acute-care inpatients
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16 in Japan. The database includes the following data: unique identifier of
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18 hospital and type of hospital (academic or non-academic); patient age and
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20 sex; diagnoses, comorbidities at admission and complications after
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22 admission recorded according to the International Classification of Diseases,
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24 Tenth Revision (ICD-10) codes and text data in Japanese language;
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26 procedures according to the original Japanese codes; drugs used; length of
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28 stay (LOS); and in-hospital deaths. The anonymous nature of the data
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30 allowed the requirement for informed consent to be waived. This study was
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32 approved by the Institutional Review Board at The University of Tokyo.
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48 *Patient selection*

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50 We included all patients who were diagnosed with VO according to the
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52 following ICD-10-based codes: vertebral osteomyelitis (M46.2), pyogenic
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5 infection of intervertebral disk (M46.3), unspecified discitis (M46.4), other
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11 spondylopathy (M46.8), unspecified inflammatory spondylopathy (M46.9),
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14 unspecified spondylopathy (M48.9), vertebral tuberculosis (A18.0 and
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19 and spondylopathy in other infectious or parasitic diseases (M49.3). We
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22 checked the Japanese text describing the detailed diagnoses in each case
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25 and all other codes indicating the presence of a specific infection
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28 (tuberculosis, other mycobacteria, brucellosis, bacterial infections, fungal
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31 infections, nosocomial infection, implant-associated infection, or
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34 endocarditis) to abstract vertebral osteomyelitis and vertebral tuberculosis
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37 cases from A18.0, M46.4, M46.5, M46.8, M46.9, M48.9 and M49.3. VO was
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40 categorized into PVO (other codes than A18.0 and M49.0) and VT (A18.0
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43 and M49.0).

44 45 46 47 48 ***Estimation of the incidence of VO***

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51 We estimated the annual incidence of VO per population per year, based on
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11 (N_i), the observation period (O_i) and the population of Japan (P_i). The
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13 coverage of the DPC hospitals (R_i) was defined as B_i divided by A_i . Values of
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15 B_i were calculated from the DPC database and data for A_i were obtained
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17 from the Survey of Medical Institutions and Hospital Report, 2010. [27] P_i
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19 was obtained from Japanese Population Census data
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22 (http://www.stat.go.jp/english/data/kokusei/index.htm). The estimated
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25 incidence of VO per population per year (Y_i) was calculated using the
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Patient characteristics

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42 age and sex; comorbidities that could potentially affect mortality in VO
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45 including diabetes, liver cirrhosis, rheumatoid arthritis, malignancy,
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48 infective endocarditis (IE) and aortic aneurysm; use of hemodialysis; spinal
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51 surgery performed during hospitalization; and type of hospital and hospital
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54 volume. We also examined use of anticoagulants for each patient, including
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5 aspirin, warfarin, clopidogrel and ticlopidine.
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8 Hospital volume was categorized into tertiles: low-volume hospitals (<7
9 cases/year), medium-volume hospitals (7–10 cases/year) and high-volume
10 hospitals (>10 cases/year). These categories were based on cutoffs that
11 yielded equivalent numbers of patients in each volume category.
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22 ***Outcome measurements***

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25 The primary outcome measured was in-hospital mortality. The secondary
26 outcome was LOS.
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33 ***Statistical analysis***

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36 We used the chi-square test for categorical variables and the Wilcoxon
37 rank-sum test for continuous variables to perform univariate comparisons
38 of patient characteristics and outcomes between subgroups. Logistic
39 regression analysis was performed to analyze the concurrent effects of
40 various factors on the occurrence of in-hospital death, while adjusting for
41 clustering of patients within hospitals using a generalized estimating
42 equation. [28] The threshold for significance was a p value <0.05. All
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5 statistical analyses were conducted using IBM SPSS version 19.0 (IBM
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8 SPSS, Armonk, NY, USA).
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10 11 12 13 **RESULTS**

14 15 16 **Estimated incidence of VO in Japan**

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18 We identified 7,118 eligible patients. Table 1 shows the estimated incidence
19
20 of VO in Japan. The overall incidence of VO between 2007 and 2010 was 6.5
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22 per 100,000 population per year. The estimated incidence increased from
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24 5.3 per 100,000 population per year in 2007 to 7.4 per 100,000 population
25
26 per year in 2010 ($p<0.001$). The incidence was lower in the population aged
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28 ≤ 59 years (1.7 per 100,000 population per year) than in those aged 60–69
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30 years (10.9), 70–79 years (21.6) or ≥ 80 years (25.1) ($p<0.001$).
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40 41 **Patient characteristics**

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43 The patients' backgrounds are shown in Table 2. Overall, 58.9% were male
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45 and the average age (\pm standard deviation) was 69.2 ± 13.9 years. There were
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47 6,807 cases of PVO and 311 of VT. The proportion of male PVO patients
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49 (59.3%) was higher than that of male VT patients (50.2%, $p=0.001$). No
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52 significant difference in age was observed between the PVO and VT groups.
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5 PVO patients were more likely to have a comorbid condition than VT
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8 patients.

10 **In-hospital mortality**

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12 In-hospital mortality for each category is shown in Table 3. The overall
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14 in-hospital mortality was 6.0%. Higher in-hospital mortality was associated
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16 with greater age ($p<0.001$), hemodialysis use (27.7%, $p<0.001$), diabetes
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18 (10.4%, $p<0.001$), liver cirrhosis (13.1%, $p<0.001$), malignancy (10.3%,
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20 $p<0.001$), IE (12.4%, $p=0.001$) and treatment in a non-academic hospital
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22 (6.3%, $p=0.003$). Higher hospital volume was significantly associated with
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24 lower mortality ($p=0.007$).
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33 **Logistic regression analysis for in-hospital mortality**

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35 Table 4 shows the results of the logistic regression analysis for in-hospital
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37 mortality. Higher mortality was significantly associated with greater age
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39 (odds ratios [ORs] of 2.78, 3.99, and 7.13 for patients aged 60–69, 70–79,
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41 and ≥ 80 years compared with those aged ≤ 59 , respectively $p<0.001$),
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43 hemodialysis use (OR 10.56; $p<0.001$), diabetes (OR 2.37; $p<0.001$), liver
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45 cirrhosis (OR 2.63; $p=0.001$), malignancy (OR 2.68; $p<0.001$) and IE (OR
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47 3.19; $p<0.001$). Patients treated in high-volume hospitals were significantly
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5 less likely to die compared with those at low-volume hospitals (OR 0.77;
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8 $p=0.029$).

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10 Overall, the median LOS (interquartile range) was 48 (25–79) days. The
11
12 median LOS was shorter in PVO patients (48 [25–78] days) than that in VT
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14 patients (56 [25.5–85.5] days), but the difference was not significant
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18 ($p=0.067$). No significant difference in LOS was observed between academic
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20 and non-academic hospitals (48 [25–76] days vs. 48 [25–79] days, $p=0.521$)
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23 or between hospital-volume groups (49 [25–81] days, 49 [25–80] days, and
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28 47 [24–74] days in low-, medium-, - and high-volume hospitals, respectively,
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31 $p=0.085$).

32 33 34 35 36 37 **DISCUSSION**

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39 The present study examined the annual trends in the occurrence of VO and
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41 risk factors for death from VO using a Japanese nationwide inpatient
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43 database. Our study had two major findings. First, the incidence of VO was
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47 significantly higher in the elderly and increased year by year. Second,
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50 higher in-hospital mortality in VO was significantly associated with various
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54 factors.
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5 Our data demonstrated that the incidence of VO in Japan increased during
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8 the study period, from 5.3 to 7.4 per 100,000 population per year. Yoshimoto
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11 et al. reported that the increase in the VO incidence could be related to the
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14 increasing ratio of aged people (65 years of age or older) in Japan. [9] A
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17 recent report of demographic shifts in Japan demonstrated the rapid
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20 increase in aged population: the percentage increase compared with 2007
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23 was 3.2 % in 2008, 6.1% in 2009, and 7.1% in 2010. [29] Based on the
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26 relationship between higher age and higher frequency of VO occurrence, as
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29 was demonstrated in this study, we believe that this increase is partly
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32 attributable to the aging population in Japan.

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34 Previous limited data have suggested that factors affecting the occurrence
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37 of VO include antecedent infection, diabetes mellitus, rheumatic diseases,
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40 immunosuppression, drug abuse, alcoholism, vertebral compression due to
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43 malignant metastasis, trauma, disc herniation, IE, and prior surgery
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46 (gastrointestinal and urogenital tract).[6] However, risk factors affecting
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49 death from VO have not been well investigated. The present study indicated
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52 that significant risk factors for death from VO were greater age,
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55 hemodialysis, diabetes, liver cirrhosis, malignancy and IE. Mortality risks
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5 of PVO were not different from those of VT.
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8 Recently, two small-scale studies of fewer than 100 cases reported that IE
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10 appeared to increase the incidence of VO, but did not increase its mortality.
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13 [5,30] Conversely, our large-scale data showed that IE was a significant
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15 factor that increased mortality associated with VO. The other factors have
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17 never previously been analysed as risk factors for death with VO.
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21 Hemodialysis use was reported to be a risk factor for hematogenous
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23 complications of intravascular catheter use associated with *S. aureus*
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27 bacteremia. [31] A case report suggested the possibility of VO in
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29 hemodialysis patients. [32] Our study is the first to demonstrate a
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31 significant relationship between hemodialysis use and death from VO.
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35 Previous reports indicated that VO patients were more likely to have
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37 diabetes mellitus (11–19%), [12, 25, 33, 34] but the present study further
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39 demonstrated that diabetes mellitus was a significant predictor for
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41 mortality in VO. Although not surprising, our study has demonstrated that
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43 age, liver cirrhosis, and malignancy were all related to death with VO.
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47 As shown in Table 4, the association of VO mortality with spinal surgery did
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49 not reach statistical significance. Randomized controlled trials are essential
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5 to verify the efficacy of spinal surgery because confounding by surgical
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8 indication affects the surgical result. However, several papers have
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11 suggested the impossibility of randomized controlled trials to decide the
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14 treatment strategy for VO, even apart from spinal surgery. [35, 36] Thus,
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17 our DPC data could not reveal the efficacy of spinal surgery for VO.

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19 The high mortality suggests that VO remains a life-threatening disease
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22 despite advances in medical practice and should be regarded as a fatal
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25 systemic disorder rather than just a localized vertebral disorder.
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28 Our data revealed that several systemic diseases increased the mortality
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31 risk of VO, underscoring the need to keep VO in mind and to catch such
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34 signs of VO as unidentified fever or back pain as soon as possible during the
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37 treatment of these background diseases.

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39 We acknowledge several limitations of the present study. First, the DPC
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42 database does not provide important clinical data such as causative
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45 microorganisms and information on post-discharge outpatient services.
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48 Second, although the sample size was large, the population
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51 representativeness was limited because the participating hospitals were
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54 skewed toward large hospitals. Third, the diagnoses recorded in the
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5 administrative database are less well validated than those made in planned
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8 prospective surveys. Fourth, the period of observation was short for showing
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11 the long term trend of VO incidence. Fifth, the increased rate of VO may be
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14 an overestimation because of several artifacts including the improvement
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17 and increased prevalence of surveillance machines. Last, the mortality of
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20 VO may be underestimated because of transfers to other hospitals. Despite
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23 these limitations, our study has resulted in several new findings regarding
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26 VO, including risk factors for death.
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31 **CONCLUSION**

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34 The present study confirmed the increasing incidence of VO using a
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37 nationwide database. Greater age, use of hemodialysis, diabetes, liver
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40 cirrhosis, malignancy, and IE were significantly associated with higher
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43 rates of in-hospital death in patients with VO. Based on the high mortality,
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46 VO remains a life-threatening, systemic disease. These novel findings will
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49 be important for improving the clinical management of VO.
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Contributors

HY, HH and KF collected the data. TA, HC, HY and KS designed the study, analysed and interpreted the data, and drafted the manuscript. All authors had full access to all data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Data Sharing

No additional data available

Competing Interests: None

References

1. Kulowski J. Pyogenic osteomyelitis of the spine: an analysis and discussion of 102 cases. *J Bone Joint Surg* 1936;**18**(2):22.
2. Sapico FL, Montgomerie JZ. Pyogenic vertebral osteomyelitis: report of nine cases and review of the literature. *Rev Infect Dis* 1979;**1**(5):754-76.
3. Colmenero JD, Jimenez-Mejias ME, Sanchez-Lora FJ, et al. Pyogenic, tuberculous, and brucellar vertebral osteomyelitis: a descriptive and comparative study of 219 cases. *Ann Rheum Dis* 1997;**56**(12):709-15.
4. Carragee EJ. Pyogenic vertebral osteomyelitis. *J Bone Joint Surg Am* 1997;**79**(6):874-80.
5. Pigrau C, Almirante B, Flores X, et al. Spontaneous pyogenic vertebral osteomyelitis and endocarditis: incidence, risk factors, and outcome. *Am J Med* 2005;**118**(11):1287.
6. Beronius M, Bergman B, Andersson R. Vertebral osteomyelitis in Goteborg, Sweden: a retrospective study of patients during 1990-95. *Scand J Infect Dis* 2001;**33**(7):527-32.
7. Chelsom J, Solberg CO. Vertebral osteomyelitis at a Norwegian university hospital 1987-97: clinical features, laboratory findings and outcome. *Scand J Infect Dis* 1998;**30**(2):147-51.
8. Legrand E, Flipo RM, Guggenbuhl P, et al. Management of nontuberculous infectious discitis. treatments used in 110 patients admitted to 12 teaching hospitals in France. *Joint, bone, spine : revue du rhumatisme* 2001;**68**(6):504-9.
9. Yoshimoto M, Takebayashi T, Kawaguchi S, et al. Pyogenic spondylitis in the elderly: a report from Japan with the most aging society. *Eur Spine J* 2011;**20**(4):649-54.
10. Gouliouris T, Aliyu SH, Brown NM. Spondylodiscitis: update on diagnosis and management. *J Antimicrob Chemother* 2010;**65 Suppl 3**:iii11-24.
11. Grammatico L, Baron S, Rusch E, et al. Epidemiology of vertebral osteomyelitis (VO) in France: analysis of hospital-discharge data 2002-2003. *Epidemiol Infect* 2008;**136**(5):653-60.
12. Krogsgaard MR, Wagn P, Bengtsson J. Epidemiology of acute vertebral osteomyelitis in Denmark: 137 cases in Denmark 1978-1982, compared to cases reported to the National Patient Register 1991-1993. *Acta Orthop Scand* 1998;**69**(5):513-7.
13. Kapeller P, Fazekas F, Krametter D, et al. Pyogenic infectious spondylitis: clinical, laboratory and MRI features. *Eur Neurol* 1997;**38**(2):94-8.
14. Hopkinson N, Stevenson J, Benjamin S. A case ascertainment study of septic discitis: clinical, microbiological and radiological features. *QJM* 2001;**94**(9):465-70.
15. Digby JM, Kersley JB. Pyogenic non-tuberculous spinal infection: an analysis of thirty

- cases. *J Bone Joint Surg Br* 1979;**61**(1):47-55.
16. Jensen AG, Espersen F, Skinhoj P, et al. Increasing frequency of vertebral osteomyelitis following *Staphylococcus aureus* bacteraemia in Denmark 1980-1990. *J Infect* 1997;**34**(2):113-8.
17. McHenry MC, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. *Clin Infect Dis* 2002;**34**(10):1342-50.
18. Hsieh PC, Wienecke RJ, O'Shaughnessy BA, et al. Surgical strategies for vertebral osteomyelitis and epidural abscess. *Neurosurg Focus* 2004;**17**(6):E4.
19. Quinones-Hinojosa A, Jun P, Jacobs R, et al. General principles in the medical and surgical management of spinal infections: a multidisciplinary approach. *Neurosurg focus* 2004;**17**(6):E1.
20. Chen WH, Jiang LS, Dai LY. Surgical treatment of pyogenic vertebral osteomyelitis with spinal instrumentation. *Eur Spine J* 2007;**16**(9):1307-16.
21. Lehovskiy J. Pyogenic vertebral osteomyelitis/disc infection. *Baillieres Best Pract Res Clin Rheumatol* 1999;**13**(1):59-75.
22. Rezai AR, Woo HH, Errico TJ, et al. Contemporary management of spinal osteomyelitis. *Neurosurgery* 1999;**44**(5):1018-25; discussion 25-6.
23. Hee HT, Majd ME, Holt RT, et al. Better treatment of vertebral osteomyelitis using posterior stabilization and titanium mesh cages. *J Spinal Disord Tech* 2002;**15**(2):149-56; discussion 56.
24. Shousha M, Boehm H. Surgical treatment of cervical spondylodiscitis: a review of 30 consecutive patients. *Spine* 2012;**37**(1):E30-6.
25. Joughin E, McDougall C, Parfitt C, et al. Causes and clinical management of vertebral osteomyelitis in Saskatchewan. *Spine* 1991;**16**(3):261-4.
26. Chikuda H, Yasunaga H, Horiguchi H, et al. Mortality and morbidity in dialysis-dependent patients undergoing spinal surgery: analysis of a national administrative database in Japan. *J Bone Joint Surg Am* 2012;**94**(5):433-8.
27. Ministry of Health LaW, Japan. Survey of Medical Institutions and Hospital Report, 2010, 2010.
28. Hubbard AE, Ahern J, Fleischer NL, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. *Epidemiology* 2010;**21**(4):467-74.
29. Ministry of Internal Affairs and Communications J. The Demographic Shift, 2012, 2012.
30. Tamura K. Clinical characteristics of infective endocarditis with vertebral osteomyelitis. *J Infect Chemother* 2010;**16**(4):260-5.

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3
4 31. Fowler VG, Jr., Justice A, Moore C, et al. Risk factors for hematogenous complications
5 of intravascular catheter-associated Staphylococcus aureus bacteremia. Clin Infect
6 Dis 2005;**40**(5):695-703.
7
8 32. Korzets A, Weinstein T, Ori Y, et al. Back pain and Staphylococcal bacteraemia in
9 haemodialysed patients--beware! Nephrol Dial Transplant 1999;**14**(2):483-6.
10
11 33. Belzunegui J, Del Val N, Intxausti JJ, et al. Vertebral osteomyelitis in northern Spain.
12 Report of 62 cases. Clin Exp Rheumatol 1999;**17**(4):447-52.
13
14 34. Harris LF, Haws FP. Disc space infection. Ala med 1994;**63**(7):12-4.
15
16 35. Darouiche RO. Spinal epidural abscess. N Engl J Med 2006;**355**(19):2012-20.
17
18 36. Zimmerli W. Clinical practice. Vertebral osteomyelitis. N Engl J Med
19 2010;**362**(11):1022-9.
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Table 1. Estimates of the incidence of VO

	No. of VO patients in the DPC hospitals (<i>N_i</i>)	Coverage rate (%) (<i>R_i</i>)	Sum of observation period (year) (<i>O_i</i>)	Population (×100,000) (<i>P_i</i>)	Incidence of VO (per 100,000 population per year) (<i>Y_i</i>)	<i>p</i>
Total	7,118	42.7%	2	1,278	6.5	
Year						
2007 (July–Dec.)	1,516	44.5%	0.5	1,278	5.3	<0.001
2008 (July–Dec.)	1,727	42.6%	0.5	1,277	6.3	
2009 (July–Dec.)	1,716	38.0%	0.5	1,275	7.1	
2010 (July–Dec.)	2,159	45.8%	0.5	1,281	7.4	

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Sex

Male 4,194 42.7% 2 623 7.9 <0.001

Female 2,924 42.7% 2 657 5.2

Age (years)

≤59 1,311 42.7% 2 878 1.7 <0.001

60–69 1,693 42.7% 2 182 10.9

70–79 2,376 42.7% 2 129 21.6

≥80 1,738 42.7% 2 81 25.1

VO: vertebral osteomyelitis; DPC: Diagnosis Procedure Combination database

Yi=Nil Ril Oi Pi

Table 2. Patient characteristics

	All		PVO		VT		<i>p</i>
	<i>N</i>	(%)	<i>N</i>	(%)	<i>n</i>	(%)	
Total	7,118		6,807		311		
Age (years)							
≤59	1,311	(18.4)	1,244	(18.3)	67	(21.5)	0.422
60–69	1,693	(23.8)	1,616	(23.7)	77	(24.8)	
70–79	2,376	(33.4)	2,279	(33.5)	97	(31.2)	
≥80	1,738	(24.4)	1,668	(24.5)	70	(22.5)	
Sex							
Male	4,194	(58.9)	4,038	(59.3)	156	(50.2)	0.001
Female	2,924	(41.1)	2,769	(40.7)	155	(49.8)	
Hemodialysis	542	(7.6)	530	(7.8)	12	(3.9)	0.011
Diabetes	1,968	(27.6)	1,909	(28.0)	59	(19.0)	<0.001
Liver cirrhosis	137	(1.9)	132	(1.9)	5	(1.6)	0.677
Rheumatoid arthritis	107	(1.5)	103	(1.5)	4	(1.3)	0.748
Anticoagulant use	1,437	(20.2)	1,392	(20.4)	45	(14.5)	0.010

Malignancy	1,111	(15.6)	1,061	(15.6)	50	(16.1)	0.816
IE	145	(2.0)	145	(2.1)	0	(0.0)	0.009
Aortic aneurysm	63	(0.9)	62	(0.9)	1	(0.3)	0.278
Spinal surgery	1,537	(21.6)	1,412	(20.7)	125	(40.2)	<0.001
Type of hospital							
Academic	1,264	(17.8)	1,190	(17.5)	74	(23.8)	0.004
Non-academic	5,854	(82.2)	5,617	(82.5)	237	(76.2)	
Hospital volume							
(cases/year)							
≤6	2,622	(36.8)	2,516	(37.0)	106	(34.1)	0.566
7–10	2,192	(30.8)	2,094	(30.8)	98	(31.5)	
≥11	2,304	(32.4)	2,197	(32.3)	107	(34.4)	

PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE:

infective endocarditis

Table 3. In-hospital mortality

		In-hospital mortality			
		<i>N</i>	<i>N</i>	(%)	<i>p</i>
All		7,118	424	(6.0)	
Diagnosis	PVO	6,807	408	(6.0)	0.536
	VT	311	16	(5.1)	
Age (years)	≤59	1,311	22	(1.7)	<0.001
	60–69	1,693	93	(5.5)	
	70–79	2,376	151	(6.4)	
	≥80	1,738	158	(9.1)	
Sex	Male	4,194	261	(6.2)	0.255
	Female	2,924	163	(5.6)	
Hemodialysis	No	6,576	274	(4.2)	<0.001
	Yes	542	150	(27.7)	
Diabetes	No	5,150	219	(4.3)	<0.001
	Yes	1,968	205	(10.4)	
Liver cirrhosis	No	6,981	406	(5.8)	<0.001
	Yes	137	18	(13.1)	

Rheumatoid arthritis	No	7,011	418	(6.0)	0.878
	Yes	107	6	(5.6)	
Anticoagulants	No	5,681	325	(5.7)	0.095
	Yes	1,437	99	(6.9)	
Malignancy	No	6,007	310	(5.2)	<0.001
	Yes	1,111	114	(10.3)	
IE	No	6,973	406	(5.8)	0.001
	Yes	145	18	(12.4)	
Aortic aneurysm	No	7,055	418	(5.9)	0.230
	Yes	63	6	(9.5)	
Spinal surgery	No	5,581	359	(6.4)	0.001
	Yes	1,537	65	(4.2)	
Type of hospital	Academic	1,264	53	(4.2)	0.003
	Non-academic	5,854	371	(6.3)	
Hospital volume	≤6	2,622	185	(7.1)	0.007
(cases/year)	7–10	2,192	124	(5.7)	
	≥11	2,304	115	(5.0)	

PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE:

infective endocarditis

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Table 4. Logistic regression analysis for in-hospital mortality

		OR	95% CI	<i>P</i>
Diagnosis	PVO	Reference		
	VT	1.28	0.77–2.14	0.348
Age (years)	≤59	Reference		
	60–69	2.78	1.71–4.53	<0.001
	70–79	3.99	2.47–6.44	<0.001
	≥80	7.13	4.36–11.69	<0.001
Sex	Male	Reference		
	Female	0.89	0.71–1.10	0.282
Hemodialysis	No	Reference		
	Yes	10.56	8.12–13.74	<0.001
Diabetes	No	Reference		
	Yes	2.37	1.89–2.98	<0.001
Liver cirrhosis	No	Reference		
	Yes	2.63	1.49–4.63	0.001
Malignancy	No	Reference		
	Yes	2.68	2.10–3.42	<0.001

IE	No	Reference		
	Yes	3.19	1.80–5.65	<0.001
Spinal surgery	No	Reference		
	Yes	0.76	0.57–1.02	0.072
Type of hospitals	Academic	Reference		
	Non-academic	1.35	0.98–1.85	0.064
Hospital volume (/year)	≤6	Reference		
	7-10	0.77	0.60–0.99	0.041
	≥11	0.74	0.56–0.97	0.029

OR: odds ratio, CI: confidence interval, PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE: infective endocarditis

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5 **Incidence and Risk Factors for Mortality of Vertebral Osteomyelitis: A**
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7 **Retrospective Analysis Using the Japanese Diagnosis Procedure**
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9 **Combination Database**
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17 Incidence and Mortal Risk Factors of Vertebral Osteomyelitis
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Keywords: vertebral osteomyelitis, Diagnosis Procedure Combination

Database, pyogenic vertebral osteomyelitis, vertebral tuberculosis,

in-hospital mortality

(2,181 words for text only, excluding title page, abstract, references, figures

and tables)

Abstract

Objective: To examine the incidence of vertebral osteomyelitis (VO) and the clinical features of VO focusing on risk factors for death using a Japanese nationwide administrative database.

Design: Retrospective observational study.

Setting and Participants: We identified 7,118 patients who were diagnosed with VO and hospitalized between July and December, 2007-2010, using the Japanese Diagnosis Procedure Combination database.

Main Outcome Measures: The annual incidence of VO was estimated. Logistic regression analysis was performed to analyse factors affecting in-hospital mortality in the VO patients. Dependent variables included patient characteristics (age, sex and comorbidities), procedures (hemodialysis and surgery) and hospital factors (type of hospital and hospital volume).

Results: Overall, 58.9% of eligible patients were male and the average age was 69.2 years. The estimated incidence of VO increased from 5.3 per 100,000 population per year in 2007 to 7.4 per 100,000 population per year in 2010. In-hospital mortality was 6.0%. There was a linear trend between

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5 higher rates of in-hospital mortality and greater age. A higher rate of
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8 in-hospital mortality was significantly associated with hemodialysis use
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10 (odds ratios, 10.56 [95% confidence interval, 8.12–13.74]), diabetes (2.37
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12 [1.89–2.98]), liver cirrhosis (2.63 [1.49–4.63]), malignancy (2.68, [2.10–3.42])
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14 and infective endocarditis (3.19 [1.80–5.65]).
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19 **Conclusions:** Our study demonstrates an increasing incidence of VO, and
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21 defines risk factors for death with a nationwide database. Several
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23 comorbidities were significantly associated with higher rates of in-hospital
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25 death in VO patients.
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Article summary

Article focus

- Vertebral osteomyelitis (VO) remains a life-threatening disease.
- Previous epidemiological studies on VO patients were limited because of small sample size.
- The present study examined the incidence of VO and clinical features of VO focusing on risk factors for death, using a nationwide database.

Key messages

- Using the Japanese Diagnosis Procedure Combination database, we analysed 7,118 VO patients.
- The estimated incidence of VO increased from 5.3 per 100,000 population per year in 2007 to 7.4 per 100,000 population per year in 2010.
- In-hospital mortality was 6.0%, which was significantly associated with greater age, hemodialysis use, diabetes, liver cirrhosis, malignancy, and infective endocarditis.

Strengths and limitations of this study

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5 - This study is the largest study on risk factors for in-hospital mortality in
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8 VO patient.

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11 - The database does not include information on causative microorganisms or
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14 post-discharge status.
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Introduction

Vertebral osteomyelitis (VO) is a rare but life-threatening disease. [1-8] Its incidence appears to be on the rise. [9-11] In developed countries, the estimated incidence ranged from 1 case per 40,000 population per year to 1 case per 250,000 population per year. [6, 7, 11-16] However, these data were based on limited-scale epidemiological studies, [11] covering small areas with fewer than 200 cases. [6, 7, 12-16] Published data on the incidence of VO are thus of low validity and reliability.

Mortality in VO has been reported to be less than 11% [2-7] but these figures were also based on relatively small studies. A recent large scale study demonstrated adverse (death or qualified recovery) risk factors of VO, but did not focus specifically on the mortality of VO. [17] Thus, factors associated with mortality in VO have not yet been fully investigated.

Understanding the current epidemiology and clinical features of VO is an urgent requirement for effective management of this condition. The aims of the present study were (i) to estimate the incidence of VO, and (ii) to examine the clinical features of VO focusing on risk factors for mortality in VO, using a Japanese nationwide administrative database. In addition, the

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5 following details were examined as relevant clinical features of VO. First,
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8 data have also been lacking on mortality following surgical procedures for
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11 VO. Indications for surgical treatment are the following: prevention of
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14 spinal cord or major neural compression, stabilization or correction of spinal
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17 destruction, reduction of intractable pain, and failure of conservative
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20 management. [18-24] The present study ascertained the mortality of VO
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23 patients following conservative or surgical treatment. Second, VO consists
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26 of vertebral tuberculosis (VT) and pyogenic vertebral osteomyelitis (PVO),
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29 but clinical details in these two conditions have not been fully described. [3,
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32 6, 11, 25] We examined the differences in patient backgrounds and
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35 mortality between these two diseases.
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40 **Materials and Methods**

41 *Data source*

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45 For this study, we utilized the Japanese Diagnosis Procedure Combination
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48 (DPC) database. Details of the database are described elsewhere. [26]

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51 Briefly, discharge abstract and administrative claim data are collected from
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54 the participating hospitals between July 1 and December 31 of each year by
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5 the DPC Study Group funded by the Japanese Ministry of Health, Labour
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8 and Welfare. The numbers of inpatients in the DPC database were 2.99
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10 million from 926 hospitals in 2007, 2.86 million from 855 hospitals in 2008,
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12 2.57 million from 818 hospitals in 2009, and 3.19 million from 952 hospitals
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14 in 2010, which covered approximately 43% of all the acute-care inpatients
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16 in Japan. The database includes the following data: unique identifier of
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18 hospital and type of hospital (academic or non-academic); patient age and
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20 sex; diagnoses, comorbidities at admission and complications after
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22 admission recorded according to the International Classification of Diseases,
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24 Tenth Revision (ICD-10) codes and text data in Japanese language;
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26 procedures according to the original Japanese codes; drugs used; length of
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28 stay (LOS); and in-hospital deaths. The anonymous nature of the data
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30 allowed the requirement for informed consent to be waived. This study was
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32 approved by the Institutional Review Board at The University of Tokyo.
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48 *Patient selection*

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50 We included all patients who were diagnosed with VO according to the
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52 following ICD-10-based codes: vertebral osteomyelitis (M46.2), pyogenic
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5 infection of intervertebral disk (M46.3), unspecified discitis (M46.4), other
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8 infective spondylopathy (M46.5), other specified inflammatory
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11 spondylopathy (M46.8), unspecified inflammatory spondylopathy (M46.9),
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14 unspecified spondylopathy (M48.9), vertebral tuberculosis (A18.0 and
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16 M49.0), *Brucella* spondylitis (M49.1), enterobacterial spondylitis (M49.2)
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18 and spondylopathy in other infectious or parasitic diseases (M49.3). We
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21 checked the Japanese text describing the detailed diagnoses in each case
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24 and all other codes indicating the presence of a specific infection
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28 (tuberculosis, other mycobacteria, brucellosis, bacterial infections, fungal
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31 infections, nosocomial infection, implant-associated infection, or
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34 endocarditis) to abstract vertebral osteomyelitis and vertebral tuberculosis
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37 cases from A18.0, M46.4, M46.5, M46.8, M46.9, M48.9 and M49.3. VO was
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40 categorized into PVO (other codes than A18.0 and M49.0) and VT (A18.0
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42 and M49.0).

Estimation of the incidence of VO

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48 We estimated the annual incidence of VO per population per year, based on
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54 the annual number of patients discharged from all acute-care hospitals in
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5 Japan (A_i), the annual number of patients discharged from all DPC
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7 hospitals in Japan (B_i), the number of VO patients in the DPC hospitals
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9 (N_i), the observation period (O_i) and the population of Japan (P_i). The
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11 coverage of the DPC hospitals (R_i) was defined as B_i divided by A_i . Values of
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13 B_i were calculated from the DPC database and data for A_i were obtained
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15 from the Survey of Medical Institutions and Hospital Report, 2010. [27] P_i
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17 was obtained from Japanese Population Census data
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19 (<http://www.stat.go.jp/english/data/kokusei/index.htm>). The estimated
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21 incidence of VO per population per year (Y_i) was calculated using the
22
23 following equation: $Y_i = N_i / R_i / O_i / P_i$.

24 25 26 27 28 29 30 31 32 33 34 35 36 37 *Patient characteristics*

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39 The following variables were abstracted from the DPC database: patient
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41 age and sex; comorbidities that could potentially affect mortality in VO
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43 including diabetes, liver cirrhosis, rheumatoid arthritis, malignancy,
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45 infective endocarditis (IE) and aortic aneurysm; use of hemodialysis; spinal
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47 surgery performed during hospitalization; and type of hospital and hospital
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49 volume. We also examined use of anticoagulants for each patient, including
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5 aspirin, warfarin, clopidogrel and ticlopidine.
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8 Hospital volume was categorized into tertiles: low-volume hospitals (<7
9 cases/year), medium-volume hospitals (7–10 cases/year) and high-volume
10 hospitals (>10 cases/year). These categories were based on cutoffs that
11 yielded equivalent numbers of patients in each volume category.
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22 ***Outcome measurements***

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25 The primary outcome measured was in-hospital mortality. The secondary
26 outcome was LOS.
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33 ***Statistical analysis***

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36 We used the chi-square test for categorical variables and the Wilcoxon
37 rank-sum test for continuous variables to perform univariate comparisons
38 of patient characteristics and outcomes between subgroups. Logistic
39 regression analysis was performed to analyze the concurrent effects of
40 various factors on the occurrence of in-hospital death, while adjusting for
41 clustering of patients within hospitals using a generalized estimating
42 equation. [28] The threshold for significance was a p value <0.05. All
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5 statistical analyses were conducted using IBM SPSS version 19.0 (IBM
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8 SPSS, Armonk, NY, USA).
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10 11 12 13 **RESULTS**

14 15 **Estimated incidence of VO in Japan**

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17 We identified 7,118 eligible patients. Table 1 shows the estimated incidence
18
19 of VO in Japan. The overall incidence of VO between 2007 and 2010 was 6.5
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21 per 100,000 population per year. The estimated incidence increased from
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23 5.3 per 100,000 population per year in 2007 to 7.4 per 100,000 population
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25 per year in 2010 ($p<0.001$). The incidence was lower in the population aged
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27 ≤ 59 years (1.7 per 100,000 population per year) than in those aged 60–69
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29 years (10.9), 70–79 years (21.6) or ≥ 80 years (25.1) ($p<0.001$).
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40 **Patient characteristics**

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42 The patients' backgrounds are shown in Table 2. Overall, 58.9% were male
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44 and the average age (\pm standard deviation) was 69.2 \pm 13.9 years. There were
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46 6,807 cases of PVO and 311 of VT. The proportion of male PVO patients
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48 (59.3%) was higher than that of male VT patients (50.2%, $p=0.001$). No
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60 significant difference in age was observed between the PVO and VT groups.

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5 PVO patients were more likely to have a comorbid condition than VT
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8 patients.

10 **In-hospital mortality**

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12 In-hospital mortality for each category is shown in Table 3. The overall
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14 in-hospital mortality was 6.0%. Higher in-hospital mortality was associated
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16 with greater age ($p<0.001$), hemodialysis use (27.7%, $p<0.001$), diabetes
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18 (10.4%, $p<0.001$), liver cirrhosis (13.1%, $p<0.001$), malignancy (10.3%,
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20 $p<0.001$), IE (12.4%, $p=0.001$) and treatment in a non-academic hospital
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22 (6.3%, $p=0.003$). Higher hospital volume was significantly associated with
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24 lower mortality ($p=0.007$).

33 **Logistic regression analysis for in-hospital mortality**

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35 Table 4 shows the results of the logistic regression analysis for in-hospital
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37 mortality. Higher mortality was significantly associated with greater age
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39 (odds ratios [ORs] of 2.78, 3.99, and 7.13 for patients aged 60–69, 70–79,
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41 and ≥ 80 years compared with those aged ≤ 59 , respectively $p<0.001$),
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43 hemodialysis use (OR 10.56; $p<0.001$), diabetes (OR 2.37; $p<0.001$), liver
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45 cirrhosis (OR 2.63; $p=0.001$), malignancy (OR 2.68; $p<0.001$) and IE (OR
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47 3.19; $p<0.001$). Patients treated in high-volume hospitals were significantly
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5 less likely to die compared with those at low-volume hospitals (OR 0.77;
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8 $p=0.029$).

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10 Overall, the median LOS (interquartile range) was 48 (25–79) days. The
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12 median LOS was shorter in PVO patients (48 [25–78] days) than that in VT
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14 patients (56 [25.5–85.5] days), but the difference was not significant
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16 ($p=0.067$). No significant difference in LOS was observed between academic
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18 and non-academic hospitals (48 [25–76] days vs. 48 [25–79] days, $p=0.521$)
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20 or between hospital-volume groups (49 [25–81] days, 49 [25–80] days, and
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22 47 [24–74] days in low-, medium-, - and high-volume hospitals, respectively,
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31 $p=0.085$).

32 33 34 35 36 37 **DISCUSSION**

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39 The present study examined the annual trends in the occurrence of VO and
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41 risk factors for death from VO using a Japanese nationwide inpatient
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43 database. Our study had two major findings. First, the incidence of VO was
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45 significantly higher in the elderly and increased year by year. Second,
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49 higher in-hospital mortality in VO was significantly associated with various
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54 factors.
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5 Our data demonstrated that the incidence of VO in Japan increased during
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8 the study period, from 5.3 to 7.4 per 100,000 population per year. Yoshimoto
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11 et al. reported that the increase in the VO incidence could be related to the
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14 increasing ratio of aged people (65 years of age or older) in Japan. [9] A
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17 recent report of demographic shifts in Japan demonstrated the rapid
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20 increase in aged population: the percentage increase compared with 2007
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23 was 3.2 % in 2008, 6.1% in 2009, and 7.1% in 2010. [29] Based on the
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26 relationship between higher age and higher frequency of VO occurrence, as
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29 was demonstrated in this study, we believe that this increase is partly
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32 attributable to the aging population in Japan.

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34 Previous limited data have suggested that factors affecting the occurrence
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37 of VO include antecedent infection, diabetes mellitus, rheumatic diseases,
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40 immunosuppression, drug abuse, alcoholism, vertebral compression due to
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43 malignant metastasis, trauma, disc herniation, IE, and prior surgery
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46 (gastrointestinal and urogenital tract).[6] However, risk factors affecting
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49 death from VO have not been well investigated. The present study indicated
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52 that significant risk factors for death from VO were greater age,
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55 hemodialysis, diabetes, liver cirrhosis, malignancy and IE. Mortality risks
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5 of PVO were not different from those of VT.
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8 Recently, two small-scale studies of fewer than 100 cases reported that IE
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10 appeared to increase the incidence of VO, but did not increase its mortality.
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13 [5,30] Conversely, our large-scale data showed that IE was a significant
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15 factor that increased mortality associated with VO. The other factors have
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17 never previously been analysed as risk factors for death with VO.
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21 Hemodialysis use was reported to be a risk factor for hematogenous
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23 complications of intravascular catheter use associated with *S. aureus*
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27 bacteremia. [31] A case report suggested the possibility of VO in
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29 hemodialysis patients. [32] Our study is the first to demonstrate a
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31 significant relationship between hemodialysis use and death from VO.
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35 Previous reports indicated that VO patients were more likely to have
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37 diabetes mellitus (11–19%), [12, 25, 33, 34] but the present study further
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39 demonstrated that diabetes mellitus was a significant predictor for
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41 mortality in VO. Although not surprising, our study has demonstrated that
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43 age, liver cirrhosis, and malignancy were all related to death with VO.
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47 As shown in Table 4, the association of VO mortality with spinal surgery did
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49 not reach statistical significance. Randomized controlled trials are essential
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5 to verify the efficacy of spinal surgery because confounding by surgical
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8 indication affects the surgical result. However, several papers have
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11 suggested the impossibility of randomized controlled trials to decide the
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14 treatment strategy for VO, even apart from spinal surgery. [35, 36] Thus,
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17 our DPC data could not reveal the efficacy of spinal surgery for VO.

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19 The high mortality suggests that VO remains a life-threatening disease
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22 despite advances in medical practice and should be regarded as a fatal
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25 systemic disorder rather than just a localized vertebral disorder.
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28 Our data revealed that several systemic diseases increased the mortality
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31 risk of VO, underscoring the need to keep VO in mind and to catch such
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34 signs of VO as unidentified fever or back pain as soon as possible during the
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37 treatment of these background diseases.

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39 We acknowledge several limitations of the present study. First, the DPC
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42 database does not provide important clinical data such as causative
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45 microorganisms and information on post-discharge outpatient services.
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48 Second, although the sample size was large, the population
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51 representativeness was limited because the participating hospitals were
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54 skewed toward large hospitals. Third, the diagnoses recorded in the
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5 administrative database are less well validated than those made in planned
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8 prospective surveys. Fourth, the period of observation was short for showing
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11 the long term trend of VO incidence. Fifth, the increased rate of VO may be
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14 an overestimation because of several artifacts including the improvement
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17 and increased prevalence of surveillance machines. Last, the mortality of
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20 VO may be underestimated because of transfers to other hospitals. Despite
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23 these limitations, our study has resulted in several new findings regarding
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26 VO, including risk factors for death.
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30 31 **CONCLUSION**

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34 The present study confirmed the increasing incidence of VO using a
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37 nationwide database. Greater age, use of hemodialysis, diabetes, liver
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40 cirrhosis, malignancy, and IE were significantly associated with higher
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43 rates of in-hospital death in patients with VO. Based on the high mortality,
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46 VO remains a life-threatening, systemic disease. These novel findings will
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49 be important for improving the clinical management of VO.
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53 54 **Contributors**

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5 HY, HH and KF collected the data. TA, HC, HY and KS designed the study,
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8 analysed and interpreted the data, and drafted the manuscript. All authors
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10 had full access to all data (including statistical reports and tables) in the
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12 study and take responsibility for the integrity of the data and the accuracy
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14 of the data analysis.
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References

1. Kulowski J. Pyogenic osteomyelitis of the spine: an analysis and discussion of 102 cases. *J Bone Joint Surg* 1936;**18**(2):22.
2. Sapico FL, Montgomerie JZ. Pyogenic vertebral osteomyelitis: report of nine cases and review of the literature. *Rev Infect Dis* 1979;**1**(5):754-76.
3. Colmenero JD, Jimenez-Mejias ME, Sanchez-Lora FJ, et al. Pyogenic, tuberculous, and brucellar vertebral osteomyelitis: a descriptive and comparative study of 219 cases. *Ann Rheum Dis* 1997;**56**(12):709-15.
4. Carragee EJ. Pyogenic vertebral osteomyelitis. *J Bone Joint Surg Am* 1997;**79**(6):874-80.
5. Pigrau C, Almirante B, Flores X, et al. Spontaneous pyogenic vertebral osteomyelitis and endocarditis: incidence, risk factors, and outcome. *Am J Med* 2005;**118**(11):1287.
6. Beronius M, Bergman B, Andersson R. Vertebral osteomyelitis in Goteborg, Sweden: a retrospective study of patients during 1990-95. *Scand J Infect Dis* 2001;**33**(7):527-32.
7. Chelsom J, Solberg CO. Vertebral osteomyelitis at a Norwegian university hospital 1987-97: clinical features, laboratory findings and outcome. *Scand J Infect Dis* 1998;**30**(2):147-51.
8. Legrand E, Flipo RM, Guggenbuhl P, et al. Management of nontuberculous infectious discitis. treatments used in 110 patients admitted to 12 teaching hospitals in France. *Joint, bone, spine : revue du rhumatisme* 2001;**68**(6):504-9.
9. Yoshimoto M, Takebayashi T, Kawaguchi S, et al. Pyogenic spondylitis in the elderly: a report from Japan with the most aging society. *Eur Spine J* 2011;**20**(4):649-54.
10. Gouliouris T, Aliyu SH, Brown NM. Spondylodiscitis: update on diagnosis and management. *J Antimicrob Chemother* 2010;**65 Suppl 3**:iii11-24.
11. Grammatico L, Baron S, Rusch E, et al. Epidemiology of vertebral osteomyelitis (VO) in France: analysis of hospital-discharge data 2002-2003. *Epidemiol Infect* 2008;**136**(5):653-60.
12. Krogsgaard MR, Wagn P, Bengtsson J. Epidemiology of acute vertebral osteomyelitis in Denmark: 137 cases in Denmark 1978-1982, compared to cases reported to the National Patient Register 1991-1993. *Acta Orthop Scand* 1998;**69**(5):513-7.
13. Kapeller P, Fazekas F, Krametter D, et al. Pyogenic infectious spondylitis: clinical, laboratory and MRI features. *Eur Neurol* 1997;**38**(2):94-8.
14. Hopkinson N, Stevenson J, Benjamin S. A case ascertainment study of septic discitis: clinical, microbiological and radiological features. *QJM* 2001;**94**(9):465-70.
15. Digby JM, Kersley JB. Pyogenic non-tuberculous spinal infection: an analysis of thirty

- cases. *J Bone Joint Surg Br* 1979;**61**(1):47-55.
16. Jensen AG, Espersen F, Skinhoj P, et al. Increasing frequency of vertebral osteomyelitis following *Staphylococcus aureus* bacteraemia in Denmark 1980-1990. *J Infect* 1997;**34**(2):113-8.
17. McHenry MC, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. *Clin Infect Dis* 2002;**34**(10):1342-50.
18. Hsieh PC, Wienecke RJ, O'Shaughnessy BA, et al. Surgical strategies for vertebral osteomyelitis and epidural abscess. *Neurosurg Focus* 2004;**17**(6):E4.
19. Quinones-Hinojosa A, Jun P, Jacobs R, et al. General principles in the medical and surgical management of spinal infections: a multidisciplinary approach. *Neurosurg focus* 2004;**17**(6):E1.
20. Chen WH, Jiang LS, Dai LY. Surgical treatment of pyogenic vertebral osteomyelitis with spinal instrumentation. *Eur Spine J* 2007;**16**(9):1307-16.
21. Lehovskiy J. Pyogenic vertebral osteomyelitis/disc infection. *Baillieres Best Pract Res Clin Rheumatol* 1999;**13**(1):59-75.
22. Rezai AR, Woo HH, Errico TJ, et al. Contemporary management of spinal osteomyelitis. *Neurosurgery* 1999;**44**(5):1018-25; discussion 25-6.
23. Hee HT, Majd ME, Holt RT, et al. Better treatment of vertebral osteomyelitis using posterior stabilization and titanium mesh cages. *J Spinal Disord Tech* 2002;**15**(2):149-56; discussion 56.
24. Shousha M, Boehm H. Surgical treatment of cervical spondylodiscitis: a review of 30 consecutive patients. *Spine* 2012;**37**(1):E30-6.
25. Joughin E, McDougall C, Parfitt C, et al. Causes and clinical management of vertebral osteomyelitis in Saskatchewan. *Spine* 1991;**16**(3):261-4.
26. Chikuda H, Yasunaga H, Horiguchi H, et al. Mortality and morbidity in dialysis-dependent patients undergoing spinal surgery: analysis of a national administrative database in Japan. *J Bone Joint Surg Am* 2012;**94**(5):433-8.
27. Ministry of Health LaW, Japan. Survey of Medical Institutions and Hospital Report, 2010, 2010.
28. Hubbard AE, Ahern J, Fleischer NL, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. *Epidemiology* 2010;**21**(4):467-74.
29. Ministry of Internal Affairs and Communications J. The Demographic Shift, 2012, 2012.
30. Tamura K. Clinical characteristics of infective endocarditis with vertebral osteomyelitis. *J Infect Chemother* 2010;**16**(4):260-5.

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3
4 31. Fowler VG, Jr., Justice A, Moore C, et al. Risk factors for hematogenous complications
5 of intravascular catheter-associated Staphylococcus aureus bacteremia. Clin Infect
6 Dis 2005;**40**(5):695-703.
7
8 32. Korzets A, Weinstein T, Ori Y, et al. Back pain and Staphylococcal bacteraemia in
9 haemodialysed patients--beware! Nephrol Dial Transplant 1999;**14**(2):483-6.
10
11 33. Belzunegui J, Del Val N, Intxausti JJ, et al. Vertebral osteomyelitis in northern Spain.
12 Report of 62 cases. Clin Exp Rheumatol 1999;**17**(4):447-52.
13
14 34. Harris LF, Haws FP. Disc space infection. Ala med 1994;**63**(7):12-4.
15
16 35. Darouiche RO. Spinal epidural abscess. N Engl J Med 2006;**355**(19):2012-20.
17
18 36. Zimmerli W. Clinical practice. Vertebral osteomyelitis. N Engl J Med
19 2010;**362**(11):1022-9.
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Table 1. Estimates of the incidence of VO

	No. of VO patients in the DPC hospitals (<i>N_i</i>)	Coverage rate (%) (<i>R_i</i>)	Sum of observation period (year) (<i>O_i</i>)	Population (×100,000) (<i>P_i</i>)	Incidence of VO (per 100,000 population per year) (<i>Y_i</i>)	<i>p</i>
Total	<u>7,118</u>	42.7%	2	1,278	<u>6.5</u>	
Year						
2007 (July–Dec.)	<u>1,516</u>	44.5%	0.5	1,278	<u>5.3</u>	<u><0.001</u>
2008 (July–Dec.)	<u>1,727</u>	42.6%	0.5	1,277	<u>6.3</u>	
2009 (July–Dec.)	<u>1,716</u>	38.0%	0.5	1,275	<u>7.1</u>	
2010 (July–Dec.)	<u>2,159</u>	45.8%	0.5	1,281	<u>7.4</u>	

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Sex

Male 4,194 42.7% 2 623 7.9 <0.001

Female 2,924 42.7% 2 657 5.2

Age (years)

≤59 1,311 42.7% 2 878 1.7 <0.001

60–69 1,693 42.7% 2 182 10.9

70–79 2,376 42.7% 2 129 21.6

≥80 1,738 42.7% 2 81 25.1

VO: vertebral osteomyelitis; DPC: Diagnosis Procedure Combination database

Yi=Nil Ril Oi Pi

Table 2. Patient characteristics

	All		PVO		VT		<i>p</i>
	<i>N</i>	(%)	<i>N</i>	(%)	<i>n</i>	(%)	
Total	<u>7,118</u>		<u>6,807</u>		311		
Age (years)							
≤59	<u>1,311</u>	<u>(18.4)</u>	<u>1,244</u>	<u>(18.3)</u>	67	(21.5)	<u>0.422</u>
60–69	<u>1,693</u>	<u>(23.8)</u>	<u>1,616</u>	<u>(23.7)</u>	77	(24.8)	
70–79	<u>2,376</u>	<u>(33.4)</u>	<u>2,279</u>	<u>(33.5)</u>	97	(31.2)	
≥80	<u>1,738</u>	<u>(24.4)</u>	<u>1,668</u>	<u>(24.5)</u>	70	(22.5)	
Sex							
Male	<u>4,194</u>	<u>(58.9)</u>	<u>4,038</u>	<u>(59.3)</u>	156	(50.2)	<u>0.001</u>
Female	<u>2,924</u>	<u>(41.1)</u>	<u>2,769</u>	<u>(40.7)</u>	155	(49.8)	
Hemodialysis	<u>542</u>	<u>(7.6)</u>	<u>530</u>	<u>(7.8)</u>	12	(3.9)	<u>0.011</u>
Diabetes	<u>1,968</u>	<u>(27.6)</u>	<u>1,909</u>	<u>(28.0)</u>	59	(19.0)	<u><0.001</u>
Liver cirrhosis	<u>137</u>	<u>(1.9)</u>	<u>132</u>	<u>(1.9)</u>	5	(1.6)	<u>0.677</u>
Rheumatoid arthritis	<u>107</u>	<u>(1.5)</u>	<u>103</u>	<u>(1.5)</u>	4	(1.3)	<u>0.748</u>
Anticoagulant use	<u>1,437</u>	<u>(20.2)</u>	<u>1,392</u>	<u>(20.4)</u>	45	(14.5)	<u>0.010</u>

Malignancy	<u>1,111</u>	<u>(15.6)</u>	<u>1,061</u>	<u>(15.6)</u>	50	(16.1)	0.816
IE	<u>145</u>	<u>(2.0)</u>	<u>145</u>	<u>(2.1)</u>	0	(0.0)	0.009
Aortic aneurysm	<u>63</u>	<u>(0.9)</u>	<u>62</u>	<u>(0.9)</u>	1	(0.3)	0.278
Spinal surgery	<u>1,537</u>	<u>(21.6)</u>	<u>1,412</u>	<u>(20.7)</u>	125	(40.2)	<0.001
Type of hospital							
Academic	<u>1,264</u>	<u>(17.8)</u>	<u>1,190</u>	<u>(17.5)</u>	74	(23.8)	<u>0.004</u>
Non-academic	<u>5,854</u>	<u>(82.2)</u>	<u>5,617</u>	<u>(82.5)</u>	237	(76.2)	
Hospital volume							
(cases/year)							
≤6	<u>2,622</u>	<u>(36.8)</u>	<u>2,516</u>	<u>(37.0)</u>	106	(34.1)	<u>0.566</u>
7–10	<u>2,192</u>	<u>(30.8)</u>	<u>2,094</u>	<u>(30.8)</u>	98	(31.5)	
≥11	<u>2,304</u>	<u>(32.4)</u>	<u>2,197</u>	<u>(32.3)</u>	107	(34.4)	

PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE:

infective endocarditis

Table 3. In-hospital mortality

		In-hospital mortality			
		<i>N</i>	<i>N</i>	(%)	<i>p</i>
All		<u>7,118</u>	<u>424</u>	<u>(6.0)</u>	
Diagnosis	PVO	<u>6,807</u>	<u>408</u>	<u>(6.0)</u>	<u>0.536</u>
	VT	311	16	(5.1)	
Age (years)	≤59	<u>1,311</u>	<u>22</u>	<u>(1.7)</u>	<0.001
	60–69	<u>1,693</u>	<u>93</u>	<u>(5.5)</u>	
	70–79	<u>2,376</u>	<u>151</u>	<u>(6.4)</u>	
	≥80	<u>1,738</u>	<u>158</u>	<u>(9.1)</u>	
Sex	Male	<u>4,194</u>	<u>261</u>	<u>(6.2)</u>	<u>0.255</u>
	Female	<u>2,924</u>	<u>163</u>	<u>(5.6)</u>	
Hemodialysis	No	<u>6,576</u>	<u>274</u>	<u>(4.2)</u>	<0.001
	Yes	<u>542</u>	<u>150</u>	<u>(27.7)</u>	
Diabetes	No	<u>5,150</u>	<u>219</u>	<u>(4.3)</u>	<0.001
	Yes	<u>1,968</u>	<u>205</u>	<u>(10.4)</u>	
Liver cirrhosis	No	<u>6,981</u>	<u>406</u>	<u>(5.8)</u>	<0.001
	Yes	<u>137</u>	<u>18</u>	<u>(13.1)</u>	

Rheumatoid arthritis	No	<u>7,011</u>	<u>418</u>	<u>(6.0)</u>	<u>0.878</u>
	Yes	<u>107</u>	<u>6</u>	<u>(5.6)</u>	
Anticoagulants	No	<u>5,681</u>	<u>325</u>	<u>(5.7)</u>	<u>0.095</u>
	Yes	<u>1,437</u>	<u>99</u>	<u>(6.9)</u>	
Malignancy	No	<u>6,007</u>	<u>310</u>	<u>(5.2)</u>	<0.001
	Yes	<u>1,111</u>	<u>114</u>	<u>(10.3)</u>	
IE	No	<u>6,973</u>	<u>406</u>	<u>(5.8)</u>	0.001
	Yes	<u>145</u>	<u>18</u>	<u>(12.4)</u>	
Aortic aneurysm	No	<u>7,055</u>	<u>418</u>	<u>(5.9)</u>	<u>0.230</u>
	Yes	<u>63</u>	<u>6</u>	<u>(9.5)</u>	
Spinal surgery	No	<u>5,581</u>	<u>359</u>	<u>(6.4)</u>	0.001
	Yes	<u>1,537</u>	<u>65</u>	<u>(4.2)</u>	
Type of hospital	Academic	<u>1,264</u>	<u>53</u>	<u>(4.2)</u>	0.003
	Non-academic	<u>5,854</u>	<u>371</u>	<u>(6.3)</u>	
Hospital volume	≤6	<u>2,622</u>	<u>185</u>	<u>(7.1)</u>	<u>0.007</u>
(cases/year)	7–10	<u>2,192</u>	<u>124</u>	<u>(5.7)</u>	
	≥11	<u>2,304</u>	<u>115</u>	<u>(5.0)</u>	

PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE:

infective endocarditis

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Table 4. Logistic regression analysis for in-hospital mortality

		OR	95% CI	<i>P</i>
Diagnosis	PVO	Reference		
	VT	<u>1.28</u>	<u>0.77–2.14</u>	<u>0.348</u>
Age (years)	≤59	Reference		
	60–69	<u>2.78</u>	<u>1.71–4.53</u>	<0.001
	70–79	<u>3.99</u>	<u>2.47–6.44</u>	<0.001
	≥80	<u>7.13</u>	<u>4.36–11.69</u>	<0.001
Sex	Male	Reference		
	Female	<u>0.89</u>	<u>0.71–1.10</u>	<u>0.282</u>
Hemodialysis	No	Reference		
	Yes	<u>10.56</u>	<u>8.12–13.74</u>	<0.001
Diabetes	No	Reference		
	Yes	<u>2.37</u>	<u>1.89–2.98</u>	<0.001
Liver cirrhosis	No	Reference		
	Yes	<u>2.63</u>	<u>1.49–4.63</u>	0.001
Malignancy	No	Reference		
	Yes	<u>2.68</u>	<u>2.10–3.42</u>	<0.001

IE	No	Reference		
	Yes	<u>3.19</u>	<u>1.80–5.65</u>	<0.001
Spinal surgery	No	Reference		
	Yes	<u>0.76</u>	<u>0.57–1.02</u>	<u>0.072</u>
Type of hospitals	Academic	Reference		
	Non-academic	<u>1.35</u>	<u>0.98–1.85</u>	<u>0.064</u>
Hospital volume	≤6	Reference		
(/year)	7-10	<u>0.77</u>	<u>0.60–0.99</u>	<u>0.041</u>
	≥11	<u>0.74</u>	<u>0.56–0.97</u>	<u>0.029</u>

OR: odds ratio, CI: confidence interval, PVO: pyogenic vertebral osteomyelitis, VT: vertebral tuberculosis, IE: infective endocarditis