

1 **Risk factors for postoperative meningitis after**
2 **microsurgery for vestibular schwannoma**

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9 **Abstract**

10 **OBJECTIVE:** Meningitis after microsurgery for vestibular schwannoma (VS) is a
11 severe complication and result in high morbidity. But few studies have focused on
12 meningitis after VS surgery alone. The purpose of this study was to identify the risk
13 factors for meningitis after VS surgery.

14 **METHODS:** We undertook a retrospective analysis of all VS patients, who underwent
15 microsurgery of VS and at least live for 7 days after surgery, between 1st June 2015
16 and 30st November 2018 at West China Hospital of Sichuan University. Univariate and
17 multivariate analyses were performed to identify the risk factors for postoperative
18 meningitis (POM).

19 **RESULTS:** We collected 410 patients, 27 of whom had POM. Through univariate
20 analysis, hydrocephalus ($p=0.018$), Koos grade IV ($p=0.04$), The operative duration
21 (> 3 hours $p=0.03$) and intraoperative bleeding volume ($\geq 400\text{ml}$ $p=0.02$) were
22 significantly correlated to POM. Multivariate analysis showed that Koos grade IV
23 ($p=0.04$; OR=3.19; 95% CI 1.032-3.190), operation duration (> 3 hours $p=0.03$ OR=
24 7.927; 95% CI 1.043-60.265), and intraoperative bleeding volume ($\geq 400\text{ml}$ $p=0.02$;
25 OR=2.551; 95% CI 1.112-5.850) are the independent influencing factors of POM.

26 **CONCLUSIONS:** Koos grade IV, the duration of operation, and the amount of
27 bleeding were identified as independent risk factors for POM after microsurgery of VS.
28 POM caused a prolonged hospital stay.

29 **Introduction**

30 Vestibular schwannomas (VS), also referred to as acoustic neuromas (AN), are
31 Histopathologically benign tumors arising from Schwann cells surrounding the
32 vestibular nerve[1], The incidence of VS is estimated to 1.9 per 100,000 per year[2],
33 Microsurgical resection is typically the gold standard for symptomatic, relatively young
34 patients[3], With the rapid development of minimally invasive neurosurgical
35 technology and electrophysiological monitoring, the surgical mortality has significantly
36 decreased[4]. However, the frequency of postoperative complications is still high.
37 Meningitis is the main fatal complication after craniocerebral surgery. Besides, the data
38 shows the incidence of postoperative meningitis (POM) of vestibular schwannoma
39 surgery is about 5.5%-9.85% [4-8]. In the event of POM, the mortality can be as high
40 as 50%[9]. However, the related research on the clinical risk factors of meningitis after
41 acoustic neuroma surgery is limited.

42 Therefore, we retrospectively analyze the risk factors for meningitis following
43 microsurgery for VS, and the frequency of this complication. The results may be able
44 to identify the factors that significantly affect POM and provide evidence for the
45 prevention and early clinical treatment of POM.

46 **Materials and methods**

47 **Patients**

48 This study retrospectively collected 410 patients at the Department of Neurosurgery in
49 West China Hospital of Sichuan University, who underwent microsurgery of VS and
50 survived at least 7 days after surgery, between 1st June 2015 and 30st November 2018.
51 We did this study from January to February 2019. The diagnosis was based on MRI and
52 pathology. MRI showed a mass rising from the vestibular nerve, and pathology showed
53 schwannoma. This study was approved by the West China Hospital Ethics Committee.
54 Written informed consent was exempted for the present study was a retrospective
55 clinical study.

56 **Data collection**

57 The basic information of these patients were collected, which include age, sex, BMI,
58 signs and symptoms, presence/absence of diabetes mellitus, preoperative white blood
59 cell count and hemoglobin concentration, presence/absence of hydrocephalus (assessed
60 by magnetic resonance imaging), side and size of the tumor, history of treatment of
61 microsurgery and/or stereotactic radiosurgery for VS, length of preoperative and
62 postoperative hospitalization, surgery duration, bleeding amount of the operation,
63 invasive operation, subcutaneous drainage and Lumbar drainage, Cerebrospinal fluid
64 test data about the patients who underwent cerebrospinal fluid drainage.

65 **Koos grade of VS**

66 Koos grade was utilized for the classification of VS, According to the magnetic
67 resonance imaging of the patients and the tumor size. VS was categorized into grade I,

68 II, III and VI.

69 **Surgical technique**

70 The surgical procedures were all performed by the senior neurosurgeon (YueKang Z).

71 Retrosigmoid approach was used for all patients. postauricular carbuncle was incised;

72 the internal auditory canal was resected; the tumor was totally or subtotally removed

73 by microscope; when electrophysiological monitoring was performed during the

74 operation, the trigeminal nerve, the facial nerve, the posterior cranial nerve and the brain

75 stem function should be perfectly protected. During the operation, prophylactic

76 antibiotics and glucocorticoids ought to be delivered to the patients and glucocorticoids

77 should be given continuously until the third day after the operation.

78 **Definition of meningitis**

79 Meningitis must meet at least 1 of the following criteria: 1. Patient has organisms

80 cultured from cerebrospinal fluid (CSF). 2. Patient has at least 1 of the following signs

81 or symptoms with no other recognized cause: fever ($> 38^{\circ}\text{C}$), headache, stiff neck,

82 meningeal signs, cranial nerve signs, or irritability and at least 1 of the following: a.

83 increased white cells, elevated protein, and/ or decreased glucose in CSF b. organisms

84 seen on Gram's stain of CSF c. organisms cultured from blood d. positive antigen test

85 of CSF, blood, or urine e. diagnostic single antibody titer (IgM) or 4-fold increase in

86 paired sera (IgG) for pathogen[10]. These data were obtained from cerebrospinal fluid

87 samples collected by lumbar puncture or lumbar cistern drainage.

88 **Statistical analysis**

89 All the data were analyzed by using SPSS software version 25.0 (IBM Corp., Armonk,
90 New York, USA). Continuous variables are described by median (range) and classified
91 variables by percentages. Chi-squared test and Fisher's exact probability test is
92 employed to complete the univariate analysis of meningitis and non-meningitis. The
93 factors ($P <0.05$) will be entered into a multivariate logistic regression analysis to
94 determine adjusted ORs. The relationship between POM and Postoperative hospital
95 stays will be analyzed through the Wilcoxon-Mann-Whitney test. During this analyzing
96 process, all statistical tests were 2-sided, if $P <0.05$, the data will be considered to have
97 remarkable statistics meaning.

98 **Results**

99 **Baseline characteristics**

100 In this study, 413 patients were enrolled, but three patients who died on the
101 postoperative day were excluded. Some basic patient information was listed in table 1.
102 The mean ages of the patients, including 172 men and 238 women, were 50 years old
103 (range, 15-79 years). Their average BMI index was 23 Kg/m^2 (range, $16-38.6 \text{ Kg/m}^2$).
104 According to Koos, 8% of vestibular schwannomas are classified as the second level
105 (II); 33.4% of them are classified as the third level (III); and 58.5% of them are
106 classified as the fourth level (IV). The results show that 27 patients (6.6 %) have POM

107 but no one died from the related meningitis.

108 **Table 1.** Patient characteristics and details of VS (vestibular schwannoma).

Variables	n (%) or median (range)
Age	50 (15–79)
Sex	
Male	172(42%)
Female	238(58%)
BMI	23(16–38.6)
Side of VS	
Left	198 (48.3%)
Right	212 (51.7%)
Koos grade of VS	
I	0(0%)
II	33 (8.0%)
III	137 (33.4%)
IV	240(58.5%)

109 **Risk factors for POM**

110 Through univariate analysis(Table 2), POM and hydrocephalus ($p=0.018$), Koos grade
111 IV ($p=0.04$) , The operative duration (> 3 hours $p=0.03$) and intraoperative bleeding
112 volume ($\geq 400\text{ml}$ $p=0.02$) were significantly correlated. Multivariate analysis (Table
113 3) showed that Koos grade IV ($p=0.04$; OR 3.1995% CI 1.032-3.190), operation duration
114 (> 3 hours $p=0.03$ OR 7.92795% CI 1.043-60.265), and intraoperative bleeding volume

115 ($\geq 400\text{ml}$ p0.02); OR 2.551v 95% CI 1.112-5.850) are the independent influencing
116 factors of POM.

117 **Table 2.** Univariate analysis of association between each factor and Postoperative meningitis.

Variables	Postoperative meningitis		p value
	Yes (n = 27)	No (n = 383)	
Age			0.064 ^a
>47	12(4.8%)	239(95.2%)	
≤ 47	15(9.4%)	144(90.6%)	
Sex			0.786 ^a
Male	12(7.0%)	160(93.0%)	
Female	15(6.3%)	223(93.7%)	
BMI			0.128 ^a
>23	8(4.5%)	171(95.5%)	
≤ 23	19(8.2%)	212(91.8%)	
Diabetes mellitus			0.057 ^b
Present	3(21.4%)	11(78.6%)	
Absent	24(6.1%)	372(93.9%)	
Hydrocephalus			0.018 ^a
Present	11(12.0%)	81(88.0%)	
Absent	16(5.0%)	302(95.0%)	
Side of tumor			0.435 ^a
Left	15(7.6%)	183(92.4%)	
Right	12(5.7%)	200(94.3%)	

Previous stereotactic radiosurgery at the same side		1.000 ^b
Yes	1(3.8%)	25(96.2%)
No	26(6.8%)	358(93.2%)
Previous microsurgery at the same side		0.657 ^b
Yes	2(8.7%)	21(91.3%)
No	25(6.7%)	362(93.3%)
Preoperative hospitalization (days)		0.869 ^a
>5	12(6.8%)	164(93.2%)
≤5	15(6.4%)	219(93.6%)
Koos grade of VS		0.004 ^b
I-III	4(2.4%)	166(97.6%)
IV	23(9.6%)	217(90.4%)
Surgery duration(hours)		0.003 ^b
>3	26(8.8%)	270(91.2%)
≤3	1(0.9%)	113(99.1%)
Bleeding amount of the operation (ml)		0.001 ^a
≥400	12(15%)	68(85%)
<400	15(4.5%)	315(95.5%)
Subcutaneous drainage		0.053 ^a
Present	13(10.1%)	116(89.9%)
Absent	14(5%)	267(95%)

Lumbar drainage		0.053 ^a
Present	8(11.9%)	59(88.1%)
Absent	19(5.5%)	324(94.5%)
Preoperative white blood cell count ($10^9/L$)		0.203 ^a
>6	14(8.5%)	151(91.5%)
≤ 6	13(5.3%)	232(94.7%)
Preoperative hemoglobin concentration (g/L)		0.286 ^b
>120	25(7.4%)	315(92.6%)
≤ 120	2(2.9%)	68(97.1%)

118 ^a Chi-square test.

119 ^b Fisher's exact test.

120 **Table 3.** Multivariate analysis of factors associated with POM

Variable	Odds ratio (95% CI)	p value
Hydrocephalus (present)	1.525(0.648-3.589)	0.333
Koos grade of VS (IV)	3.190(1.032-9.861)	0.044
Surgery duration (>3hours)	7.927(1.043-60.265)	0.045
Bleeding amount of the operation ($\geq 400ml$)	2.551(1.112-5.850)	0.027

121 **Association between POM and postoperative hospitalization**

122 The average length of hospital stay for patients with meningitis after surgery was 16.26,
123 with the median to be 13. The average length of hospital stay for patients without
124 meningitis after surgery was 7.28, with the median to be 6. The result shows $p < 0.001$.

125 Therefore, there was a significant difference in postoperative hospital stay between the
126 two groups of people.

127 **Pathogens of POM**

128 In this study. 27 POM patients were cultured with bacteria and fungi in CSF. The
129 culture time was three days. However, all the culture results were negative.

130 **Discussion**

131 Meningitis is divided into aseptic meningitis and bacterial meningitis. According to
132 the previous study, the positive rate of CSF culture is about 33% [11, 12]. However, in
133 this meningitis patient, no bacteria were cultured in the CSF culture, which may be due
134 to the intraoperative prophylactic administration of an antibiotic, and the prophylactic
135 administration of antibiotics in the case of postoperative infection symptoms or signs.

136 The positive rate of CSF or blood culture decreased significantly if antibiotic is used
137 more than 24 hours before diagnosis[13]. The culturing result turns to be negative but
138 many cases of culture-negative (aseptic) meningitis are bacterial meningitis[14]. In this
139 research, the incidence of meningitis after microsurgery of vestibular schwannoma is
140 less than 6.6%, which is lower than the results reported by Huang Xiang. In their
141 research, the incidence of meningitis after microsurgery of vestibular schwannoma is
142 9.85% [4]. What makes the results of the two researches inconsistent with each other is
143 follows. First, 8% patients of ours have a tumor with the volume of less than 30 x 20

144 mm; Second, the data we implement in our research comes from those years from 2015
145 to 2018, when the surgical equipment and relevant facilities are more advanced. Third,
146 we routinely used glucocorticoids intraoperatively and postoperatively to reduce
147 cerebral edema and to suppress inflammatory responses. Through our data analysis,
148 Koos grade, the duration of surgery and intraoperative blood loss are observed to be the
149 significant factors in the development of meningitis after microsurgery of vestibular
150 schwannoma. Besides, POM will significantly prolong the length of hospital stay.

151 The current research shows that the size of acoustic neuroma can significantly affect
152 the preservation of postoperative facial nerve function[15], cerebrospinal fluid
153 leakage[16] and postoperative pneumonia[17]. However, no literature indicates that the
154 size of acoustic neuroma is related to POM. For the first time, our research points out
155 that the size of the tumor significantly increased the risk of POM in the vestibular
156 schwannoma. However, and the specific mechanism between them is still unclear. The
157 possible mechanisms may be included as the following. First, large acoustic neuroma
158 compress surrounding brain tissue, causing brain cells to undergo edema, damage, and
159 inflammation; second, Grinding away the internal auditory canal produces more bone
160 chips; third, the inflammation is caused due to the excessive traction of brain tissue
161 during the surgery.

162 In addition, our study also found that the duration of surgery will significantly
163 affect the occurrence of POM, which is consistent with previous studies. Patir et al.[18]
164 discovered that a surgical time of more than 4 hours was significantly associated with

165 higher postoperative infection rates. The mechanism may be that with prolonged
166 operation time, the chance of external bacteria entering the cranium increased, and the
167 immune function of patients was inhibited under anesthesia. Dang, Y et al.[19] claimed
168 that Anesthesia affected the number and activity of immune cells and the secretion of
169 cytokines. Meninges and soft tissue are retracted for surgical exposure, resulting in
170 reduced perfusion and time-dependent reduced local immunological defense [20]. With
171 the prolongation of the operation time, the fatigue of the operator increases, which
172 easily pollutes the operation area.

173 Intraoperative hemorrhage is also an independent risk factor for meningitis in
174 patients with vestibular schwannoma after microsurgery. Chen, C et al.[21] Chen, S et
175 al.[22] all studied the risk factors of meningitis after microsurgery, but did not consider
176 intraoperative hemorrhage as a risk factor. However, we found that intraoperative
177 bleeding (> 400 ml) increased the risk of post-operative meningitis by 2.551 times. The
178 possible reason entails further study but one possibility is that massive intraoperative
179 hemorrhage will reduce the immune function of patients. At the same time, after
180 massive intraoperative blood, allogeneic transfusion is often performed, but transfusion
181 of allogeneic blood will complicate immune suppression [23]. The anti-infective ability
182 of patients with decrease when immunity is reduced, and meningitis is prone to occur.
183 Naidech, A. M. et al.[24] believed that the meningitis after operation was caused by
184 subarachnoid congestion, while the blood was easily accumulated in the
185 cerebellopontine region after vestibular schwannoma microsurgery, leading to

186 meningitis. When patients have the above risk factors, once they have symptoms of
187 infection, they should strongly suspect the occurrence of meningitis, and timely use
188 effective antibiotics to control the infection.

189 Once meningitis occurs after surgery, many literatures reported that the hospital stay
190 of patients with acoustic neuroma after microsurgery will be significantly
191 prolonged[25], which is consistent with the results of this study. In addition, it will
192 increase the medical expenses of patients, prolong the time to return to work, and
193 increase the burden on society.

194 In order to prevent the complication of meningitis after the operation of acoustic
195 neuroma, the first step is to make an early diagnosis when the acoustic neuroma is still
196 relatively small. Larger tumors are associated with more severe symptoms and surgical
197 complications[26]. Improving surgeon proficiency and strengthening communication
198 and logistics among operational professionals can reduce the operation time.
199 Golebiowski, A.[20] confirms that the duration of surgery may be shorter in older
200 patients, so when younger patients are undergoing surgery, we should pay more
201 attention to the control of operation time. Intraoperative hemostasis is exact, and the
202 traction of brain tissue should be reduced. Some studies have pointed out that
203 administration of tranexamic acid significantly reduced blood loss in patients
204 undergoing elective craniotomy for excision of intracranial meningioma [27].
205 Tranexamic acid may be used to reduce intraoperative bleeding in acoustic neuroma in
206 the future.

207 The disadvantage of this study is that it is a single-center study. There are admission
208 deviations in our sample. In addition, surgical instruments and methods vary among
209 hospitals, so our findings need to be verified in other hospitals. The average
210 hospitalization time of our patients is only 7 days. Thus, patients suffering from
211 meningitis after discharge are omitted from the statistics. Our study did not produce
212 bacteria and therefore failed to analyze the distribution of meningitis bacteria. In the
213 future, studies with a larger sample, multi-center, and more rational prospective are
214 needed to analyze the bacterial species of meningitis in order to facilitate better
215 treatment.

216 Conclusion

217 In this study, the probability of meningitis after acoustic neuroma microsurgery is 6.6%.
218 The risk factors of meningitis after microsurgery are Koos grade IV, the duration of
219 operation (>3 hours), and the amount of bleeding (≥ 400 ml). In addition, POM has a
220 significant association with the increase of hospitalization days after operation.
221 Therefore, in order to prevent POM, we should shorten the operation time and reduce
222 intraoperative bleeding.

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I	0(0%)
II	33 (8.0%)
III	137 (33.4%)
IV	240(58.5%)

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Table 2. Univariate analysis of association between each factor and Postoperative meningitis.

Variables	Postoperative meningitis		p value
	Yes (n = 27)	No (n = 383)	
Age			0.064 ^a
>47	12(4.8%)	239(95.2%)	
≤47	15(9.4%)	144(90.6%)	
Sex			0.786 ^a
Male	12(7.0%)	160(93.0%)	
Female	15(6.3%)	223(93.7%)	
BMI			0.128 ^a
>23	8(4.5%)	171(95.5%)	
Diabetes mellitus	19(8.2%)	213(91.8%)	0.057 ^b
Present	3(21.4%)	11(78.6%)	
Absent	24(6.1%)	372(93.9%)	
Hydrocephalus			0.018 ^a
Present	11(12.0%)	81(88.0%)	
Absent	16(5.0%)	302(95.0%)	
Side of tumor			0.435 ^a
Left	15(7.6%)	183(92.4%)	
Right	12(5.7%)	200(94.3%)	
Previous stereotactic radiosurgery at the same side			1.000 ^b
Yes	1(3.8%)	25(96.2%)	
No	26(6.8%)	358(93.2%)	
Previous microsurgery at the same side			0.657 ^b
Yes	2(8.7%)	21(91.3%)	
No	25(6.7%)	362(93.3%)	
Preoperative hospitalization (days)			0.869 ^a
>5	12(6.8%)	164(93.2%)	
≤5	15(6.4%)	219(93.6%)	
Koos grade of VS			0.004 ^b
I-III	4(2.4%)	166(97.6%)	
IV	23(9.6%)	217(90.4%)	
Surgery duration(hours)			0.003 ^b
>3	26(8.8%)	270(91.2%)	
≤3	1(0.9%)	113(99.1%)	
Bleeding amount of the operation (ml)			0.001 ^a
≥400	12(15%)	68(85%)	
<400	15(4.5%)	315(95.5%)	

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Subcutaneous drainage			0.053 ^a
Present	13(10.1%)	116(89.9%)	
Absent	14(5%)	267(95%)	
Lumbar drainage			0.053 ^a
Present	8(11.9%)	59(88.1%)	
Absent	19(5.5%)	324(94.5%)	
Preoperative white blood cell count (10⁹/L)			0.203 ^a
>6	14(8.5%)	151(91.5%)	
≤6	13(5.3%)	232(94.7%)	
Preoperative hemoglobin concentration (g/L)			0.286 ^b
>120	25(7.4%)	315(92.6%)	
≤120	2(2.9%)	68(97.1%)	

^a Chi-square test.

^b Fisher's exact test.

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Table 3. Multivariate analysis of factors associated with POM

Variable	Odds ratio (95% CI)	p value
Hydrocephalus (present)	1.525(0.648-3.589)	0.333
Koos grade of VS (IV)	3.190(1.032-9.861)	0.044
Surgery duration (>3hours)	7.927(1.043-60.265)	0.045
Bleeding amount of the operation ($\geq 400\text{ml}$)	2.551(1.112-5.850)	0.027

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