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Complete List of Authors:	Akiyama, Toru; Saitama Medical Center, Jichi Medical University, Department of Orthopaedic Surgery Chikuda, Hirotaka; Faculty of Medicine, The University of Tokyo, Department of Orthopaedic Surgery Yasunaga, Hideo; Graduate School of Medicine, The University of Tokyo, Department of Health Management and Policy Horiguchi, Hiromasa; Graduate School of Medicine, The University of Tokyo, Department of Health Management and Policy Saita, Kazuo; Saitama Medical Center, Jichi Medical University, Department of Orthopaedic Surgery Fushimi, Kiyohide; Tokyo Medical and Dental University Graduate School of Medicine, Department of Health Policy and Informatics
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Incidence and Mortal Risk Factors of Vertebral Osteomyelitis

Toru Akiyama, MD, PhD[1], Hirotaka Chikuda, MD, PhD[2], Hideo Yasunaga, MD, PhD[3], Hiromasa Horiguchi, MD, PhD[3], Kiyohide Fushimi, MD, PhD[4], Kazuo Saita, MD, PhD[1*]

[1]Department of Orthopaedic Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan

[2]Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

[3]Department of Health Management and Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[4]Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine,

Tokyo, Japan

*Corresponding author: postal address; Department of Orthopaedic Surgery, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma, Omiya-ku, Saitama, Saitama 330-8503, Japan,

telephone, +81-48-647-2111; fax, +81-48-648-5188; email, saita-k@jichi.ac.jp

Keywords: vertebral osteomyelitis, Diagnosis Procedure Combination Database, pyogenic vertebral osteomyelitis, vertebral tuberculosis, in-hospital mortality

(2,135 words for text only, excluding title page, abstract, references, figures and tables)

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.

In-hospital mortality was 5.7%. There was a linear trend between higher in-hospital mortality and greater age. Higher in-hospital mortality was significantly associated with hemodialysis use (odds ratios, 10.62 [95% confidence 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]), infective endocarditis (3.22 [1.82–5.70]) and treatment in non-academic hospital (1.36 [1.00–1.86]).

Conclusions: Our study is the first to demonstrate the increasing incidence of VO, its mortality and risk factors for death with a nationwide database. Several comorbidities were significantly associated with higher rates of in-hospital death in VO patients. We believe these novel findings are important for improving the clinical management of VO.

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'

- This study is the first to report significant risk factors for death in VO patients.

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

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

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

Materials and Methods

Data source

For this study, we utilized the Japanese Diagnosis Procedure Combination (DPC) database. Details of the database are described elsewhere[25]. Briefly, discharge abstract and administrative claim data are collected from the participating hospitals between July 1 and December 31 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, Tenth 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: vertebral

osteomyelitis (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), vertebral tuberculosis (M49.0), *Brucella* spondylitis (M49.1), enterobacterial spondylitis (M49.2), spondylopathy in other infectious or parasitic diseases (M49.3), and acute osteomyelitis located within the spinal column, head, neck, cranium or trunk (M86.0.8, M86.1.8). VO was categorized into PVO and VT.

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 Report, 2010[26]. *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 background

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 hemodialysis; spinal surgery performed during hospitalization; 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 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

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 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[27]. 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. 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 (± 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, 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 longer 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 was observed between academic and non-academic hospitals (47 [24–75] days vs. 47 [24–78] days, p=0.511) or between hospital-volume groups (47 [24–80] days, 48 [24–79] days and 47 [24–74] days in low-, medium- and high-volume hospitals, respectively, p=0.145).

DISCUSSION

The present study examined the annual trends in the VO occurrence and risk factors for death from VO using a Japanese nationwide inpatient database. Our 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 5.6 to 7.7 per 100,000 population per year. Yoshimoto et al. 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[9]. A recent report of demographic shift in Japan demonstrated the rapid increase in aged population; the increasing percentage compared to 2007 was 3.2 % in 2008, 6.1% in 2009 and 7.1% in 2010, respectively[28]. Based on the relationship between higher age and the higher frequency of VO occurrence, as was demonstrated in this study, we believe that this increase is partly attributable to aging population in Japan.

Previous limited data suggested that factors affecting the occurrence of VO included 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)[1]. 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, hemodialysis, diabetes, liver cirrhosis, malignancy and IE. Mortal 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 [29 30]. Conversely, our large-scale data showed that IE was a significant factor that increased mortality of VO. The other factors have never previously been analysed as risk factors for death in VO.

Hemodialysis use was reported to be a risk factor for hematogenous complications of intravascular catheter use associated with *S. aureus* bacteremia[31]. A case report suggested the possibility of VO in hemodialysis patients [32]. Our study is the first to demonstrate a significant relationship between hemodialysis use and death from VO.

Previous reports indicated that VO patients were more likely to have diabetes mellitus (11–19%)[1 7 33-35], but the present study further demonstrated that diabetes mellitus was a significant predictor of mortality in VO. Although not surprising, that our study first demonstrated that age, liver cirrhosis and malignancy were all related to death from VO.

As shown in table 4, spinal surgery did not reach statistical significance. Randomized controlled trial is essential to verify the efficacy of spinal surgery, because confounding factor by surgical indication affect the surgical result. However several papers suggested the impossibility of randomized controlled trials to decide the treatment strategy of VO, not limited in spinal surgery [36 37]. Thus, our DPC date could not reveal the efficacy of spinal surgery of 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 localized vertebral disorder.

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 post-discharge outpatient services. Second, although the sample size was large, the population representativeness was limited because the participating hospitals were skewed toward large hospitals. Third, the diagnoses recorded in the administrative database are less well validated

than those made in planned prospective surveys. Lastly, the mortality of VO may be underestimated because of transferring to other hospitals. Despite these limitations, our study made 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 hemodialysis, 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, we believe that VO remains a life-threatening, systemic disease. These novel findings will be important for improving the clinical management of VO.

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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Competing Interests

We declare that there are no competing interests for publication.

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.

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Table 1. Estimates of the incidence of VO

	No. of VO patients in the DPC hospitals (*Ni*)	Coverage rate (%) (*Ri*)	Sum of observation period (year) (*Oi*)	Population (×100,000) (*Pi*)	Incidence of VO (per 100,000 population per year) (*Yi*)
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

Sex					
Male	4,373	42.7%	2	623	8.2
Female	3,081	42.7%	2	657	5.5
Age (years)					
≤59	1,396	42.7%	2	878	1.9
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

$Yi=Ni/Ri/Oi/Pi$

Table 2. Patient backgrounds

	All		PVO		VT		
	N	(%)	*n*	(%)	*n*	(%)	*p*
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		
		N	*n*	(%)	*p*
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	*P*
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 Vertebral Osteomyelitis: A Retrospective Analysis Using the Japanese Diagnosis Procedure Combination Database

Incidence and Mortal Risk Factors of Vertebral Osteomyelitis

Toru Akiyama, MD, PhD[1], Hirotaka Chikuda, MD, PhD[2], Hideo Yasunaga, MD, PhD[3], Hiromasa Horiguchi, MD, PhD[3], Kiyohide Fushimi, MD, PhD[4], Kazuo Saita, MD, PhD[1*]

[1]Department of Orthopaedic Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan

[2]Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

[3]Department of Health Management and Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[4]Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan

*Corresponding author: (Postal address) Department of Orthopaedic Surgery, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma, Omiya-ku, Saitama, Saitama 330-8503, Japan

Telephone +81-48-647-2111; Fax +81-48-648-5188; Email saita-k@jichi.ac.jp

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(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

higher rates of in-hospital mortality and greater age. A higher rate of in-hospital mortality was significantly associated with hemodialysis use (odds ratios, 10.62 [95% confidence 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]), infective endocarditis (3.22 [1.82–5.70]) and treatment in non-academic hospital (1.36 [1.00–1.86]).

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 7,454 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'

- 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 post-discharge 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 (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

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, stabilization 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 utilized 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 July 1 and December 31 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, Tenth 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: vertebral osteomyelitis (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), vertebral tuberculosis (M49.0), *Brucella* spondylitis (M49.1), enterobacterial spondylitis (M49.2), spondylopathy in other infectious or parasitic diseases (M49.3), and acute osteomyelitis located within the spinal column, head, neck, cranium or trunk (M86.0.8, M86.1.8). VO was categorized into PVO (other codes than M49.0) and VT (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 Report, 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 hemodialysis; spinal surgery performed during hospitalization; 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 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 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 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 (± 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

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

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 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 5.6 to 7.7 per 100,000 population per year. Yoshimoto et al. 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. [9] 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, hemodialysis, 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.

Hemodialysis use was reported to be a risk factor for hematogenous complications of intravascular catheter use associated with *S. aureus* bacteremia. [31] A case report suggested the possibility of VO in hemodialysis patients. [32] Our study is the first to demonstrate a significant relationship between hemodialysis 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. Randomized 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 randomized 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 localized 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 post-discharge outpatient services. Second, although the sample size was large, the population representativeness was limited because the participating hospitals were skewed toward 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 artifacts 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 hemodialysis, 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.

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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Table 1. Estimates of the incidence of VO

	No. of VO patients in the DPC hospitals (*Ni*)	Coverage rate (%) (*Ri*)	Sum of observation period (year) (*Oi*)	Population (×100,000) (*Pi*)	Incidence of VO (per 100,000 population per year) (*Yi*)	*p*
Total	7,454	42.7%	2	1,278	6.8	
Year						
2007 (July–Dec.)	1,599	44.5%	0.5	1,278	5.6	<0.001
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	

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

$Yi=Ni|Ri|Oi|Pi$

Table 2. Patient backgrounds

	All		PVO		VT		
	N	(%)	*n*	(%)	*n*	(%)	*p*
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		
		N	*n*	(%)	*p*
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	*P*
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 ~~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

Toru Akiyama, MD, PhD[1], Hirotaka Chikuda, MD, PhD[2], Hideo Yasunaga, MD, PhD[3], Hiromasa Horiguchi, MD, PhD[3], Kiyohide Fushimi, MD, PhD[4], Kazuo Saita, MD, PhD[1*]

[1]Department of Orthopaedic Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan

[2]Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

[3]Department of Health Management and Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[4]Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan

*Corresponding author: postal address; Department of Orthopaedic Surgery, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma, Omiya-ku, Saitama, Saitama 330-8503, Japan,

telephone, +81-48-647-2111; fax, +81-48-648-5188; email, saita-k@jichi.ac.jp

Keywords: vertebral osteomyelitis, Diagnosis Procedure Combination Database, pyogenic vertebral osteomyelitis, vertebral tuberculosis, in-hospital mortality

(2,135 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~~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

higher rates in-hospital mortality and greater age. ~~Higher~~ A higher rate of in-hospital mortality was significantly associated with hemodialysis use (odds ratios, 10.62 [95% confidence 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]), infective endocarditis (3.22 [1.82–5.70]) and treatment in non-academic hospital (1.36 [1.00–1.86]).

Conclusions: Our study demonstrates an increasing incidence of VO, and defines risk factors~~Our study is the first to demonstrate the increasing incidence of VO, its mortality and risk factors~~ for death with a nationwide database. Several comorbidities were significantly associated with higher rates of in-hospital death in VO patients. ~~We believe these novel findings are important for improving the clinical management of VO.~~

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'

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

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

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, ~~[1]~~[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

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. In addition, the following details were examined as relevant clinical features of VO. ~~Additionally, the following details were examined.~~ First, data have also been lacking on mortality following surgical procedures for VO. Indications for surgical treatment are the following:~~decided by the following factors;~~ prevention of spinal cord or major neural compression, stabilization or correction of spinal destruction, reduction of intractable pain, and failure of conservative management. [18-24]~~prevention for spinal cord or major neural compression, stabilization or correction of spinal construction, reduction of intractable pain and failure of conservative management.[17-22][23]~~ The present study ascertained the~~verified~~ mortality of VO patients following conservative or surgical treatment~~s~~. 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 17 18].~~ [3, 6, 11, 25] We examined the difference in

patient backgrounds and mortality between these two diseases.

Materials and Methods

Data source

For this study, we utilized the Japanese Diagnosis Procedure Combination (DPC) database. Details of the database are described elsewhere~~[19]~~[26]. Briefly, discharge abstract and administrative claim data are collected from the participating hospitals between July 1 and December 31 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, Tenth 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: vertebral osteomyelitis (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), vertebral tuberculosis (M49.0), *Brucella* spondylitis (M49.1), enterobacterial spondylitis (M49.2), spondylopathy in other infectious or parasitic diseases (M49.3), and acute osteomyelitis located within the spinal column, head, neck, cranium or trunk (M86.0.8, M86.1.8). ~~VO was categorized into PVO and VT.~~ VO was categorized into PVO (other codes than M49.0) and VT (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 Report, 2010~~[20]~~. [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 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,

infective endocarditis (IE) and aortic aneurysm; use of hemodialysis; spinal surgery performed during hospitalization; 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 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 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 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~~[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 (± 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,

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

DISCUSSION

The present study examined the annual trends in the VO occurrence and risk factors for death from VO using a Japanese nationwide inpatient database. Our 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 5.6 to 7.7 per 100,000 population per year. Yoshimoto et al. 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~~[9]~~. [9] A recent report of demographic shift in Japan demonstrated the rapid increase in aged population; the increasing percentage compared to 2007 was 3.2 % in 2008, 6.1% in 2009 and 7.1% in 2010, respectively~~[22]~~. [29] Based on the relationship between higher age and the higher frequency of VO occurrence, as was demonstrated in this study, we believe that this increase is partly attributable to aging population in Japan.

Previous limited data suggested that factors affecting the occurrence of VO included 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]~~.[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, hemodialysis, diabetes, liver cirrhosis, malignancy and IE. Mortal 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 23]~~.[5, 30] Conversely, our large-scale data showed that IE was a significant factor that increased mortality of VO. The other factors have never previously been analysed as risk factors for death in VO.

Hemodialysis use was reported to be a risk factor for hematogenous complications of intravascular catheter use associated with *S. aureus* bacteremia~~[24]~~. [31] A case report suggested the possibility of VO in hemodialysis patients ~~[25]~~. [32] Our study is the first to demonstrate a significant relationship between hemodialysis use and death from VO.

Previous reports indicated that VO patients were more likely to have diabetes mellitus (11–19%)~~[6 16 26-28]~~, [12, 25, 33, 34] but the present study further demonstrated that diabetes mellitus was a significant predictor of mortality in VO. Although not surprising, ~~that~~ our study ~~first~~has demonstrated that age, liver cirrhosis and malignancy were all

related to death ~~from~~ with VO.

As shown in table 4, the association of VO mortality with spinal surgery did not reach statistical significance. Randomized controlled trials are~~is~~ essential to verify the efficacy of spinal surgery, because confounding ~~factor~~ by surgical indication affects the surgical result. However several papers have suggested the impossibility of randomized controlled trials to decide the treatment strategy of VO, not limited in spinal surgery ~~[36 37]~~. [35, 36] Thus, our DPC date could not reveal the efficacy of spinal surgery for~~of~~ 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 localized 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 post-discharge outpatient services.

Second, although the sample size was large, the population representativeness was limited because the participating hospitals were skewed toward 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 artifacts including the improvement and increased prevalence of surveillance machines. Last~~ly~~, the mortality of VO may be underestimated because of transferring to other hospitals. Despite these limitations, our study made 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 hemodialysis, 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, we believe that VO remains a life-threatening, systemic disease. These novel

findings will be important for improving the clinical management of VO.

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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Table 1. Estimates of the incidence of VO

	No. of VO patients in the DPC hospitals (*Ni*)	Coverage rate (%) (*Ri*)	Sum of observation period (year) (*Oi*)	Population (×100,000) (*Pi*)	Incidence of VO (per 100,000 population per year) (*Yi*)	*p*
Total	7,454	42.7%	2	1,278	6.8	
Year						
2007 (July–Dec.)	1,599	44.5%	0.5	1,278	5.6	<0.001
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	

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=Ni/Ri/Oi/Pi

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Table 2. Patient backgrounds

	All		PVO		VT		
	N	(%)	*n*	(%)	*n*	(%)	*p*
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							

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		
		N	*n*	(%)	*p*
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

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	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**

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(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	*P*
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**		

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	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

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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 Vertebral Osteomyelitis: A Retrospective Analysis Using the Japanese Diagnosis Procedure Combination Database

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

Incidence and Mortal Risk Factors of Vertebral Osteomyelitis

Toru Akiyama, MD, PhD[1], Hirotaka Chikuda, MD, PhD[2], Hideo Yasunaga, MD, PhD[3], Hiromasa Horiguchi, MD, PhD[3], Kiyohide Fushimi, MD, PhD[4], Kazuo Saita, MD, PhD[1*]

[1]Department of Orthopaedic Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan

[2]Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

[3]Department of Health Management and Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[4]Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan

*Corresponding author: (Postal address) Department of Orthopaedic Surgery, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma, Omiya-ku, Saitama, Saitama 330-8503, Japan

Telephone +81-48-647-2111; Fax +81-48-648-5188; Email saita-k@jichi.ac.jp

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(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

higher rates of in-hospital mortality and greater age. A higher rate of in-hospital mortality was significantly associated with hemodialysis use (odds ratios, 10.56 [95% confidence interval, 8.12–13.74]), diabetes (2.37 [1.89–2.98]), liver cirrhosis (2.63 [1.49–4.63]), malignancy (2.68, [2.10–3.42]) and infective endocarditis (3.19 [1.80–5.65]).

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 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

- 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 post-discharge 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 (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

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, stabilization 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 utilized 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 July 1 and December 31 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, Tenth 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: vertebral osteomyelitis (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), vertebral tuberculosis (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 vertebral osteomyelitis and vertebral tuberculosis cases from A18.0, M46.4, M46.5, M46.8, M46.9, M48.9 and M49.3. VO was categorized 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 Report, 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 hemodialysis; spinal surgery performed during hospitalization; 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 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 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 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 7,118 eligible patients. Table 1 shows the estimated incidence of VO in Japan. The overall incidence of VO between 2007 and 2010 was 6.5 per 100,000 population per year. The estimated incidence increased from 5.3 per 100,000 population per year in 2007 to 7.4 per 100,000 population per year in 2010 ($p<0.001$). The incidence was lower in the population aged ≤59 years (1.7 per 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 male and the average age (± standard deviation) was 69.2±13.9 years. There were 6,807 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 6.0%. Higher in-hospital mortality was associated with greater age (p<0.001), hemodialysis 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 (odds ratios [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), hemodialysis 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 (interquartile range) 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] days, 49 [25–80] days, and 47 [24–74] days in low-, medium, - 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 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 per 100,000 population per year. Yoshimoto et al. 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. [9] 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, hemodialysis, 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.

Hemodialysis use was reported to be a risk factor for hematogenous complications of intravascular catheter use associated with *S. aureus* bacteremia. [31] A case report suggested the possibility of VO in hemodialysis patients. [32] Our study is the first to demonstrate a significant relationship between hemodialysis 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. Randomized 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 randomized 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 localized 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 post-discharge outpatient services. Second, although the sample size was large, the population representativeness was limited because the participating hospitals were skewed toward 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 artifacts 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 hemodialysis, 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.

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

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Table 1. Estimates of the incidence of VO

	No. of VO patients in the DPC hospitals (*Ni*)	Coverage rate (%) (*Ri*)	Sum of observation period (year) (*Oi*)	Population (×100,000) (*Pi*)	Incidence of VO (per 100,000 population per year) (*Yi*)	*p*
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	

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

$Yi=Ni/Ri/Oi/Pi$

Table 2. Patient characteristics

	All		PVO		VT		
	N	(%)	*N*	(%)	*n*	(%)	*p*
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		
		N	*N*	(%)	*p*
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

Table 4. Logistic regression analysis for in-hospital mortality

		OR	95% CI	*P*
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	**≤6**	**Reference**		
(/year)	**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

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

Incidence and Mortal Risk Factors of Vertebral Osteomyelitis

Toru Akiyama, MD, PhD[1], Hirotaka Chikuda, MD, PhD[2], Hideo Yasunaga, MD, PhD[3], Hiromasa Horiguchi, MD, PhD[3], Kiyohide Fushimi, MD, PhD[4], Kazuo Saita, MD, PhD[1*]

[1]Department of Orthopaedic Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan

[2]Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

[3]Department of Health Management and Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[4]Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan

*Corresponding author: (Postal address) Department of Orthopaedic Surgery, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma, Omiya-ku, Saitama, Saitama 330-8503, Japan

Telephone +81-48-647-2111; Fax +81-48-648-5188; Email saita-k@jichi.ac.jp

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

higher rates of in-hospital mortality and greater age. A higher rate of in-hospital mortality was significantly associated with hemodialysis use (odds ratios, 10.56 [95% confidence interval, 8.12–13.74]), diabetes (2.37 [1.89–2.98]), liver cirrhosis (2.63 [1.49–4.63]), malignancy (2.68, [2.10–3.42]) and infective endocarditis (3.19 [1.80–5.65]).

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 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

- 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 post-discharge 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 (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

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, stabilization 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 utilized 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 July 1 and December 31 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, Tenth 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: vertebral osteomyelitis (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), vertebral tuberculosis (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 vertebral osteomyelitis and vertebral tuberculosis cases from A18.0, M46.4, M46.5, M46.8, M46.9, M48.9 and M49.3. VO was categorized 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 Report, 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 hemodialysis; spinal surgery performed during hospitalization; 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 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 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 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 7,118 eligible patients. Table 1 shows the estimated incidence of VO in Japan. The overall incidence of VO between 2007 and 2010 was 6.5 per 100,000 population per year. The estimated incidence increased from 5.3 per 100,000 population per year in 2007 to 7.4 per 100,000 population per year in 2010 ($p<0.001$). The incidence was lower in the population aged ≤59 years (1.7 per 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 male and the average age (± standard deviation) was 69.2±13.9 years. There were 6,807 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 6.0%. Higher in-hospital mortality was associated with greater age (p<0.001), hemodialysis 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 (odds ratios [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), hemodialysis 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 (interquartile range) 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] days, 49 [25–80] days, and 47 [24–74] days in low-, medium, - 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 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 per 100,000 population per year. Yoshimoto et al. 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. [9] 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, hemodialysis, 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.

Hemodialysis use was reported to be a risk factor for hematogenous complications of intravascular catheter use associated with *S. aureus* bacteremia. [31] A case report suggested the possibility of VO in hemodialysis patients. [32] Our study is the first to demonstrate a significant relationship between hemodialysis 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. Randomized 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 randomized 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 localized 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 post-discharge outpatient services. Second, although the sample size was large, the population representativeness was limited because the participating hospitals were skewed toward 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 artifacts 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 hemodialysis, 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.

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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Table 1. Estimates of the incidence of VO

	No. of VO patients in the DPC hospitals (*Ni*)	Coverage rate (%) (*Ri*)	Sum of observation period (year) (*Oi*)	Population (×100,000) (*Pi*)	Incidence of VO (per 100,000 population per year) (*Yi*)	*p*
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

$Yi=Ni/Ri/Oi/Pi$

Table 2. Patient characteristics

	All		PVO		VT		
	N	(%)	*N*	(%)	*n*	(%)	*p*
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		
		N	*N*	(%)	*p*
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

Table 4. Logistic regression analysis for in-hospital mortality

		OR	95% CI	*P*
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	**≤6**	**Reference**		
(/year)	**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