Life Expectancy Is Poor in Patients with Diffuse Idiopathic Skeletal Hyperostosis-Related Pyogenic Vertebral Osteomyelitis

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Abstract:

Introduction: Pyogenic vertebral osteomyelitis (PVO) is an uncommon but life-threatening infectious disease. Diffuse idiopathic skeletal hyperostosis (DISH) is an age-related disorder and sometimes problematic in terms of spinal instability or high mortality, especially in cases of DISH-related fracture. Meanwhile, no reports have focused on the impact of DISH on the clinical outcomes after treatment for PVO. We hypothesized that PVO occurring at DISH-related segments might contribute to poor clinical results or high mortality rates. The purpose of this study was to investigate the impact of DISH on mortality after treatment for PVO in a retrospective cohort study.

Methods: This study involved patients who were hospitalized and treated for PVO at a single institution. DISH-related PVO was defined as PVO within a segment ossified by DISH or PVO at the neighboring intervertebral level of the segment ossified by DISH. Differences in mortality between patients with DISH-related and non-DISH-related PVO were investigated.

Results: This study included 55 patients. DISH-related PVO was observed in 13 patients. The mortality rate was significantly higher in patients with DISH-related PVO than in those with non-DISH-related PVO (62% and 23%, respectively; p=0.016). Propensity score-adjusted analysis showed that DISH-related PVO was an independent risk factor for mortality (adjusted hazard ratio, 2.79; p=0.034). The survival probability was significantly shorter in patients with DISH-related PVO than in those with non-DISH-related PVO (p=0.006). PVO in which the intravertebral body was the center of involvement was significantly more common in DISH-related PVO than in non-DISH-related PVO (38% and 5%, respectively; p=0.006).

Conclusions: DISH-related PVO was associated with a higher mortality rate and shorter life expectancy than non-DISH-related PVO. Similar to advanced age, PVO at the segment ossified by DISH should be recognized as a risk factor for mortality when choosing the optimal treatment strategy.

Keywords:

pyogenic vertebral osteomyelitis, diffuse idiopathic skeletal hyperostosis, mortality, single institution, propensity score-adjusted analysis

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Introduction

Pyogenic vertebral osteomyelitis (PVO) is an uncommon but life-threatening infectious disease of the spine. The reported incidence of PVO is 2.2-7.4 per 100,000 inhabitants of the general populations in France, Japan, and Denmark[1-3)] and has risen in recent years with the growth of the aged population[2)]. The mortality rate associated with PVO reportedly ranges from 2% to 25%[2,4-9)]. Risk factors for increased mortality include older age[5,6,9)], comorbidities[2,5-10)], an elevated C-reactive protein (CRP) concentration at admission[6)], neurological deficits[5)], delayed diagnosis[5)], and a higher number of affected vertebral levels[9)].

Diffuse idiopathic skeletal hyperostosis (DISH) is an age-related disorder characterized by calcification and ossification of soft tissues, predominantly ligaments and entheses[11)]. In patients with DISH, the spinal longitudinal ligaments and entheses slowly become ossified and show decreased mobility in the affected region until complete ankylosis occurs. Complications of DISH include unstable spinal fractures,

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dysphagia, postural abnormalities, difficult intubation, difficult gastroscopy, aspiration pneumonia, and neurological disorders[12-17]. Among these complications, DISH-related spinal fractures (i.e., spinal fractures occurring at the vertebra within the segment ossified by DISH) have become particularly problematic. Westerveld et al.[13] demonstrated that the mortality rate of patients with DISH-related fractures was as high as 38.1%. In patients with DISH-related spinal fractures, the fracture segments are exposed to higher mechanical stress because of the longer lever arm caused by ossification of the spinal column. This mechanism has been thought to cause the high rate of neurological deterioration and mortality in patients with DISH-related PVO as well as comorbidity in patients with DISH[13,17,18].

We hypothesized that PVO occurring at DISH-related segments might be associated with poor clinical results or high mortality. However, no reports have focused on the effect of DISH on the clinical outcomes after treatment for PVO. Therefore, this study was performed to investigate mortality after treatment for PVO and the impact of DISH on mortality.

Materials and Methods

Patients

This retrospective cohort study was performed at a single institution in a suburban area in Osaka, the second largest city in Japan. This hospital has been characterized as a secondary general hospital for middle-aged and elderly people in the neighboring community. In principle, diagnosis and conservative treatment for PVO are performed by general physicians in consultation with the Department of Orthopedic Surgery and Infection control team. The surgical indications for PVO or epidural abscesses are decided by the orthopedic surgeon.

This study was approved by the Clinical Research Ethics Committee of the hospital. Patients who were hospitalized and treated for PVO from 2010 to 2020 were identified using the hospital's coding system. The search was restricted to the years in which digital medical and radiographic records were available to facilitate access to medical reports and images and thus confirm the presence of osteomyelitis.

PVO was confirmed by clinical, radiologic, and microbiologic analyses. For culture-negative cases, PVO was diagnosed if the patient had a history of a clinical (fever, back pain, or abnormal inflammatory value of blood examination) and radiological inflammatory process that could be associated with PVO. Radiologic criteria were bony destruction of the affected vertebrae evident on plain radiographs or computed tomography (CT) images or a diffuse signal change within the vertebral body on both T1- and T2-weighted magnetic resonance images (MRIs). Patients were excluded if their PVO was caused by mycobacterial, fungal, or *Brucella* species or if their antibiotic treatment was <28 days. PVO due to surgical site infection, PVO complicated by either epidural injection or nerve root block, or PVO associated with malignancy were also excluded from this study.

Investigated parameters

DISH was diagnosed based on plain radiographs or CT images at hospital admission according to the criteria proposed by Resnick and Niwayama[11]: at least four contiguous vertebral segments, preservation of the intervertebral disc spaces, and absence of apophyseal joint ankylosis or sacroiliac inflammatory changes. The vertebrae fused by DISH were investigated. DISH-related PVO was defined as follows: (1) The PVO-affected level was within the segment ossified by DISH or (2) the PVO-affected level was the cranial/distal intervertebral level of the segment ossified by DISH. Furthermore, the type of PVO was investigated according to the location of the center of PVO: disc level or intravertebral body (Fig. 1).

The potential covariables for mortality included age, sex, comorbidities, and symptoms at the time of hospitalization. Comorbidities were assessed as including frailty using the modified frailty index (mFI), which was calculated from diabetes mellitus, the functional status, chronic obstructive pulmonary disease or pneumonia, congestive heart failure, myocardial infarction, a previous percutaneous procedure or angina, medically treated hypertension, peripheral vascular disease, impaired sensorium, transient ischemic attack or cerebrovascular accident, and neurologic deficit after previous cerebrovascular accident[9,19]. A neurological deficit due to PVO was defined as the presence of muscle weakness with a manual muscle test score of <3.

The following PVO-associated variables were investigated: the level affected by PVO, multilevel PVO, synchronous infection (epidural abscess, iliopsoas abscess, or endocarditis), microbiologic details, laboratory markers at admission (albumin, estimated glomerular filtration rate, CRP concentration, and white blood cell count), and treatment (duration of intravenous antibiotic treatment or surgical intervention).

Outcome measurements

Mortality and cause of death were investigated from the medical records. If the patients were lost to follow-up within 2 years after admission for PVO, a telephone survey of the patients or their family was conducted.

Statistical analysis

Results are shown as median (interquartile range). Differences in categorical variables and continuous variables between patients with DISH-related and non-DISH-related PVO were examined using the chi-square test and Mann-Whitney U test, respectively. Survival curves were produced using the Kaplan-Meier method. Cox proportional hazards regression was used to analyze the impact of DISH on PVO-related mortality. The hazard ratio (HR) with 95% confidence interval (CI) for mortality was calculated. The multivariate models were determined according to covariates that

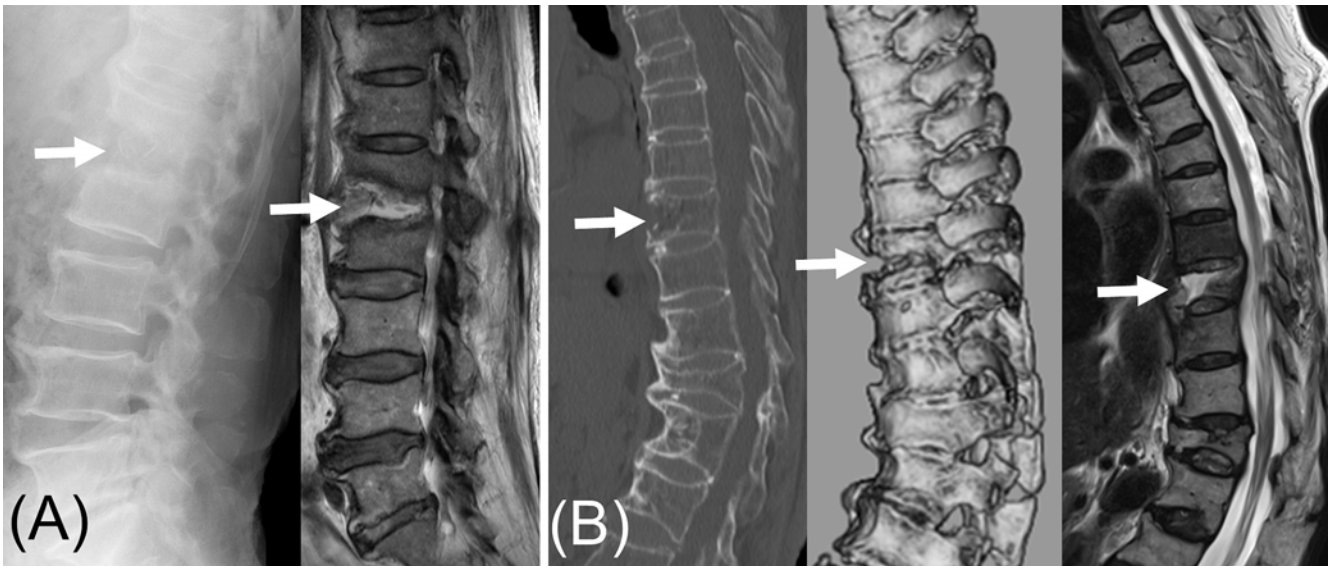

Figure 1. PVO locations. (A) The center of PVO (arrow) was at the disc level. (B) The center of PVO (arrow) was at the intravertebral body, which seemed to occur at the site of vertebral fracture.
PVO, pyogenic vertebral osteomyelitis

were detected as risk factors for mortality in patients with PVO in previous studies. The first model was adjusted for age, sex, and mFI as the most frequently reported risk factors. The second model was adjusted for covariates with age, sex, mFI, CRP concentration, muscle weakness, and multilevel infection as previously reported risk factors. The second model was performed using the propensity score-adjusted analysis, which was estimated by logistic regression because the number of events per confounder decreased. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA).

Results

Fifty-six patients with PVO were identified for our analyses. Fourteen of these patients were lost to follow-up within 2 years after admission for PVO; thus, we conducted a telephone survey of these patients. Thirteen of the 14 patients who were lost to follow-up were investigated to determine their mortality and cause of death. One of the 14 patients could not be contacted because her phone number has changed. Therefore, this study included 55 patients with PVO and a >2-year follow-up regarding mortality. The median (IQR) follow-up regarding mortality from the time of admission for PVO was 3.3 (1.1-5.5) years.

Table 1 shows the patient demographics and characteristics of PVO. The patients' median (IQR) age was 73 (66-80) years, and 30 patients (55%) were male. The PVO-affected lesion was located in the cervical spine in 4 patients (7%), thoracic spine in 12 (22%), and lumbar spine in 39 (71%). PVO exhibited multilevel involvement in 5 patients (9%). Table 2 shows the microbiologic diagnoses. The causative organism was identified in 33 patients (60%). *Staphylococcus aureus* was the most common causative bacteria. The period of intravenous antibiotic treatment was 6 (4.4-8.9) weeks with and without subsequent oral antibiotic treatment. Surgeries were performed in 13 patients (24%). Overall, 18 patients (33%) died during follow-up.

DISH-related PVO

DISH-related PVO was present in 13 patients (24%). Table 3 shows the characteristics of all patients with DISH-related PVO. In 6 patients, PVO involved the level within the segment ossified by DISH. In 7 patients, PVO involved the cranial/distal intervertebral level of the segment ossified by DISH.

The mortality rate of patients with DISH-related PVO was 62% (8 of 13 patients). The mean prognosis after admission was 0.7 years: 88% (7 of 8 patients) died within 1 year after admission for PVO. The Kaplan-Meier survival curve showed that the mortality of patients with DISH-related PVO increased within 2 years compared with that of patients with non-DISH-related PVO (Fig. 2).

Table 4 shows the differences between patients with and without DISH-related PVO. Mortality was significantly higher in patients with DISH-related PVO than in patients with non-DISH-related PVO (62% and 23%, p=0.016), whereas patients with DISH-related PVO were significantly older (79 and 72 years, p=0.002) and had a significantly higher CRP concentration at admission (145 and 62 mg/L, p =0.011). Sepsis as the cause of death was observed in 6 of 8 patients (75%) with DISH-related PVO and 5 of 10 patients with non-DISH-related PVO. Notably, the intravertebral body as the center of PVO involvement was observed significantly more often in patients with DISH-related PVO than in those with non-DISH-related PVO (5 [38%] and 2 [5%], respectively; p=0.006).

The multivariate analysis (Table 5) shows that DISH-

Table 1. Demographics and Clinical Characteristics among Patients with PVO.

	N=55
Age, years	73 (66–80)
Sex, male	30 (55)
BMI, kg/m^2	21.0 (18.7–23.9)
Comorbidities	
Diabetes mellitus	16 (29)
Cancer	15 (27)
Chronic heart failure	7 (12)
Chronic kidney disease	21 (38)
Liver cirrhosis	4 (7)
Chronic obstructive pulmonary disease	4 (7)
Modified frailty index	2 (1–3)
Affected lesion	
Cervical level	4 (7)
Thoracic level	12 (22)
Lumbar/sacral level	39 (71)
Multilevel PVO	5 (9)
Symptoms	
Fever	34 (62)
Axial pain	53 (96)
Muscle weakness*	5 (9)
Synchronous infection	
Epidural abscess	19 (35)
Iliopsoas abscess	16 (29)
Endocarditis	1 (2)
Laboratory markers	
Albumin, g/dL	3.0 (2.6–3.5)
eGFR, mL/min	65 (44.3–86.4)
CRP, mg/L	92 (35–187)
WBC, cells /μ	11,100 (8,300–14,600)
Microbiological diagnosis	33 (60)
Blood culture	29 (53)
Needle biopsy	6 (11)
Surgical biopsy	4 (7)
Treatment	
IV antibiotic duration, weeks	6 (4.4–8.9)
Surgery	13 (24)

Data are represented as median (interquartile range) or n (%).

*Muscle weakness score of ≤3 on manual muscle testing

BMI, body mass index; PVO, pyogenic vertebral osteomyelitis; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; WBC, white blood cells; IV, intravenous

Table 2. Microbiological Identification.

Organism	Total, n (%) n=55	DISH-related PVO, n (%) n=13	Non-DISH-related PVO, n (%) n=42
Methicillin-sensitive *Staphylococcus aureus*	10 (18)	3 (23)	7 (17)
Methicillin-resistant *Staphylococcus aureus*	5 (9)	2 (15)	3 (7)
Staphylococcus epidermidis	2 (4)	0 (0)	2 (5)
Streptococcal species	7 (13)	3 (23)	4 (10)
Enterococcus faecalis	1 (2)	1 (8)	0 (0)
Escherichia coli	5 (9)	1 (8)	4 (10)
Klebsiella pneumoniae	1 (2)	0 (0)	1 (2)
Others	4 (7)	2 (15)	2 (5)
Unidentified	20 (36)	1 (8)	19 (45)

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Table 3. Characteristics of Patients with DISH-related PVO.

No.	Age, years	Sex	BMI, kg/m^2	mFI	Level of PVO	Level of DISH	Microbiological identification	CRP at admission, mg/L	IV antibiotic duration, days	Antibiotics	Surgery	Follow-up, years	Survival	Cause of death
1	90	F	29.5	3	L2–3	T5–L2	*Streptococcus mitis*	249	42	ABPC/SBT		0.2	Dead	Sepsis
2	90	M	19.7	2	T12	T3–12 L1–S	MRSA	213	31	VCM		0.1	Dead	Sepsis
3	86	M	26.5	1	L1	T8–L1	Unknown	153	42	PIPC		0.8	Dead	Sepsis
4	84	F	17.8	3	L1	T2–L1	MSSA	109	35	MEPM CEZ		2.1	Dead	Heart failure
5	74	M	25.7	3	L2	T8–L2	MRSA	205	56	VCM		0.9	Dead	Sepsis
6	79	M	23.9	4	L1–2	T5–L1	MSSA	115	63	CEZ	Posterior drainage	0.8	Dead	Sepsis
7	77	M	21.1	1	T11–12	T6–11	MSSA	193	37	CEZ		0.4	Dead	Gastrointestinal hemorrhage
8	83	M	19.2	1	T12–L1	T9–12	*Streptoc. dysgal./canis*	123	68	CTRX		0.8	Dead	Sepsis
9	72	M	19.6	3	T9–10	T7–11	*Citrobacter koseri*	104	42	CEZ		5.3	Alive	
10	80	M	17.2	2	T10	T3–12	*Enterococcus faecalis*	103	39	CEZ		5.7	Alive	
11	74	F	21.4	2	L3–4	T9–L3	*Streptococcus anginosus*	145	56	CEZ		5.0	Alive	
12	53	F	24.5	1	L2–3	T7–L2	*Escherichia coli*	71	122	CEZ	Anterior debridement with fusion	6.7	Alive	
13	70	F	25.8	3	T8–9	T9–12	*Klebsiella oxytoca*	227	50	CEZ	Posterior drainage	5.9	Alive	

BMI, body mass index; mFI, modified frailty index; PVO, pyogenic vertebral osteomyelitis; DISH, diffuse idiopathic skeletal hyperostosis; CRP, C-reactive protein; IV, intravenous; F, female; M, male; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; ABPC/SBT, ampicillin/sulbactam; VCM, vancomycin; PIPC, piperacillin; MEPM, meropenem; CEZ, cefazolin; CTRX, ceftriaxone sodium hydrate

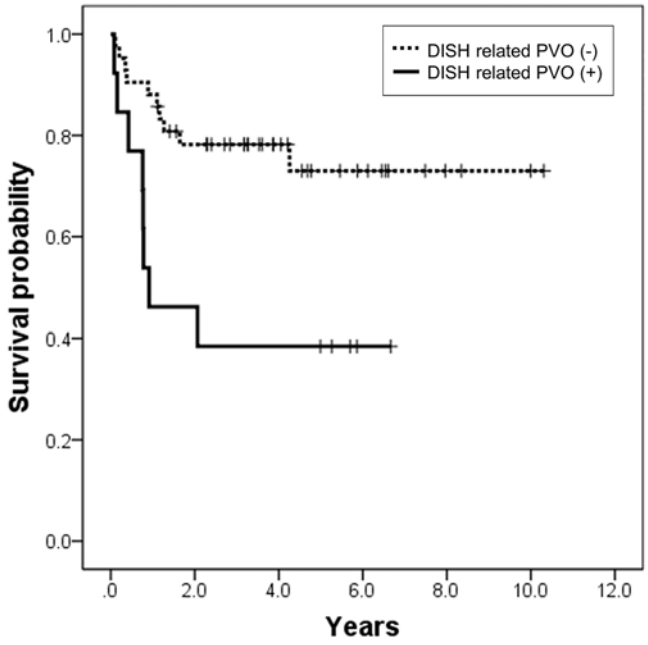

Figure 2. Kaplan-Meier analysis of survival probability in patients with and without DISH-related PVO. Patients with DISH-related PVO had a lower prognosis (log-rank, p=0.006). DISH, diffuse idiopathic skeletal hyperostosis; PVO, pyogenic vertebral osteomyelitis

related PVO is an independent risk factor for mortality. DISH-related PVO is significantly associated with an increased risk of mortality in Model 1 (adjusted HR [aHR], 2.73; 95% CI, 1.02-7.30; p=0.045). In Model 2, DISH-related PVO was also associated with a significantly increased risk of mortality (aHR, 2.79 95% CI, 1.08-7.20; p= 0.034).

Representative case

An 84-year-old woman had been diagnosed with an L1 vertebral fracture caused by a fall (Fig. 3A) 1 month prior to hospitalization for a fever of unknown origin. Ossification by DISH was observed between T2 and L2. PVO at the L1 vertebra with an iliopsoas abscess was diagnosed by CT (Fig. 3B) and MRI (Fig. 3C). Microbiological examination identified methicillin-sensitive *S. aureus* (Fig. 3D). After 9 weeks of antibiotic treatment, the patient's fever and CRP concentration improved. However, she could not walk. She died of heart failure 2 years after initial admission.

Discussion

Despite its limited data, this study proposed that DISH-related PVO may be a notable pathology of PVO that may affect life expectancy. Patients with DISH-related PVO had a shorter life expectancy than those with non-DISH-related PVO. The mortality rate of patients with DISH-related PVO was high (62% at the median 3.3-year follow-up). Furthermore, among the patients with DISH-related PVO who died, the majority (88%) died within 1 year after diagnosis of PVO in spite of standard treatment for PVO.

This study cannot elucidate why mortality in patients with DISH-related PVO was high because the outcome measurement was only about mortality and cause of death, and several reasons have arisen.

First, DISH-induced spinal instability might affect prolonged infection/pain or neurological deficit in DISH-related PVO. Especially in patients with DISH-related fracture, cumulative stress at the fracture site might cause neurological deterioration or lead to the need for surgical intervention[17,20,21]. In cases of DISH-related PVO, spinal destruction due to infection is exposed to cumulative stress in the same manner as the DISH-related fracture. This greater DISH-induced spinal instability can be an inhibiting factor for the healing process of spinal infection. This study indicated that the rate of sepsis to the cause of death was high (75%) in DISH-related PVO, although it is statistically not significant compared with that of non-DISH-related PVO because of a small number. A high rate of sepsis contributed a hypothesis that PVO might not have been completely healed despite standardized antibiotic therapy in some cases of DISH-related PVO.

The first-line treatment of PVO is >6 weeks of antibiotic therapy against the identified microorganisms[22,23]. Stabilization of the affected spinal segment is also important. Immobilization with a short period of bed rest and subsequent mobilization with a rigid orthosis is a generally accepted strategy[22]. Recent studies have reported the positive healing effect of posterior internal fixation using minimum invasive technique even without anterior debridement and bone grafting[24-27]. Therefore, surgical stabilization for DISH-related PVO may also improve the mortality or clinical outcomes, although further investigations are needed.

Comorbidity, which is concomitant with patients with DISH, is another possible explanation of why patients with DISH-related PVO have high mortality. Age and comorbidities are well-known risk factors for mortality in patients with PVO[2,5-10]. DISH has been demonstrated to have associations with advanced age, obesity, hypertension, cardiovascular disease, and diabetes mellitus[12]. In this study, mFI was used as evaluation for comorbidities because vulnerability (frailty) increased by comorbidities negatively influenced clinical outcomes and complication rates in spinal disorders[19]. Recent studies have evaluated the mFI as a tool to measure frailty in the analysis of morbidity and mortality in patients with PVO[9,10]. The mFI was not related to mortality in the multivariate analysis of the present study, in contrast with previous reports[9,10]. Comorbidities might have been underreported in the present study, or the patients might have been affected by comorbidities not yet diagnosed. Additionally, the high mortality rate of patients with DISH-related PVO might be explained by the inability to treat them surgically because of their general physical status despite their surgical indication (PVO-induced segmental instability). In this series, only one patient with DISH-related PVO underwent surgical debridement and stabilization. Further pro-

Table 4. Differences between DISH-related PVO and Non-DISH-related PVO.

	DISH-related PVO n=13	Non-DISH-related PVO n=42	p
Age, years	79 (73–85)	72 (62–78)	**0.019**
Sex, male	8 (62)	22 (52)	0.562
BMI, kg/m^2	21.4 (19.4–25.8)	20.8 (18.4–23.4)	0.373
Diabetes mellitus	5 (38)	11 (26)	0.302
mFI	2 (1–3)	2 (1–3)	0.270
Affected lesion			**0.024**
Thoracic	6 (46)	6 (14)	
Cervical/lumbar/sacral	7 (54)	36 (86)	
Multilevel infection	1 (8)	4 (10)	0.663
Location of center of PVO, intravertebral body	5 (38)	2 (5)	**0.006**
Symptom			
Fever	9 (69)	25 (59)	0.386
Axial pain	13 (100)	40 (95)	0.58
Muscle weakness*	2 (15)	3 (7)	0.337
Laboratory marker			
eGFR, mL/min	59 (45–80)	68 (44–89)	0.494
CRP, mg/L	145 (106–210)	62 (31–166)	**0.011**
WBC, cells/μL	11,900 (10,600–15,400)	10,500 (7,950–13,925)	0.184
Associated infection			
Epidural abscess	2 (15)	14 (33)	0.187
Iliopsoas abscess	4 (31)	15 (36)	0.743
Endocarditis	0 (0)	1 (2)	0.764
Microbiological diagnosis, any	12 (92)	21 (50)	**0.007**
Treatment			
IV antibiotic duration, weeks	6 (5.4–8.5)	6 (4–9.3)	0.53
Surgery	3 (23)	10 (24)	0.603
Follow-up period, years	0.9 (0.6–5.5)	3.4 (1.5–5.6)	0.132
Mortality	8 (62)	10 (23)	**0.016**
Cause of death			0.235
Sepsis	6 (75)	5 (50)	
Heart failure	1 (13)	2 (20)	
Malignant tumor	0 (0)	3 (30)	
Others	1 (13)	0 (0)	

Data are represented as median (interquartile range) or n (%). Significant p values are indicated in bold font.

*Muscle weakness score of ≤3 on manual muscle testing.

DISH, diffuse idiopathic skeletal hyperostosis; PVO, pyogenic vertebral osteomyelitis; BMI, body mass index; mFI, modified frailty index; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; WBC, white blood cells; IV, intravenous

spective studies detailing evaluations regarding complications are needed to clarify the impact of comorbidity or frailty on mortality in patients with DISH-related PVO.

An additional interesting finding in this study is that patients with DISH-related PVO had a significantly higher rate of PVO that developed at the intravertebral body (38%), which indicates that osteomyelitis seemed to occur at the site of vertebral fracture than in patients with non-DISH-related PVO (5%). Most patients with PVO exhibit involvement of the disc space and two adjacent vertebral bodies through destruction of the endplate. McHenry et al.[28] first reported six cases of PVO with infection of a single vertebra that presented with a collapsed vertebral body as atypical PVO. They also reported that such cases of atypical vertebral osteomyelitis had an incidence of 11% among 253 patients with vertebral osteomyelitis[5]. In more recent studies, Ribera et al. reported that vertebral fractures in PVO were observed in a higher frequency of 35% than what was previously reported[29]. They also reported that patients with vertebral fracture showed slower clinical improvement than those without in PVO. Uto et al.[30] reported that PVO following osteoporotic vertebral fracture was rare (4 of 554 patients, 0.7%) but led to serious events: all patients died of sepsis. There was no description of DISH in those previous reports of PVO at the fracture site. This study proposed the possibility of an association of DISH with PVO following osteoporotic vertebral fracture.

The small sample size and lack of evaluation of outcomes other than mortality were notable limitations of this study. Therefore, we assessed several models in the multivariate analysis of mortality, including propensity score-adjusted analysis. However, these might not be considered statisti-

Table 5. Mortality Risk Analysis including DISH-related PVO.

	Crude model			Model 1 *			Model 2 **		
	HR	p	95% CI	aHR	p	95% CI	aHR	p	95% CI
Age, per 1 year	1.115	**0.002**	1.041–1.194	1.106	**0.004**	1.033–1.184			
Sex, male	0.677	0.412	0.267–1.717	0.831	0.716	0.307–2.253			
DISH-related PVO	3.405	**0.01**	1.336–8.677	2.732	**0.045**	1.023–7.297	2.789	**0.034**	1.081–7.197
mFI, per 1 point	1.008	0.96	0.731–1.391	0.841	0.427	0.549–1.289			
CRP, per 1 mg/L	1.004	0.109	0.999–1.009						
Muscle weakness†	0.569	0.584	0.076–4.280						
Multilevel infection	0.483	0.48	0.064–3.637						
Propensity score, per 0.1							1.463	**<0.001**	1.081–7.197

Significant p values are indicated in bold font.

* Cox proportional hazards model was adjusted for age, sex, DISH-related PVO, and mFI

** Propensity score-adjusted Cox proportional hazards model: Propensity score was estimated from age, sex, mFI, CRP concentration, muscle weakness, and multilevel infection.

† Muscle weakness score of ≤3 on manual muscle testing.

DISH, diffuse idiopathic skeletal hyperostosis; PVO, pyogenic vertebral osteomyelitis; HR, hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio; mFI, modified frailty index; CRP, C-reactive protein

cally adequate models because (1) statistical power was not sufficient due to the small sample size, and (2) we could not include sufficient potential confounders such as PVO at the fracture site in the analysis, despite several factors showing significant differences between patients with and without DISH-related PVO. Therefore, further large and prospective studies that include outcomes for quality of life, pain, or neurological status are needed to clarify the impact of DISH on PVO. Despite these limitations, a strong point of this study is the high follow-up rate (98%) in terms of mortality by direct telephone survey; only one patient was lost to follow-up. Additionally, the distribution of PVO (location, positive rate of microbiological diagnosis, and identified organism) in this study was almost the same as that in large-sample reports[1-3]. The only exception was the age distribution; patients were older in this study because of the characteristics of the hospital. Therefore, the findings of this study are valid for discussion.

In conclusions, we found a higher mortality rate in DISH-related PVO (62%) than in non-DISH-related PVO during a median 3.3-year follow-up. The mortality of patients with DISH-related PVO increased within 2 years after the onset of PVO. These results may influence the treatment strategy for DISH-related PVO. Similar to advanced age, PVO at the segment ossified by DISH should be recognized as a risk factor for mortality when choosing the optimal treatment strategy.

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Ethical Approval: This study was approved by the Institutional Review Board of Fuchu Hospital (Approval number: 2020011, Approval date: December 28, 2020).

Informed Consent: Informed consent was obtained in the form of opt-out on the Fuchu Hospital website.

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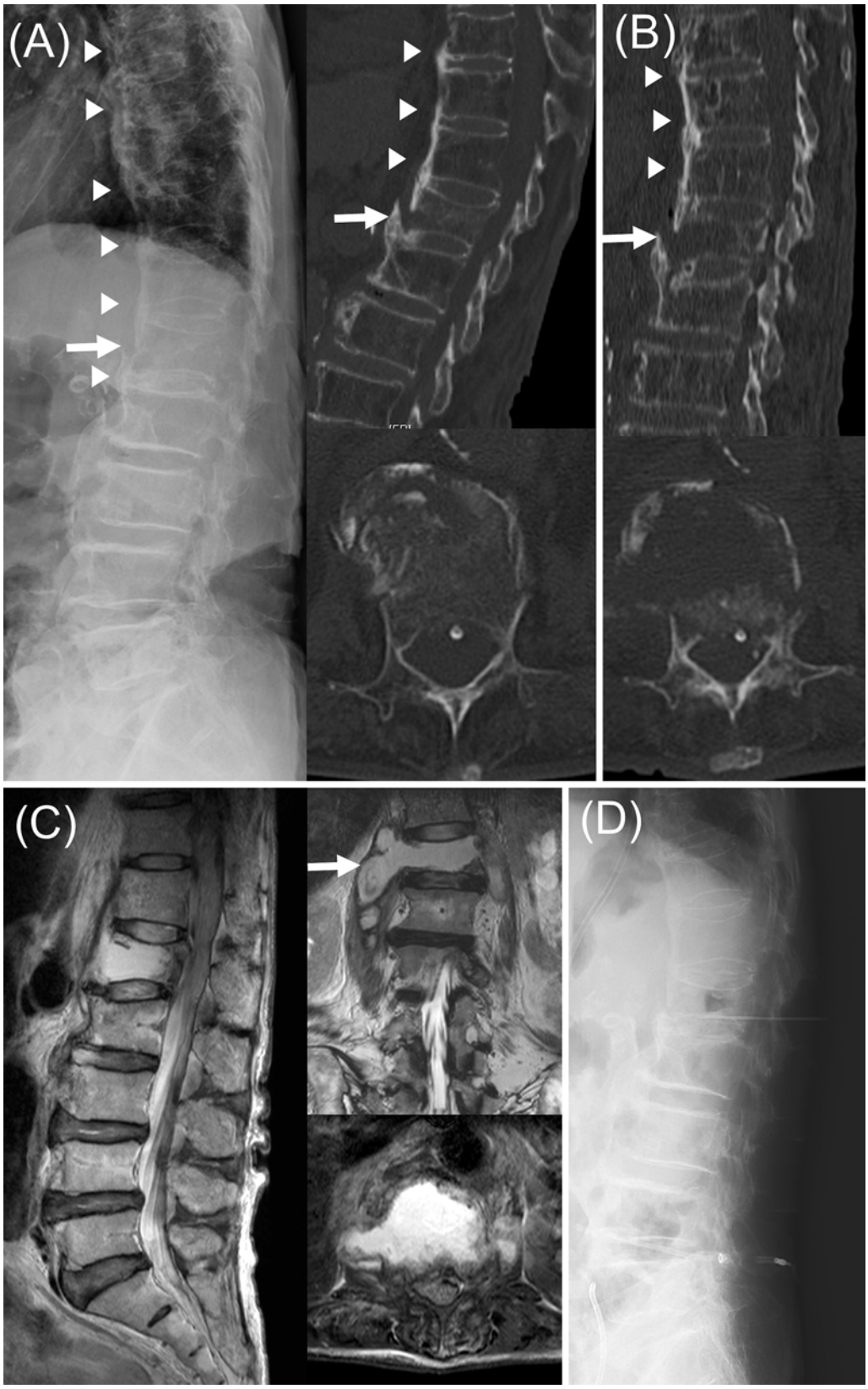

Figure 3. Representative case of an 84-year-old woman. (A) Plain radiograph (left) and CT (right) showed an osteoporotic vertebral fracture (arrow) at L1 caused by a fall. Ossification by DISH was observed between T2 and L2 (triangle). (B) CT at admission for a fever of 39°C with an elevated CRP concentration of 260 mg/L. Osteolytic change was observed at the fracture site of L1 (arrow). (C) MRI at admission. The fracture site of L1 had severe fluid collection. A psoas abscess was observed on the right side (arrow). (D) Needle biopsy and drainage were performed.
CT, computed tomography; DISH, diffuse idiopathic skeletal hyperostosis; CRP, C-reactive protein; MRI, magnetic resonance imaging

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