Identification of Risk Factors for Mortality and Prolonged Hospitalization in Patients Treated With Surgical Drainage for Otogenic Intracranial Complications: A Nationwide Study Using a Japanese Inpatient Database

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Objective: Data on risk factors for otogenic intracranial complications including cerebral abscess have been limited. Using a nationwide database, the aim was to identify the factors related to mortality and delayed discharge.
Study Design: Retrospective.
Setting: Nationwide database using the Diagnostic Procedure Combination database.
Main Outcome Measures: Data of 145 patients were extracted from a Japanese inpatient database between 2012 and 2020. The main outcome was survival at discharge. In a subgroup analysis of the 137 surviving patients, the second outcome was delayed discharge.
Results: The mortality rate was 5.5% (8 of 145). Logistic regression analyses identified intracerebral complications (adjusted odds ratio [OR], 3.09) and more than 2-day delay of the first surgery after admission (adjusted OR, 4.68) as risk factors for mortality. Specifically, consciousness level evaluated by the Japan Coma Scale (JCS) was significantly related to prolonged hospitalization or mortality: JCS I (adjusted OR, 3.40) and JCS ≥II (adjusted OR, 25.1).
Conclusions: Although otogenic intracranial complications are rare, and their mortality is decreasing because of the progress in imaging and clinical strategies, they remain the most severe complications of suppurative otitis media and/or cholesteatoma. Consciousness level at admission, comorbid diabetes mellitus, and a greater than 2-day delay of surgical intervention were related to prolonged hospitalization or mortality.
Key Words: Cholesteatoma—DPC database—Intracranial complications—Japan Coma Scale (JCS)—Logistic regression analysis—Mortality—Odds ratio—Otitis media.

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INTRODUCTION

Chronic suppurative otitis media (COM) with or without cholesteatoma implies an active and potentially progressive process (1–3). The complications of COM are classified as intracranial and extracranial or meningeal and nonmeningeal (4,5). Of them, an intracranial otologic abscess is generally regarded as a destructive process with high morbidity and mortality if not diagnosed at an early stage and treated appropriately. Despite improvements in diagnostic methods, surgical technique, and intensive care protocols, otogenic intracranial complications (OICs) have been reported to be life-threatening, with mortality rates ranging from 8 to 25% (3,4,6–9). Although the etiology and clinical outcomes of treating them have been extensively reported, almost all of them are case series from a single institution, having several limitations attributed to their relatively small sample size from a single medical center. Moreover, their infrequency has been one reason for the difficulties in prospective investigations of these patients. Duarte et al. (3) recently conducted a systematic review of otogenic brain abscess and reported that appropriate imaging studies and multidisciplinary expertise are crucial in diagnosis and management. However, no precise clinical factors related to mortality

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Contributions: H.H. designed and supervised the study. K.T., F.K., and K.F. acquired all clinical data. All authors performed data analysis and interpretation. O.T. and S.A. assisted in the statistical analyses. H.H. and H.I. wrote the manuscript. All authors read and approved the final manuscript.

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and therapeutic schema have been proposed, and optimal surgical strategies, including delay in surgery until the patients stabilize, are controversial (2,6,7,10,11).

The present report describes a study that used a nationwide inpatient database in Japan to investigate the factors associated with mortality and prolonged hospitalization in patients who underwent surgical drainage for OICs.

MATERIALS AND METHODS

Data Source

Data were extracted from the Diagnostic Procedure Combination (DPC) database, a national inpatient database in Japan. The details of the DPC database have been described previously (12–14). Briefly, the DPC database includes administrative claims data and detailed medical data collected for all inpatients discharged from participating hospitals. More than 80% of acute inpatient care in Japan is included in the DPC system (12,13,15–17). The dates of hospital admission, surgery, discharge, bedside procedures, and drugs administered are recorded using a uniform data submission format (13).

All patient identifiers were removed from this database. Because of the anonymous nature of the data, the need for informed consent was waived. Study approval was obtained from the Institutional Review Board of the Tokyo Medical and Dental University (protocol number: M2000-788-15) and Kansai Medical University (protocol number: 2019316).

Patient Selection and Characteristics

From the 63.7 million inpatients in the DPC database over a total of 8 years (between April 2012 and March 2020), patients satisfying the following inclusion criteria according to surgical interventions encoded with original Japanese codes were selected: 1 exploratory craniotomy (Japanese code: K148) or drainage of brain abscess (Japanese code: K150) or surgery for OICs (Japanese code: K152) including otogenic epidural abscess (Japanese code: K152–2).

The following background characteristics of the patients were assessed: age; sex; main diagnosis; comorbidities at admission including level of consciousness evaluated by the Japan Coma Scale (JCS), diabetes mellitus (DM; *International Classification of Diseases, 10th Revision* [*ICD-10*] codes: E10–E14), and sepsis (*ICD-10* codes: A40–A41, D65) classified according to the *ICD-10* and test data in Japan (12–17); number of surgical interventions; length of stay; and discharge status.

The JCS is one of the most widely used grading scales for assessing impaired consciousness, consisting of four main categories: 0, alert consciousness; 1–3 (single digit), awake without any stimuli; 10–30 (double digits), arousable by some stimuli but reverts to previous state if stimulus stops; and 100–300 (triple digits), unarousable by any stimuli (18–20).

Outcome Measurement

The primary outcome was survival at discharge and length of hospitalization. The patients who were alive at discharge were divided into two groups according to the median interval between admission and discharge. The patients were then categorized into three groups: in-hospital death, longer hospitalization, and shorter hospitalization.

Statistical Analysis

Differences in frequencies between the groups were evaluated using the Fisher exact test. Multiple logistic regression analysis was performed to compare multiple outcome categories, assessing the independent effect on the severity of intracranial complications. Inclusion of independent variables in the model was based on earlier research and existing knowledge in terms of the following risk factors for aggravation of intracranial complication and abscesses in the head and neck region (2–5,11,14,21): age, sex, pathogenesis (cholesteatoma or other otitis media), type of complication (subdural abscess including cerebral abscess or other intracranial complications such as epidural abscess or meningitis), level of consciousness evaluated by the JCS, comorbid DM and sepsis, and repeated surgical interventions.

A p value <0.05 was considered significant. All statistical analyses were conducted using EZR software (22).

RESULTS

Demographic Data

During the study period, a total of 47,206 cases fulfilled the inclusion criteria according to the surgical screening, as shown in Figure 1. Of these cases, 46,954 were excluded because of no clarifying *ICD-10* codes including middle ear and/or otitis media. Of the remaining 252 patients, 107 were excluded because their operations were attributed to reasons other than otogenic complications, as follows: brain hemorrhage and/or hydrocephalus in 46 cases, tumor or congenital anomaly in 34 cases, brain contusion in 4 cases, and inflammation of other than otogenic origin in 23 cases. Of the resulting 145 patients who were selected for qualitative analyses, 57 had *ICD* codes corresponding to cholesteatoma.

Of the total 145 patients, the 137 patients who were alive at discharge were divided into two groups according to the median interval (45 d) between admission and discharge. Namely, group A and group B included cases with intervals less than <45 and ≥45 days, respectively. Another eight patients who died in hospital were assigned to group C. Table 1 summarizes the baseline characteristics of each group of patients. The median ages of groups A, B, and C were 60, 62, and 75 years, respectively. Group C showed a higher interquartile range for age (19–96 yr) than the other groups ($p < 0.05$, Kruskal-Wallis test). Conversely, the male to female ratios of the three groups were not significantly different. Regarding otological pathogenesis, the prevalences of cholesteatoma in groups A, B, and C were 50.7, 29.4, and 25%, respectively. Group A showed a significantly higher prevalence of cholesteatoma than the other two groups ($p < 0.05$).

Regarding intracranial complications, the patients were classified into two groups: 1) subdural and/or intracerebral abscess, and 2) other complications without these two *ICD-10* codes, mainly representing epidural abscess. The prevalences of subdural complications of groups A, B, and C were 37.7, 72.1, and 62.5%, respectively. Group A

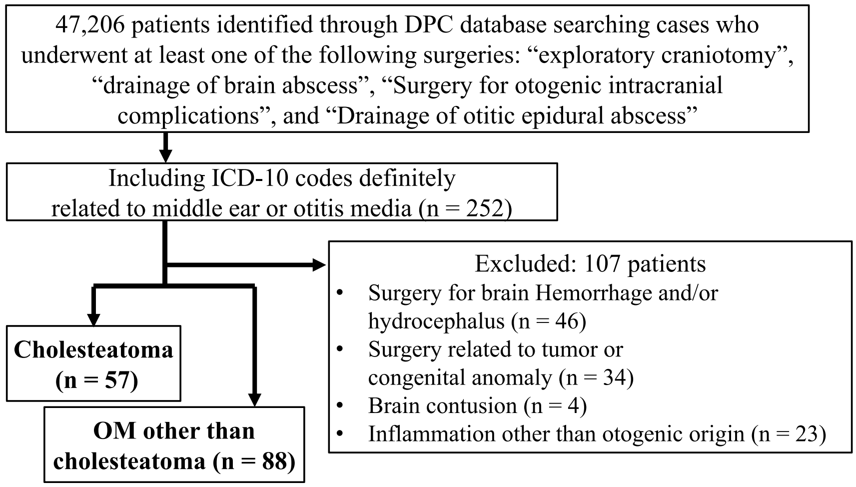

FIG. 1. Schematic illustration of patient selection. DPC indicates Diagnostic Procedure Combination; OM, otitis media.

TABLE 1. *Baseline characteristics of patients categorized by survival at discharge and prolonged hospitalization with otogenic intracranial complications*

	Group			
	A (No. = 69)	B (No. =68)	C (No. = 8)	*p*
Age, yr				0.048[a]
Median	60	62	75	
Range	1–85	0–86	52–95	
Interquartile range	44–69	44–71	62–81.3	
Sex				0.23[b]
Male	48 (69.6%)	46 (67.6%)	4 (50%)	
Female	21 (30.4%)	22 (32.4%)	4 (50%)	
Pathogenesis				0.026[b]
Cholesteatoma	35 (50.7%)	20 (29.4%)	2 (25%)	
Otitis media other than cholesteatoma	34 (49.3%)	48 (70.6%)	6 (75%)	
Intracerebral complications				<0.001[b]
No	43 (62.3%)	19 (27.9%)	3 (37.5%)	
Yes	26 (37.7%)	49 (72.1%)	5 (62.5%)	
Consciousness level (JCS)				<0.001[b]
0	55 (79.7%)	27 (39.7%)	0	
I	13 (18.8%)	21 (30.9%)	3 (37.5%)	
II	1 (1.4%)	12 (17.6%)	0	
III	0	8 (11.8%)	1 (12.5%)	
Unknown	0	0	4 (50%)	
Diabetes mellitus				0.001[b]
No	64 (92.8%)	48 (70.6%)	5 (62.5%)	
Yes	5 (7.2%)	20 (29.4%)	3 (37.5%)	
Sepsis				<0.001[b]
No	68 (98.6%)	57 (83.8%)	5 (62.5%)	
Yes	1 (1.4%)	11 (16.2%)	3 (37.5%)	
Surgical intervention/more than once				0.08[b]
No	65 (94.2%)	56 (82.4%)	7 (87.5%)	
Yes	4 (5.8%)	12 (17.6%)	1 (12.5%)	
Delay of first surgery after admission				0.07[b]
≤2	40 (58.0%)	26 (38.2%)	4 (50.0%)	
>2	29 (42.0%)	42 (17.6%)	4 (50.0%)	
Steroid administration				0.138[b]
No	31 (44.9%)	20 (29.4%)	2 (25.0%)	
Yes	38 (55.1%)	48 (70.6%)	6 (75.0%)	

Patients were categorized into three groups according to outcomes related to survival at discharge and prolonged hospitalization, as follows: A) alive at discharge 44 days after admission, B) alive at discharge for more than or equal to 45 days after admission, and C) died in hospital.

[a] Kruskal-Wallis test.

[b] Fisher exact test, conducted for other than unknown cases for each characteristic.

JCS indicates Japan Coma Scale; No., number of patients.

showed a significantly lower prevalence of subdural and/or intracerebral abscesses ($p < 0.001$).

Impaired consciousness evaluated by the JCS score showed significant differences among the groups. Specifically, the prevalence of a score > I was only 1.4% (1 of 69) in group A compared with 29% (20 of 68) in group B. None of group C showed a JCS score of zero.

Concerning disease comorbidity, the prevalence of DM was higher in group C (37.5%) than in group A (7.2%) and group B (29.4%) ($p < 0.01$). In addition, comorbid sepsis was significantly higher in group C (37.5%) than in group A (1.4%) and group B (16.2%) ($p < 0.001$).

Regarding surgical interventions, the prevalence of repeated surgical interventions (more than one surgical drainage) was not significantly different. Both the prevalence of delayed surgery (>2 d after admission) and receiving steroid therapy showed no significant differences among the three groups.

Risk Factors Contributing to Prolonged Hospitalization or Mortality

As shown in Table 1, group C consisted of only eight cases, representing a few cells of independent variables with low counts including zero. Moreover, regarding the JCS score, none of the group A and C patients showed level III and level II, respectively (Table 1). To avoid separation and convergence failure in logistic regression, groups B and C, comprising cases with prolonged hospitalization or mortality, were combined. Therefore, patients in group B (longer hospitalization) and group C (in-hospital death) were defined as the "prolonged hospitalization or mortality" group, resulting in categorizing the outcomes into two groups. The cases with JCS scores of II and III were also combined, comprising the group with JCS score ≥ II.

Logistic regression analysis showed that the following factors were significant with respect to prolonged hospitalization or mortality: pathogenesis, intracranial complications comprising cerebral and/or subdural abscess, JCS score, DM, sepsis, repeated surgery, more than 2-day interval between admission and the first surgery, and steroid therapy with the crude odds ratios (ORs) as shown in Table 2. Of these factors, the following were significant with ORs adjusted by the other variables (adjusted ORs): intracranial complications comprising cerebral and/or subdural abscess, OR of 3.09 (95% confidence interval [CI], 1.20–7.97); JCS score I, OR of 3.4 (95% CI, 1.1–10.5); JCS score ≥II, OR of 25.1 (95% CI, 2.49–253); DM, OR of 3.85 (95% CI, 1.12–13.2); and more than 2-day interval between admission and the first surgery, OR of 4.68 (95% CI, 1.64–13.3)

DISCUSSION

OICs continue to present late and are associated with significant mortality and morbidity, despite advances in diagnostic and treatment modalities (1,4,11,23,24). In this study, a total of 145 patients throughout Japan who underwent drainage surgery for OICs were investigated using a Japanese nationwide inpatient database. Because the database was screened according to intracranial surgery, almost all of them would be classified as intracranial abscesses. To the best of our knowledge, this is the first study to investigate the factors affecting prolonged hospitalization or mortality in patients with OICs including intracranial abscesses in a nationwide clinical setting. In the present study, the mortality rate was 5.5% (8 of 145), showing similar rates to the recent systematic review after the advent of CT (3).

Several previous case series reported that otogenic brain abscesses were more common in adults than in children (3,5,11,23). Consistent with these studies, the present study showed that OICs were less common in children younger than 18 years, with a prevalence of 9% (13 of 145) and a male predominance of 68% (98 of 145). These results were also consistent with previous reports showing that most patients with otogenic intracranial abscesses were middle-aged men, and children were a clear minority (5,11). Although higher age tended to increase the morbidity and mortality of OICs, the present study failed to identify age as an independent risk factor in the age group of ≥75 years. These results contrast with those of our previous nationwide study addressing deep neck infection (11), where advanced age (≥75 yr) was significantly associated with mortality (adjusted OR, 5.57; 95% CI, 2.8–11.1). These differences might be attributed to a lower prevalence of cases with such advanced age in OICs than those with deep neck infection. Conversely, sex did not contribute to morbidity and mortality, similar to the results for deep neck infection (14).

COM with cholesteatoma has been reported to be the most common pathogenesis of OICs followed by COM without cholesteatoma (5,8,9). Specifically, the latter is characterized by constant purulent otorrhea and is associated with the presence of granulation tissue (2,4). According to a recent systematic review, eight studies explicitly mentioned that the prevalence of cholesteatoma ranged from 21 to 100% as the pathogenesis of otogenic intracranial abscess (3). In the present study, 32% (47 of 145) of cases presented as cholesteatoma. Regarding the 98 other cases, most cases were presumed to be attributed to suppurative COM. However, the detailed pathogenesis could not be defined because of the absence of many records with only otitis media without specifying acute otitis media or COM. Although otitis media other than cholesteatoma showed higher prevalences of prolonged hospitalization and mortality, pathogenesis was not found to be a significant factor. One background hypothesis is that the severity of suppurative COM would not be inferior to that of cholesteatoma. In addition, less accurate data may also contribute only to identify otitis media with failure to specify which type of otitis media, such as acute otitis media or COM.

Regarding the types of OICs, the prevalence of subdural or intracerebral abscess was less than 40% in the group with shorter hospitalization. These complications were the most severe types of OICs, and it is plausible that patients with subdural and/or intracranial abscesses showed severe morbidity and mortality. This factor was shown to be a significant risk factor, with an adjusted OR of 3.09 (95% CI, 1.20–7.97).

Of patients with intracerebral abscesses, some have symptoms of increased intracranial pressure or focal neurological signs at the time of presentation, whereas in others, the onset of intracranial abscess is relatively asymptomatic and detected only during routine imaging studies (2).

TABLE 2. *Multiple logistic regression analysis of risk factors for prolonged hospitalization or mortality in patients who underwent surgical intervention for otogenic intracranial complications*

	Crude OR (95% CI)	Adjusted OR (95% CI)
Age, yr		
<50	1.00	1.00
50≤, <75	1.37 (0.65–2,89)	1.24 (0.46–3.35)
≥75	1.84 (0.71–4.78)	1.36 (0.36–5.12)
Sex: female (versus male)	1.19 (0.59–2.39)	1.53 (0.59–3.98)
Pathogenesis		
Cholesteatoma	1.00	1.00
Otitis media other than cholesteatoma	2.53 (1.27–5.01)	1.52 (0.59–3.89)
Intracerebral complications		
No	1.00	1.00
Yes	4.06 (2.03–8.13)	3.09 (1.20–7.97)
Consciousness level (JCS)		
0	1.00	1.00
I	3.76 (1.66–8.51)	3.40 (1.10–10.50)
≥II	42.80 (5.46–335.0)	25.10 (2.49–253.0)
Diabetes mellitus	5.55 (1.98–15.60)	3.85 (1.12–13.20)
Sepsis	13.10 (5.52–10.6)	8.16 (0.76–87.80)
Surgical intervention/more than once	3.35 (1.04–10.80)	1.55 (0.34–7.17)
Delay of first surgery after admission		
≤2	1.00	1.00
>2	2.21 (1.09–4.11)	4.68 (1.64–13.30)
Steroid administration	2.00 (1.01–3.98)	1.91 (0.75–4.81)

CI indicates confidence interval; JCS = Japan Coma Scale; OR = odds ratio.

Although depressed consciousness level has been reported to be the most common presenting symptom of intracranial abscess (2,5,7), previous studies have yet to evaluate whether the prognosis of OICs correlates with consciousness level. The DPC database has an advantage in including the JCS score at admission, which has been widely used to assess patients' consciousness levels in Japan (18–20). In the present study, this advantage was used to show that consciousness level was a significant factor related to prolonged hospitalization or mortality, as compared with patients with JCS score 0 (alert). JCS score I (alert or awake without stimuli) was a significant factor, with an adjusted OR of 3.40 (95% CI, 1.10–10.50). Specifically, JCS score II (arousable by some stimuli but reverts to previous state if stimulus stops) or III (unarousable by any forceful stimuli) was also a significant factor, with an adjusted OR of 25.10 (95% CI, 2.49–253.0). In addition to identifying consciousness level as a significant factor, mortality was correlated with increases of the JCS score.

The presence of systemic disease is an important predisposing factor for the severity of severe infections, including those in the head and neck region (14). Of them, comorbid DM is a well-known risk factor (14,25,26). The present study showed that DM was correlated with prolonged hospitalization or mortality, with an adjusted OR of 3.85 (95% CI, 1.12–13.2). These results are similar to our nationwide study focusing on deep neck infections using the DPC database, showing that DM was correlated with mortality, with an adjusted OR of 2.47 (95% CI, 1.69–3.62) (14).

Of the systemic diseases contributing to mortality, sepsis is also a well-known complication, as in the severe infections in the head and neck region (2,14,25). Although the present study showed a higher prevalence of sepsis (37.5%) in patients with in-hospital death, logistic regression analysis failed to identify it as a significant risk factor for prolonged hospitalization or mortality in OICs. One hypothesis for these inconsistencies is that fewer cases across the three groups had sepsis (10.3%) than had DM (19.3%), as shown in Table 1.

Management of otogenic intracranial abscess is controversial (3,11). Regarding surgical interventions, some surgeons advocate early craniotomy and excision of the abscess (27), whereas other reports prefer a combined approach with abscess drainage first, followed by mastoidectomy in the same setting (10,28). However, these simultaneous ear operations would lead to longer procedures that critically ill patients would not always be able to tolerate (5). Others have advocated a radical mastoidectomy approach with evacuation of the abscess through the mastoid cavity (9). Conversely, Murthy and colleagues (28) stated that first neurosurgical drainage and later ear surgery should be done. In the present study using the DPC database, only 11.7% (17 of 145) underwent more than one surgery. Repeated surgery was not identified as a risk factor for mortality or morbidity. According to these results, we should not hesitate to perform multiple surgical interventions in cases with inadequate initial drainage. One of the hypotheses contributing to the small prevalence of repeated surgery is that some patients are discharged after intracranial drainage, and tympanomastoidectomy is conducted later in another admission. Therefore, we have yet to conclude whether ear surgery should be conducted simultaneously with or after neurosurgical drainage. Vashishth and colleagues (29) suggested that final outcomes should not differ as long as surgical management of both the intracranial component and the cholesteatoma is carried out urgently and within a reasonable time frame of each other.

Debate also continues regarding the timing of surgery for ICA (2). Some authors recommend emergent drainage including mastoidectomy within 24 hours (6,10), and others favor a more delayed surgical intervention, citing the high effectiveness of medical therapy (2,7). Seven et al. (2) reported that the time of surgical decision making in intracranial abscess was based on the extent of disease, the patient's clinical condition, and the response to medical therapy including intravenous antibiotic therapy within the first 48 hours. The present study showed that more than a 2-day delay to undergoing the first surgery after admission was a risk factor for prolonged hospitalization or mortality, with an adjusted OR of 4.68 (95% CI, 1.64–13.30), in accordance with the aforementioned strategy (2) for intracranial abscess.

Finally, other than intravenous broad-spectrum antibiotics, intravenous steroids have also been started initially in patients to reduce swelling, edema, and inflammation (11). Although steroid administration was not identified as a significant factor for prolonged hospitalization or mortality, more than 70% of patients underwent steroid therapy in the groups with longer hospitalization and in-hospital death. Conversely, this prevalence was reduced to 55.1% in the group with shorter hospitalization. These results correspond to the situations where more severe patients would undergo steroid administration.

Several limitations of this study need to be acknowledged. First, this was a retrospective, cohort study using a national Japanese database, and generalization of the results outside Japan, specifically to a country where CT has yet to become available, may not be appropriate. Second, our screening method involved restricting the cases to those who underwent intracranial surgical intervention first, and then narrowing them down to the otogenic cases. This strategy remains a weakness because OIC patients without surgical interventions, such as those with meningitis or lateral sinus thrombosis, were not included, because many of these patients would not undergo neurosurgical interventions (11). Third, comorbidities are less accurately recorded in administrative claims databases than in planned prospective studies. Fourth, the absence of records of vital signs, blood tests, radiological findings, and bacteriological cultures in the DPC database precluded a more rigorous definition of DM and sepsis (13,14). Moreover, DPC data come from an inpatient database, and it is difficult to evaluate the prognosis of delay from onset to intervention and neurological sequelae at discharge.

Within these limitations, the current study using a nationwide database has several advantages for the management of OICs. Subdural and/or intracerebral abscess, consciousness level at admission, DM, and a greater than 2-day delay in surgical interventions were found to be risk factors for mortality.

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