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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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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: Hospitals adopting the Diagnosis Procedure Combination system during 2007–2010.

Participants: We identified 7118 patients who were diagnosed with VO (International Classification of Diseases, 10th Revision codes: A18.0, M46.4, M46.5, M46.8, M46.9, M48.9 and M49.3, checked with the detailed diagnoses in each case and all other codes indicating the presence of a specific infection) and hospitalised 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 (haemodialysis and surgery) and hospital factors (type of hospital and hospital volume).

Results: Overall, 58.9% of eligible patients were men and the average age was 69.2 years. The estimated incidence of VO increased from 5.3/100 000 population per year in 2007 to 7.4/100 000 population per year in 2010. In-hospital mortality was 6%. There was a linear trend between higher rates of in-hospital mortality and greater age. A higher rate of in-hospital mortality was significantly associated with haemodialysis use (ORs, 10.56 (95% CI 8.12 to 13.74)), diabetes (2.37 (1.89 to 2.98)), liver cirrhosis (2.63 (1.49 to 4.63)), malignancy (2.68, (2.10 to 3.42)) and infective endocarditis (3.19 (1.80 to 5.65)).

Conclusions: Our study demonstrates an increasing incidence of VO, and defines risk factors for death with a nationwide database. Several comorbidities were significantly associated with higher rates of in-hospital death in VO patients.

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 5.3/100 000 population per year in 2007 to 7.4/100 000 population per year in 2010.
- In-hospital mortality was 6%, which was significantly associated with greater age, haemodialysis use, diabetes, liver cirrhosis, malignancy and infective endocarditis.

Strengths and limitations of this study

- This study is the largest study on risk factors for in-hospital mortality in VO patient.
- The database does not include information on causative microorganisms or postdischarge status.

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 (1) to estimate the incidence of VO and (2) to examine the clinical features of VO focusing on risk factors for mortality in VO, using a Japanese nationwide administrative database. In addition, the following details were examined as relevant clinical features of VO. First, data have also been lacking on mortality following surgical procedures for VO. Indications for surgical treatment are the following: prevention of spinal cord or major neural compression, stabilisation or correction of spinal destruction, reduction of intractable pain and failure of conservative management.[18–24] The present study ascertained the mortality of VO patients following conservative or surgical treatment. Second, VO consists of vertebral tuberculosis (VT) and pyogenic vertebral osteomyelitis (PVO), but clinical details in these two conditions have not been fully described.[3 6 11 25] We examined the differences in patient backgrounds and mortality between these two diseases.

MATERIALS AND METHODS

Data source

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

Patient selection

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

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 (Ai), the annual number of patients discharged from all DPC hospitals in Japan (Bi), the number of VO patients in the DPC hospitals (Ni), the observation period (Oi) and the population of Japan (Pi). The coverage of the DPC hospitals (Ri) was defined as Bi divided by Ai. Values of Bi were calculated from the DPC database and data for Ai were obtained from the Survey of Medical Institutions and Hospital Reports, 2010.[27] Pi 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 (Yi) was calculated using the following equation: Yi=Ni/Ri/Oi/Pi.

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

Hospital volume was categorised 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 cut-offs that yielded equivalent numbers of patients in each volume category.

Outcome measurements

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

Statistical analysis

We used the χ^2 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 analyse the concurrent effects of various factors on the occurrence of in-hospital deaths, while adjusting for clustering of patients within hospitals using a generalised estimating equation.[28] The threshold for significance was a p<0.05. All statistical analyses were conducted using IBM SPSS V.19.0 (IBM SPSS, Armonk, New York, USA).

RESULTS

Estimated incidence of VO in Japan

We identified 7118 eligible patients. Table 1 shows the estimated incidence of VO in Japan. The overall incidence of VO between 2007 and 2010 was 6.5/100 000 population per year. The estimated incidence increased from 5.3/100 000 population per year in 2007 to 7.4/100 000 population per year in 2010 (p<0.001). The incidence was lower in the population aged ≤59 years (1.7/100 000 population per year) than in those aged 60–69 years (10.9), 70–79 years (21.6) or ≥80 years (25.1; p<0.001).

Patient characteristics

The patients' backgrounds are shown in table 2. Overall, 58.9% were men and the average age (±SD) was 69.2 ±13.9 years. There were 6807 cases of PVO and 311 of VT. The proportion of male PVO patients (59.3%) was higher than that of male VT patients (50.2%, p=0.001). 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 6%. Higher in-hospital mortality was associated with greater age (p<0.001), haemodialysis use (27.7%, p<0.001), diabetes (10.4%, p<0.001), liver cirrhosis (13.1%, p<0.001), malignancy (10.3%, p<0.001), IE (12.4%, p=0.001) and treatment in a non-academic hospital (6.3%, p=0.003). Higher hospital volume was significantly associated with lower mortality (p=0.007).

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 (ORs of 2.78, 3.99 and 7.13 for patients aged 60–69, 70–79 and ≥80 years compared with those aged ≤59, respectively p<0.001), haemodialysis use (OR 10.56; p<0.001), diabetes (OR 2.37; p<0.001), liver cirrhosis (OR 2.63; p=0.001), malignancy (OR 2.68; p<0.001) and IE (OR 3.19; p<0.001). Patients treated in high-volume hospitals were significantly less likely to die compared with those at low-volume hospitals (OR 0.77; p=0.029).

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

DISCUSSION

The present study examined the annual trends in the occurrence of VO and risk factors for death from VO using a Japanese nationwide inpatient database. Our

Table 1 Estimates of the incidence of VO

	Number of VO patients in the DPC hospitals (Ni)	Coverage rate (%) (Ri)	Sum of observation period (year) (Oi)	Population (×100000) (Pi)	Incidence of VO (per 100 000 population per year) (Yi)	p Value
Total	7118	42.7	2	1278	6.5	
Year						
2007 (July–December)	1516	44.5	0.5	1278	5.3	<0.001
2008 (July–December)	1727	42.6	0.5	1277	6.3	
2009 (July–December)	1716	38.0	0.5	1275	7.1	
2010 (July–December)	2159	45.8	0.5	1281	7.4	
Sex						
Male	4194	42.7	2	623	7.9	<0.001
Female	2924	42.7	2	657	5.2	
Age (years)						
≤59	1311	42.7	2	878	1.7	<0.001
60–69	1693	42.7	2	182	10.9	
70–79	2376	42.7	2	129	21.6	
≥80	1738	42.7	2	81	25.1	

Yi=Ni/Ri/Oi/Pi.
DPC, Diagnosis Procedure Combination database; VO, vertebral osteomyelitis.

Table 2 Patient characteristics

	All		PVO		VT		
	N	(%)	N	(%)	N	(%)	p Value
Total	7118		6807		311		
Age (years)							
≤59	1311	(18.4)	1244	(18.3)	67	(21.5)	0.422
60–69	1693	(23.8)	1616	(23.7)	77	(24.8)	
70–79	2376	(33.4)	2279	(33.5)	97	(31.2)	
≥80	1738	(24.4)	1668	(24.5)	70	(22.5)	
Sex							
Male	4194	(58.9)	4038	(59.3)	156	(50.2)	0.001
Female	2924	(41.1)	2769	(40.7)	155	(49.8)	
Haemodialysis	542	(7.6)	530	(7.8)	12	(3.9)	0.011
Diabetes	1968	(27.6)	1909	(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	1437	(20.2)	1,392	(20.4)	45	(14.5)	0.010
Malignancy	1111	(15.6)	1061	(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	1537	(21.6)	1412	(20.7)	125	(40.2)	<0.001
Type of hospital							
Academic	1264	(17.8)	1190	(17.5)	74	(23.8)	0.004
Non-academic	5854	(82.2)	5617	(82.5)	237	(76.2)	
Hospital volume (cases/year)							
≤6	2622	(36.8)	2516	(37.0)	106	(34.1)	0.566
7–10	2192	(30.8)	2094	(30.8)	98	(31.5)	
≥11	2304	(32.4)	2197	(32.3)	107	(34.4)	

IE, infective endocarditis; PVO, pyogenic vertebral osteomyelitis; VT, vertebral tuberculosis.

study had two major findings. First, the incidence of VO was significantly higher in the elderly and increased year by year. Second, higher in-hospital mortality in VO was significantly associated with various factors.

Our data demonstrated that the incidence of VO in Japan increased during the study period, from 5.3 to 7.4/100 000 population per year. Yoshimoto *et al*[9] reported that the increase in the VO incidence could be related to the increasing ratio of aged people (65 years of age or older) in Japan. A recent report of demographic shifts in Japan demonstrated the rapid increase in aged population: the percentage increase compared with 2007 was 3.2% in 2008, 6.1% in 2009 and 7.1% in 2010.[29] Based on the relationship between higher age and higher frequency of VO occurrence, as was demonstrated in this study, we believe that this increase is partly attributable to the aging population in Japan.

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

Recently, two small-scale studies of fewer than 100 cases reported that IE appeared to increase the incidence of VO, but did not increase its mortality.[5 30] Conversely, our large-scale data showed that IE was a significant factor that increased mortality associated with VO. The other factors have never previously been analysed as risk factors for death with VO. Haemodialysis use was reported to be a risk factor for haematogenous complications of intravascular catheter use associated with *Staphylococcus aureus* bacteraemia.[31] A case report suggested the possibility of VO in haemodialysis patients.[32] Our study is the first to demonstrate a significant relationship between haemodialysis use and death from VO. Previous reports indicated that VO patients were more likely to have diabetes mellitus (11–19%),[12 25 33 34] but the present study further demonstrated that diabetes mellitus was a significant predictor for mortality in VO. Although not surprising, our study has demonstrated that age, liver cirrhosis and malignancy were all related to death with VO.

As shown in table 4, the association of VO mortality with spinal surgery did not reach statistical significance. Randomised controlled trials are essential to verify the efficacy of spinal surgery because confounding by surgical indication affects the surgical result. However, several papers have suggested the impossibility of randomised

Table 3 In-hospital mortality

	N	In-hospital mortality		
		N	(%)	p Value
All	7118	424	(6.0)	
Diagnosis				
PVO	6807	408	(6.0)	0.536
VT	311	16	(5.1)	
Age (years)				
≤59	1311	22	(1.7)	<0.001
60–69	1693	93	(5.5)	
70–79	2376	151	(6.4)	
≥80	1738	158	(9.1)	
Sex				
Male	4194	261	(6.2)	0.255
Female	2924	163	(5.6)	
Haemodialysis				
No	6576	274	(4.2)	<0.001
Yes	542	150	(27.7)	
Diabetes				
No	5150	219	(4.3)	<0.001
Yes	1968	205	(10.4)	
Liver cirrhosis				
No	6981	406	(5.8)	<0.001
Yes	137	18	(13.1)	
Rheumatoid arthritis				
No	7011	418	(6.0)	0.878
Yes	107	6	(5.6)	
Anticoagulants				
No	5681	325	(5.7)	0.095
Yes	1437	99	(6.9)	
Malignancy				
No	6007	310	(5.2)	<0.001
Yes	1111	114	(10.3)	
IE				
No	6973	406	(5.8)	0.001
Yes	145	18	(12.4)	
Aortic aneurysm				
No	7055	418	(5.9)	0.230
Yes	63	6	(9.5)	
Spinal surgery				
No	5581	359	(6.4)	0.001
Yes	1537	65	(4.2)	
Type of hospital				
Academic	1264	53	(4.2)	0.003
Non-academic	5854	371	(6.3)	
Hospital volume (cases/year)				
≤6	2622	185	(7.1)	0.007
7–10	2192	124	(5.7)	
≥11	2304	115	(5.0)	

IE, infective endocarditis; PVO, pyogenic vertebral osteomyelitis; VT, vertebral tuberculosis.

Table 4 Logistic regression analysis for in-hospital mortality

	OR	95% CI	p Value
Diagnosis			
PVO	Reference		
VT	1.28	0.77 to 2.14	0.348
Age (years)			
≤59	Reference		
60–69	2.78	1.71 to 4.53	<0.001
70–79	3.99	2.47 to 6.44	<0.001
≥80	7.13	4.36 to 11.69	<0.001
Sex			
Male	Reference		
Female	0.89	0.71 to 1.10	0.282
Haemodialysis			
No	Reference		
Yes	10.56	8.12 to 13.74	<0.001
Diabetes			
No	Reference		
Yes	2.37	1.89 to 2.98	<0.001
Liver cirrhosis			
No	Reference		
Yes	2.63	1.49 to 4.63	0.001
Malignancy			
No	Reference		
Yes	2.68	2.10 to 3.42	<0.001
IE			
No	Reference		
Yes	3.19	1.80 to 5.65	<0.001
Spinal surgery			
No	Reference		
Yes	0.76	0.57 to 1.02	0.072
Type of hospitals			
Academic	Reference		
Non-academic	1.35	0.98 to 1.85	0.064
Hospital volume (/year)			
≤6	Reference		
7–10	0.77	0.60 to 0.99	0.041
≥11	0.74	0.56 to 0.97	0.029

IE, infective endocarditis; PVO, pyogenic vertebral osteomyelitis; VT, vertebral tuberculosis.

controlled trials to decide the treatment strategy for VO, even apart from spinal surgery.[35 36] Thus, our DPC data could not reveal the efficacy of spinal surgery for VO.

The high mortality suggests that VO remains a life-threatening disease despite advances in medical practice and should be regarded as a fatal systemic disorder rather than just a localised vertebral disorder.

Our data revealed that several systemic diseases increased the mortality risk of VO, underscoring the need to keep VO in mind and to catch such signs of VO as unidentified fever or back pain as soon as possible during the treatment of these background diseases.

We acknowledge several limitations of the present study. First, the DPC database does not provide important clinical data such as causative microorganisms and information on postdischarge outpatient services. Second, although the sample size was large, the population representativeness was limited because the participating hospitals were skewed towards large hospitals. Third, the diagnoses recorded in the administrative database are less well validated than those made in planned prospective surveys. Fourth, the period of observation was short for showing the long-term trend of VO incidence. Fifth, the increased rate of VO may be an

overestimation because of several artefacts including the improvement and increased prevalence of surveillance machines. Last, the mortality of VO may be underestimated because of transfers to other hospitals. Despite these limitations, our study has resulted in several new findings regarding VO, including risk factors for death.

CONCLUSION

The present study confirmed the increasing incidence of VO using a nationwide database. Greater age, use of haemodialysis, diabetes, liver cirrhosis, malignancy and IE were significantly associated with higher rates of in-hospital death in patients with VO. Based on the high mortality, VO remains a life-threatening, systemic disease. These novel findings will 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 complete 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. All authors read and approved the final manuscript.

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