Research paper

Risk factors of postoperative intracranial infection in individuals suffering from hypertensive intracerebral hemorrhage

Keywords
hypertensive intracerebral hemorrhage, intracranial infection, risk factors, total parenteral nutrition, type 1 diabetes

Abstract

Introduction

It can be fatal for individuals with hypertensive intracerebral hemorrhage (HICH) to have a postoperative intracranial infection. It's yet unknown what risk factors led to this emergence. Therefore, the clinical variables for intracranial infection following HICH surgery were investigated.

Material and methods

3253 HICH patients who underwent hematoma removal surgery were enrolled. For every patient, clinical traits were obtained. To determine the variables that were independently linked to intracranial infection following HICH surgery, univariate/multivariate logistic regression analyses were used. The analysis of the receiver operating characteristic (ROC) curve was carried out to ascertain the threshold values for continuous parameters that predict postoperative intracranial infection in HICH patients.

Results

300 patients suffered from intracranial infection. Multivariate logistic regression indicated that, following HICH surgery, drainage tube retention time, duration of total parenteral nutrition (TPN) time, cerebrospinal fluid (CSF) leakage, type 1 diabetes, and plasma albumin levels were the separate susceptibility variables for cerebral infection. The ROC curve displayed that the area under the curve for drainage tube retention time (cutoff value, 7.5 days), plasma albumin levels (cutoff value, 33.75 g/L), and duration of TPN time (cutoff value, 7.5 days) were 0.756, 0.977, and 0.895, respectively.

Conclusions

Duration of TPN time ≥ 7.5 days, type 1 diabetes, CSF leakage, drainage tube retention time ≥ 7.5 days, and plasma albumin levels < 33.75 g/L were independent risk factors for postoperative intracranial infection in HICH patients. More attention should be provided to the contributors to minimize the frequency of this complication.

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Keywords: Hypertensive intracerebral hemorrhage; Intracranial infection; Risk factors; Total parenteral nutrition; Type 1 diabetes

Introduction

With a high probability of clinical death and disability, hypertensive intracerebral hemorrhage (HICH) occurs as a frequent serious emergency.[1,2] A prompt surgical hematoma removal is a useful therapy option for some of these patients. However, due to the invasive nature of surgical procedures, patients undergoing surgical treatment may suffer from intracranial infections after surgery due to the combined influence of various factors.[3,4] Intracranial infection greatly affects treatment effectiveness, prolongs hospitalization time, increases hospitalization costs, and may also pose a serious threat to patient safety.[5]

After surgery for HICH, a variety of pathogens, including bacteria, fungi, and even viruses, can result in intracranial infections; the most common ones are bacteria. Unclear distribution of pathogens can lead to unreasonable use of antibiotics, reduce antibacterial efficacy, and increase the production of drug-resistant strains.[6] Although previous reports have investigated the factors contributing to cerebral infection after surgery,[7,8] the factors that raise the incidence of postoperative intracranial infection in HICH patients remain controversial. In order to improve the prognosis of HICH patients undergoing surgical treatment, it is crucial to analyze the distribution characteristics of pathogenic bacteria and related risk factors of intracranial infection in patients with HICH following hematoma removal surgery, identify high-risk patients with cerebral infection early, and modify treatment strategies and patient physical fitness to reduce the occurrence of intracranial infection. We aim to examine the distribution patterns of harmful bacteria along with related indicators of vulnerability for cerebral infections following HICH surgery.

Methods

Patients

This was a multicenter retrospective cross-sectional study. The study comprised 3253 individuals with HICH who underwent hematoma removal surgery between January 2023 and August 2024. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Medical Ethics Committee of the Second Affiliated Hospital of Nanchang University (approval No. BR/AF/SG-03/1.0). The requirements for inclusion were as follows: patients who received surgery after fulfilling the diagnostic requirements outlined in the 2022 Guideline for the Management of Patients with Spontaneous Intracerebral Hemorrhage;[9] complete clinical data; no infectious diseases before surgery. An intracerebral infection is identified by pathogen culture and is diagnosed using the relevant criteria of the "Diagnosis Standards for Hospital Infection (Trial) (2001)" published by the Ministry of Health of the People's Republic of China.[10] The infection manifests with headache, positive meningeal irritation signs (such as stiff neck, Kernig sign, Brudzinski sign, etc.), severe fever, and chills. Patients with cerebral arteriovenous malformations, intracranial vascular abnormalities, and brain tumor apoplexy were excluded, as were those with hematological disorders, patients whose vital organs (like those of the kidneys, liver, and heart) are malfunctioning, patients with infectious diseases prior to admission, and patients with incomplete clinical data. Based on whether intracranial infection had occurred, patients were split into groups based on whether they had intracranial infection or not.

Clinical treatment

All patients underwent hematoma evacuation surgery. For patients with acute hydrocephalus and/or ventricular cast hematoma, extraventricular drainage surgery was performed. Craniectomy was performed on patients with high intracranial pressure after hematoma evacuation. Prophylactic antibiotics (such as ceftazidime, etc.) were injected half an hour before surgery, and if the surgery time exceeded three hours, another dose was injected. Postoperative sodium valproate treatment was implemented to take precautions against secondary epilepsy. According to the drug sensitivity results of sputum culture, sensitive antibiotics were used to treat postoperative pneumonia. In addition, other postoperative complications and underlying diseases were also prevented and treated.

Data collection

The parameters collected for patients included sex, age, anamnesis (such as diabetes, hyperlipidemia, hypoimmunity, etc.), and the perioperative clinical status of patients, including preoperative Glasgow Coma Scale (GCS) score, hematoma volume, operation opportunity, operation duration, intraoperative blood loss, number of drainage tubes, drainage tube retention time, hospitalization in the intensive care unit (ICU), lumbar puncture, intrathecal injection, plasma albumin levels, duration of total parenteral nutrition (TPN) time, and pathogenic bacteria confirmed by cerebrospinal fluid culture, etc.

Immunocompromised patients included patients with autoimmune diseases (such as systemic sclerosis, periodic febrile syndrome, Hashimoto's disease, antiphospholipid syndrome, etc.), individuals who have a human immunodeficiency virus infection, patients with renal failure who require hemodialysis, patients treated with immunosuppressive agents for a long term, or patients with hematological malignancy. Any surgery carried out within 24 hours of the onset was considered an emergency operation. Surgery carried out 24 hours following the onset was referred to as a selective procedure. Blood samples were taken within 1 hour before surgery to measure albumin levels. For measuring fasting blood lipids, blood samples were taken the morning after admission. On the day of suspected intracranial infection, 2-3 ml of cerebrospinal fluid (CSF) was collected for pathogen cultivation.

Statistical analysis

The statistical analysis was conducted using SPSS 20.0 program. The presentation of categorical parameters was done using frequencies (%), while the continuous values were shown as mean ± standard deviation. The two groups' differences were compared using the *t*-test for continuous parameters and the chi-square test for categorical parameters. The study employed univariate and multivariate logistic regression analysis to assess the risk factors linked to postoperative intracranial infection in patients with HICH. The receiver operating characteristic (ROC) analysis was used to establish the postoperative intracranial infection cutoff values for continuous parameters, with a statistical significance cutoff of $P < 0.05$.

Results

Basic information of patients with HICH

3253 HICH patients who underwent surgical treatment were recruited: 1649 males and 1604 females. The average age of the patients, who ranged in age from 37 to 81, was 62.5 ± 11.2 years. The intracranial hematoma volume ranged from 30 to 82 ml, with an average hematoma volume of 49.0 ± 8.1 ml. The patients' clinical features were enumerated in Table 1. Age, sex, hyperlipidemia, preoperative GCS scores, hematoma volume, surgical method, surgical duration, intraoperative blood loss, number of drainage tubes, hospitalization in the ICU, lumbar puncture, or intrathecal injection did not significantly differ between the two groups. The intracranial infection group scored considerably higher in type 1 diabetes, hypoimmunity, pulmonary infection, sepsis, and cerebrospinal fluid leakage than the non-intracranial infection group did. The drainage tube retention time and TPN duration were noticeably longer in the intracranial infection group. The intracranial infection group's plasma albumin levels were substantially lower.

Pathogenic characteristics of postoperative cerebral infection in individuals with HICH

Among 3253 HICH patients, 300 patients suffered from postoperative intracranial infection, with an infection rate of 9.2%. As shown in Table 2, 310 strains of pathogenic bacteria were isolated, including 187 Gram-positive bacteria, 109 Gram-negative bacteria, and 14 fungi, representing 60.3%, 35.2%, and 4.5% of the total.

Univariate assessment of risk variables for postoperative cerebral infection among HICH patients

We found significant differences between the two groups in the prevalence of type 1 diabetes, hypoimmunity, pulmonary infection, sepsis, and CSF leakage using univariate logistic regression analysis, as indicated in Table 3. Additionally, the two groups differed by a significant margin in drainage tube retention time, TPN duration, and plasma albumin levels.

Multivariate assessment of risk variables for postoperative cerebral infection among HICH patients

We incorporated these 8 factors identified by univariate analysis into a multivariate logistic regression model for further analysis and identified 5 variables that contribute to cerebral infection following HICH surgery, including duration of TPN time, type 1 diabetes, drainage tube retention time, CSF leakage, and plasma albumin levels (Table 4). Accordingly, the sensitivity, specificity, positive predictive value, and negative predictive value of the logistic regression model were 90.7%, 99.3%, 93.2%, and 99.1%, respectively. The area under the curve (AUC) of drainage tube retention time, according to the ROC curve analysis, was 0.756 (95% confidence interval (CI) 0.719-0.793; $P < 0.001$). With a 57.0% sensitivity and a 94.0% specificity, the drainage tube retention time cutoff value was 7.5 days (Fig. 1A). Plasma albumin levels had an AUC of 0.977 (95% CI 0.967-0.987; $P < 0.001$). The results showed that the plasma albumin levels had 94.4% and 96.0% sensitivity and specificity, respectively; the cutoff value was 33.75 g/L (Fig. 1B). With a 73.7% sensitivity and a 94.0% specificity at a cutoff value of 7.5 days, the duration of TPN time had an AUC of 0.895 (95% CI 0.873-

0.916; $P < 0.001$) (Fig. 1C).

Discussion

Postoperative cerebral infection in patients with HICH is devastating and may result in serious clinical consequences and even death. Intracerebral infection may be avoided, and the clinical prognosis of HICH patients may be improved with a comprehensive awareness and assessment of the independent risk factors for this infection. This study aimed at exploring the distribution characteristics of pathogens and related independent contributory variables for cerebral infection following HICH surgery. In line with earlier studies,[11] our findings suggested that the incidence of intracranial infection after surgery for HICH was 9.2%. In addition, we also found that duration of TPN time ≥ 7.5 days, type 1 diabetes, drainage tube retention time ≥ 7.5 days, CSF leakage, and plasma albumin levels < 33.75 g/L were independent contributory variables for cerebral infection following HICH surgery.

310 harmful bacterial strains were identified in our investigation, with Gram-positive bacteria accounting for 60.3%, followed by Gram-negative bacteria and fungi. which suggests that Gram-positive bacteria are the main pathogen of postoperative intracranial infection in patients with HICH. Our findings are similar to previous studies indicating that Gram-positive pathogens dominate the pathogens of postoperative intracranial infections.[12] However, another study suggests that the main pathogenic bacteria for intracranial infections after cranial operation are gram-negative bacteria.[13] The differences in the distribution of pathogenic bacteria may be related to primary neurological diseases and regional differences.

Our result has certain guiding significance for preventive and empirical anti-infection treatment for HICH patients with postoperative intracranial infections.

Multivariate logistic analysis and ROC curve analysis showed that duration of TPN time ≥ 7.5 days, type 1 diabetes, CSF leakage, drainage tube retention time ≥ 7.5 days, and plasma albumin levels < 33.75 g/L were contributory variables for cerebral infection following HICH surgery. As is well known, sustained hyperglycemia can lead to microcirculation disorders, weaken the healing ability of surgical incisions, provide a suitable environment for the proliferation of pathogens, and then increase the risk of surgical site infections. Diabetes lowers a patient's quality of life and raises the chance of a cerebral infection following surgery for cerebral aneurysms, according to earlier research.[14,15] However, some studies suggested that diabetes or postoperative blood glucose levels are not risk factors for postoperative intracranial infection.[16,17] The difference may be caused by the different proportions of diabetes subtypes in various studies. It is well known that the blood glucose of type 1 diabetes patients is more difficult to control than that of type 2 diabetes patients. Furthermore, type 1 diabetes is more likely to cause secondary damage.[18] Our study found that type 1 diabetes, rather than type 2 diabetes, is one of the independent contributory variables for cerebral infection following HICH surgery.

TPN provides nutritional support for HICH patients who cannot receive enteral nutrition due to complications such as gastric retention and stress ulcers. However, TPN has been confirmed to be closely related to nosocomial infection.[19] In patients undergoing craniotomy for craniocerebral injury, TPN doesn't increase the incidence of intracranial infections.[20] Nevertheless, a previous study has shown that TPN increases the incidence of intracranial infections after traumatic brain injury.[21] Few studies have found a link between TPN and intracerebral infections after HICH surgery. In patients with HICH, we have verified that TPN is a separate contributory variable for cerebral infection following surgery. The potential pathogenic mechanism may be that TPN causes complications such as dysbiosis of gut microbiota, which leads to dysregulated gut-brain communication, altering the intestinal barrier and immune responses, increasing the risk of infection and inflammation throughout the body, and changing the prognosis for stroke.[22-24] Using ROC curve analysis, we further demonstrated that a duration of TPN time $\geq$ 7.5 days was one of the separate contributory variables in cerebral infection after HICH surgery.

Postoperative CSF leakage has been generally accepted as an important influencing factor for intracranial infection.[25] CSF is a colorless liquid that is rich in nutrients and almost free of immune cells, immune proteins, and other immune-active substances, making it very suitable for bacterial reproduction. Once a CSF incision leakage occurs, pathogens are easily colonized and rapidly proliferate at the incision site, leading to intracranial infection. We found that drainage tube retention time was one of the separate contributory variables for cerebral infection following HICH surgery. A similar conclusion was drawn from a previous study, which indicated that drainage duration was one of the factors affecting the clinical outcomes of intracranial infection patients.[26] However, the study did not propose the specific duration of the drainage tube affecting intracranial infection. To solve this problem, we have determined the cutoff value for the duration of drainage, which was achieved through the ROC curve and AUC analysis. In prognosing the occurrence of postoperative intracranial infection, as we have seen, the cutoff value of drainage tube retention time was 7.5 days, suggesting that postoperative intracranial infection happens more commonly in HICH patients with drainage tube retention time over 7.5 days. Nevertheless, some studies suggested that extraventricular drainage was not associated with the occurrence of intracranial infections.[27] Different conclusions may be partly due to differences in the studied diseases and drainage times.

In many medically related fields, albumin is considered a nutritional indicator and closely related to immune function.[28] Hypoalbuminemia often means weakened immunity and malnutrition. Recently, hypoalbuminemia has been proven to be associated with the severity of sepsis and the poor clinical prognosis of multiple diseases.[28,29] Previous research has confirmed the correlation between albumin and infective complications in patients suffering from stroke.[30] However, the relationship between albumin and cerebral infection following HICH surgery remains unclear. Our study showed a significant correlation between albumin and postoperative intracranial infection in HICH patients. Further research using ROC curve analysis demonstrated that plasma albumin levels < 33.75 g/L were one of the separate contributory variables for cerebral infection following HICH surgery.

There are a few limitations to our research. First, the patients in our study mainly came from the central and southern regions of China; the influence of regional medical factors cannot be ruled out. Moreover, it is still impossible to completely exclude confounding variables that may affect postoperative intracranial infection in HICH patients, although we tried our best to adopt strict exclusion criteria. It is also impossible to guarantee the complete inclusion of all factors that may be involved in intracerebral infection following HICH surgery. Finally, it is impossible to overlook the influence of surgical procedures and postoperative comprehensive care, which includes the prudent use of antibiotics, on postoperative intracranial infection in HICH patients; however, it presently exists inadequate methodology to measure this.

Conclusion

The current investigation validated a few independent predictive variables for the occurrence of intracerebral infection following HICH surgery, suggesting that duration of TPN time ≥ 7.5 days, type 1 diabetes, CSF leakage, drainage tube retention time ≥ 7.5 days, and plasma albumin levels < 33.75 g/L were separate contributory variables for cerebral infection after HICH surgery. More attention should be provided to the contributors that may raise the risk of postoperative intracranial infection for patients with HICH so as to reduce the incidence of this complication.

Conflict of Interest

The authors have no potential conflicts of interest to disclose.

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Figure legends

Fig. 1. The drainage tube retention time, plasma albumin levels, and duration of TPN time ROC curves. (A) The drainage tube retention time cutoff point for surgical cerebral infection. The cutoff level of 7.5 days displays a 57.0% sensitivity coupled with a 94.0% specificity. It has an AUC of 0.756. (B) The plasma albumin levels cutoff value for surgical cerebral infection in HICH patients. The cutoff level of 33.75 g/L displays a 94.4% sensitivity coupled with a 96.0% specificity. It has an AUC of 0.977. (C) The duration of TPN time cutoff point for surgical cerebral infection in HICH patients. The sensitivity and specificity at the 7.5-day cutoff point are 73.7% and 94.0%, respectively. AUC is 0.895.

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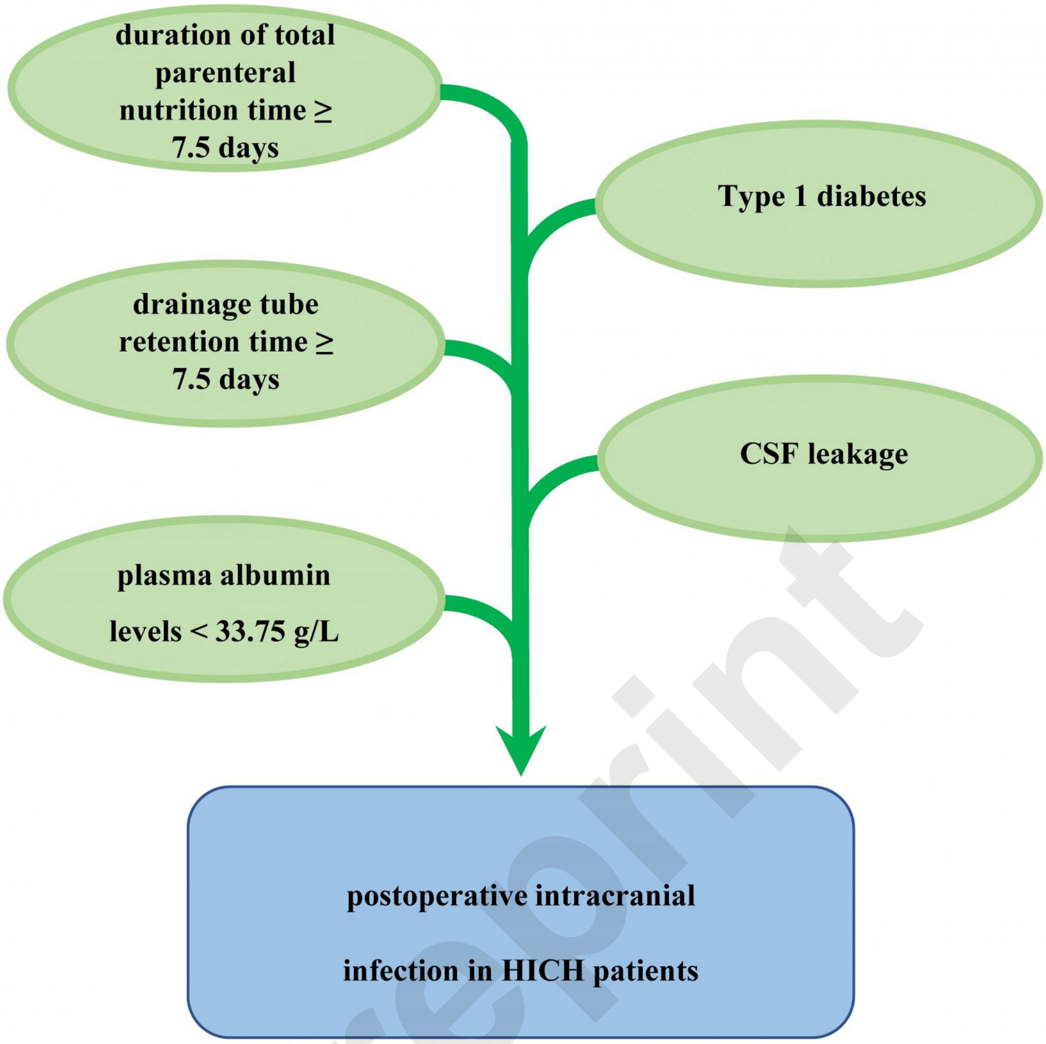

duration of total parenteral nutrition time ≥ 7.5 days
Type 1 diabetes
drainage tube retention time ≥ 7.5 days
CSF leakage
plasma albumin levels < 33.75 g/L
postoperative intracranial infection in HICH patients

Table 1 The clinical features of patients with HICH

Characteristics	Groups		*P*-value
	Infection (n=300)	Non-infection (n=2953)	
Sex (female) (%)	149 (49.7)	1455 (49.3)	0.90
Age (years)	62.1 ± 11.9	62.5 ± 11.1	0.10
Diabetes			
Non-diabetes (%)	143 (47.7)	2128 (72.0)	< 0.001
Type 1 diabetes (%)	95 (31.7)	102 (3.5)	
Type 2 diabetes (%)	62 (20.6)	723 (24.5)	
Hyperlipidemia (%)	64 (21.3)	698 (23.6)	0.39
Hypoimmunity (%)	55 (18.3)	68 (2.3)	< 0.001
Hematoma volume (ml)	49.1 ± 7.3	48.9 ± 8.3	0.13
GCS score	7.1 ± 1.1	7.2 ± 1.2	0.07
Operation opportunity			
Emergency operation (%)	278 (92.7)	2659 (90.0)	0.15
Selective operation (%)	22 (7.3)	294 (10.0)	
Operation duration (hours)	3.3 ± 0.3	3.3 ± 0.4	0.34
Number of operations			
Once (%)	285 (95.0)	2835 (96.0)	0.36
More than once (%)	15 (5.0)	118 (4.0)	
Intraoperative blood loss (ml)	576.5 ± 102.0	575.9 ± 104.6	0.77
Invasive intracranial pressure monitoring (%)	139 (46.3)	1296 (43.9)	0.43
Number of drainage tubes			
1 drainage tube (%)	39 (13.0)	389 (13.2)	0.96
2 drainage tubes (%)	132 (44.0)	1318 (44.6)	
3 drainage tubes (%)	129 (43.0)	1246 (42.2)	
Drainage tube retention time (days)	8.2 ± 4.0	4.6 ± 2.0	< 0.001
Lumbar puncture (%)	52 (17.3)	532 (18.0)	0.81
Intrathecal injection (%)	32 (10.7)	289 (9.8)	0.61
Pulmonary infection (%)	193 (64.3)	1564 (53.0)	< 0.001
Length of stay in the ICU (days)	6.1 ± 2.5	6.1 ± 3.3	0.27
Sepsis (%)	92 (30.7)	67 (2.3)	< 0.001
Cerebrospinal fluid leakage (%)	98 (32.7)	40 (1.4)	< 0.001
Plasma albumin levels (g/L)	28.0 ± 3.3	42.8 ± 4.3	< 0.001
Duration of TPN time (days)	11.7 ± 3.4	5.3 ± 2.2	< 0.001

GCS, glasgow coma scale; ICU, intensive care unit; TPN, total parenteral nutrition.

Table 2 Pathogenic characteristics of postoperative intracranial infection in HICH patients

Pathogenic bacteria	Bacterial strain (n=208)	Constituent ratio (%)
Gram positive bacteria		
Coagulase-negative staphylococcus	50	24.0
Staphylococcus aureus	34	16.4
Enterococcus faecalis	21	10.1
Staphylococcus epidermidis	11	5.3
Others	4	1.9
Gram negative bacteria		
Pseudomonas aeruginosa	25	12.0
Acinetobacter baumannii	22	10.6
Klebsiella pneumoniae	17	8.2
Escherichia coli	12	5.8
Others	4	1.9
Fungi		
Candida albicans	5	2.4
Candida glabrata	3	1.4

Table 3 Univariate analysis of risk factors for postoperative intracranial infection in HICH patients

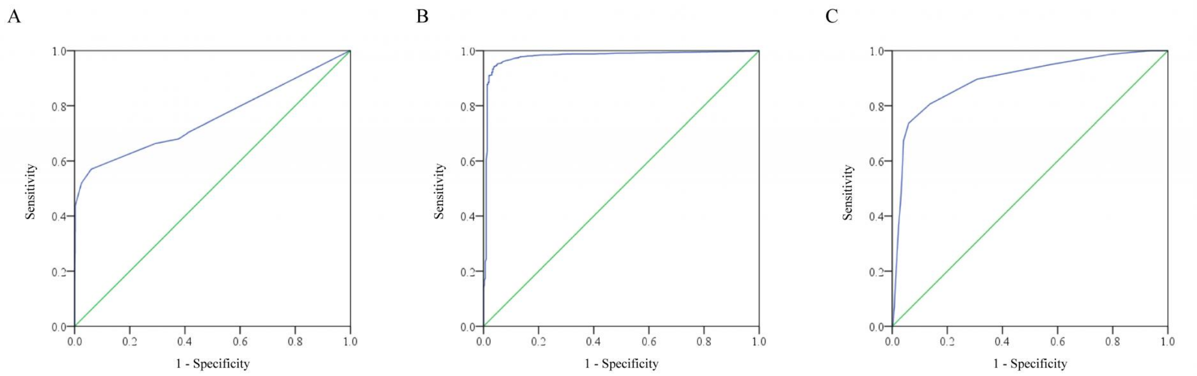
Factors	Intracranial infection				
	B	S.E.	Wals	*P*-value	OR (95% CI)
Type 1 diabetes	2.629	0.167	248.681	<0.001	13.860 (9.997-19.216)
Hypoimmunity	2.254	0.193	136.130	<0.001	9.524 (6.522-13.908)
Pulmonary infection	0.471	0.126	13.976	<0.001	1.602 (1.251-2.051)
Drainage tube retention time	0.491	0.026	354.567	<0.001	1.634 (1.553-1.720)
Sepsis	2.947	0.176	280.651	<0.001	19.052 (13.496-26.896)
CSF leakage	3.565	0.201	313.782	<0.001	35.331 (23.815-52.415)
Plasma albumin levels	-0.478	0.025	357.509	<0.001	0.620 (0.590-0.652)
Duration of TPN time	0.457	0.022	441.449	<0.001	1.579 (1.513-1.648)

CSF, cerebrospinal fluid; TPN, total parenteral nutrition.

Table 4 Multivariate analysis of risk factors for postoperative intracranial infection in HICH patients

Factors	Intracranial infection				
	B	S.E.	Wals	*P*-value	OR (95% CI)
Type 1 diabetes	3.153	0.637	24.470	<0.001	23.412 (6.712-81.664)
Drainage tube retention time	0.408	0.063	42.158	<0.001	1.503 (1.329-1.700)
CSF leakage	3.928	0.685	32.877	<0.001	50.828 (13.271-194.662)
Plasma albumin levels	-0.466	0.040	134.000	<0.001	0.627 (0.580-0.679)
Duration of TPN time	0.470	0.052	81.223	<0.001	1.600 (1.445-1.772)

CSF, cerebrospinal fluid; TPN, total parenteral nutrition.


A
B
C
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0