Retrospective Study
Risk factors for delayed intracranial hemorrhage secondary to ventriculoperitoneal shunt: A retrospective study

Jun-Chen Chen, Shou-Xing Duan, Ze-Bin Xue, Sen-Yuan Yang, Yong Li, Run-Long Lai, Dian-Hui Tan

Abstract
BACKGROUND
Delayed intracranial hemorrhage (DICH), a potential complication of ventriculoperitoneal (VP) shunts, has been associated with high mortality, but its risk factors are still unclear.

AIM
To investigate the risk factors of DICH after VP shunts.

METHODS
We compared the demographic and clinical characteristics of DICH and non-DICH adult patients with VP shunts between January 2016 and December 2020.

RESULTS
The 159 adult VP shunt patients were divided into 2 groups according to the development of DICH: the DICH group (n = 26) and the non-DICH group (n = 133). No statistically significant difference was found in age, sex, laboratory examination characteristics or preoperative modified Rankin Scale (mRS) score between the DICH and non-DICH groups (P > 0.05); however, a history of an external ventricular drain (EVD) [P = 0.045; odds ratio (OR): 2.814; 95%CI: 1.024-7.730] and postoperative brain edema around the catheter (P < 0.01; OR: 8.397; 95%CI: 3.043-23.171) were associated with a high risk of DICH. A comparison of preoperative mRS scores between the DICH group and the non-DICH group showed no significant difference (P = 0.553), while a significant difference was
found in the postoperative mRS scores at the 3-mo follow-up visit ($P = 0.024$).

**CONCLUSION**

A history of EVD and postoperative brain edema around the catheter are independent risk factors for DICH in VP shunt patients. DICH patients with a high mRS score are vulnerable to poor clinical outcomes.

**Key Words:** Delayed intracranial hemorrhage; Ventriculoperitoneal shunt; Hydrocephalus; Risk factor; Retrospective study

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** A retrospective study of 109 patients after ventriculoperitoneal shunts indicates that a history of external ventricular drain and postoperative brain edema around the catheter are independent risk factors for delayed intracranial hemorrhage (DICH). The DICH patients are vulnerable to poor clinical outcomes with a high modified Rankin Scale score.

**INTRODUCTION**

Ventriculoperitoneal (VP) shunting is a commonly performed surgical procedure for the treatment of hydrocephalus. Reports show that VP shunts are associated with various potential complications, such as infection, shunt obstruction and shunt malformation[1-4]. Delayed intracranial hemorrhage (DICH) refers to a subsequent cerebral hemorrhage that was not found in the first postoperative computed tomography (CT) scan of the VP shunt. Compared with other complications, DICH was regarded as a rare complication of VP shunts[5,6]. In 1985, Matsumura et al.[7] provided a case report that was the first to describe DICH[7]. Since then, many case reports related to DICH[8] of the VP shunt have been published[9-13]. DICH, a severe complication with a high mortality (50%), has caused concern for neurosurgeons for the past few years. Recognizing the risk factors for DICH could benefit neurosurgeons and improve treatment for patients. Several retrospective studies related to DICH were recently performed to explore the risk factors and prognosis related to DICH[14-18]. However, the risk factors for DICH have yet to be fully defined and more data are still needed. This retrospective study aims to include more patients and variables and explore the potential risk factors and mechanisms of DICH.

**MATERIALS AND METHODS**

**Study design**

This retrospective study was reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Shantou University Medical College (No. 2019034). All data were anonymously analyzed after the patient provided consent. The medical records of the hydrocephalus patients who received VP shunts at the First Affiliated Hospital of Shantou University Medical College between January 2016 and December 2020 were reviewed. The inclusion criteria were as follows: (1) Aged between 18 years and 75 years; (2) Received a Medtronic Strata Adjustable Pressure VP Shunt with the pressure valve set at 2.0; and (3) Intact clinical data including laboratory tests and radiographic imaging. The exclusion criteria were as follows: (1) A history of severe diseases such as coronary artery atherosclerosis, hepatosclerosis, and coagulation dysfunction; (2) Not followed up for more than 3 mo after treatment; (3) Used other brands of adjustable pressure VP shunts; and (4) Used nonadjustable pressure VP shunts. A flowchart of patient selection is summarized in Figure 1. A retrospective study of 159 patients who met the criteria was retrospectively reviewed in this study.
Data collection
All medical records were reviewed for parameters including age, sex, primary intracranial lesion, history of surgery [craniotomy, decompression, external ventricular drain (EVD), and cranioplasty], history of hypertension, smoking habit, prior blood transfusion, preoperative lumbar puncture, and routine laboratory examinations. The primary intracranial lesion was classified as traumatic brain injury, intracranial hemorrhage, subarachnoid hemorrhage (SAH) (aneurysm rupture), SAH (Arteriovenous malformation), cerebral infarction, tumor, infection, or primary hydrocephalus. All patients underwent lumbar puncture before VP shunting and cerebrospinal fluid (CSF) pressure and laboratory indicators (CSF protein level, glucose level, and nucleated cells) were recorded in detail. Laboratory examinations, such as routine blood tests, were obtained within 3 d before the operation. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio were calculated from routine blood results to explore the relationship with DICH. The two new variables were analyzed independently to prevent bias. Other basic diseases, such as diabetes and gout, were controlled for.

The details of VP shunt surgery included the operation time, location of the VP shunt (frontal or occipital), and other postoperative complications. An initial cranial CT scan was performed within 24 h after the VP shunt was implanted, and a cranial CT scan was performed on postoperative days 5, 6, and 7. A postoperative emergency CT scan was performed if the patients showed signs of neurological deterioration during hospitalization. The radiographic characteristics that were collected were as follows: Presence of DICH, type of hematoma, volume of hematoma, and brain edema around the catheter. The volume of hematoma was calculated based on CT scan results using the volumetric computer on Advantage Windows 3D Workstation 4.1 (Shantou, China). Interreader variability was determined by analyzing the CT images by two independent radiologists who were blinded to the details of the study. Other postoperative complications, such as infection and shunt obstruction, were also recorded.

We assessed the clinical outcomes at the 3-mo follow-up visit. The general postoperative outcomes were evaluated based on the modified Rankin Scale (mRS) score. The mRS score was divided into two categories: Low (0-2) and high (3-5). In addition, the preoperative mRS score was also recorded to evaluate VP shunt clinical outcomes.

Statistical analysis
All statistical analyses were performed using statistical software (SPSS Version 23.0, SPSS. IBM Corp., Armonk, NY, United States). Continuous variables are expressed as the means ± SD. Comparisons between the 2 groups were analyzed using the $x^2$ test (or Fisher’s exact test) for categorical data and the t test for continuous data. The relationship between each variable and DICH outcome was analyzed by univariate analysis, followed by multivariate logistic regression analysis. $P$ values < 0.05 were considered statistically significant.
RESULTS
A total of 159 patients were divided into the DICH group (n = 26, 16.4%) or the non-DICH group (n = 133, 83.6%) according to the presence of a new hematoma after the first postoperative CT scan. Table 1 shows the general demographic and clinical characteristics of the patients in this study. For continuous variables, values are expressed as the mean ± SD; for categorical variables, the values are numbers. No significant differences were found for most variables, such as sex and laboratory examination results. A significant difference was found in the history of EVD between these 2 groups (P = 0.004). Regarding radiographic characteristics, a significant difference in the brain edema around the catheter was observed between the 2 groups (P < 0.01).

Univariate analysis between each variable and the DICH outcome in the original 159 patients revealed that a history of EVD and brain edema around the catheter were significantly correlated with DICH outcome (Table 2). Multivariate analysis showed that these two variables were significantly correlated with DICH outcome: History of EVD [P = 0.045; odds ratio (OR): 2.814; 95% CI: 1.024-7.730] and presence of brain edema around the catheter (P < 0.01; OR: 8.397; 95% CI: 3.043-23.171) (Table 3). Table 4 shows the clinical data summary of 26 DICH patients after VP shunt. Among these patients, 3 had a subdural hematoma, 9 had an intraventricular hemorrhage, and 14 had an intracerebral hemorrhage around the catheter (Figure 2). No epidural hemorrhage or other types of intracranial hemorrhage were noted. The mean onset day of DICH was 4.19 ± 3.35 d, which ranged from 1 to 11 d. The mean hematoma volume was 10.92 ± 14.53 mL, which ranged from 2 to 56 mL. Two DICH patients with severe neurological deterioration underwent secondary surgical intervention for intracranial hematoma evacuation; 24 patients received conservative treatment because of the low-volume hematoma. A comparison of preoperative mRS scores between the DICH group and the non-DICH group showed a significant difference (P = 0.553). Seventeen of 26 (65%) DICH patients and 35 of 133 (41%) non-DICH patients were included in the high postoperative mRS group. A significant difference was found in the postoperative mRS score at the 3-mo follow-up visit (P = 0.024).

DISCUSSION
We performed a literature review of retrospective studies on DICH that was associated with VP shunts, and then we summarized these preview studies (Table 5). From these 6 studies, the incidence of DICH ranged from 1.6% to 23.7%. In our study, the incidence of DICH was 16.4%, which corresponded to the incidence range of previous studies. The wide range of incidence may be related to the neglect of minor hematoma volume, lower frequency of postoperative CT scan examinations, and different inclusion and exclusion criteria in different studies[6,19]. We suppose that the real incidence range of DICH will be more accurate with careful surveillance, such as imaging and unified standards, in the future.

Thirty-seven variables were included to achieve a better comparison between the DICH group and the non-DICH group in our study, which is more than other prior retrospective studies. The analysis of these variables provides a better description of the actual baseline demographic information and clinical characteristics better. In our study, a history of EVD and the presence of brain edema around the catheter were significantly correlated with DICH in a univariate analysis. The selection of covariates for the multivariate analysis was based on previous studies that assessed the risk factors for DICH and our univariate analysis. In these studies, advanced age, craniotomy history, presence of brain edema around the catheter, manipulation of the valve system, location of the shunt (frontal or occipital), delayed partial thromboplastin time, postoperative low-molecular-weight heparin (LMWH) therapy, dual antiplatelet therapy and elevated levels of postoperative NLR and preoperative NLR were found to be positively associated with DICH[18-20]. Considering our available data, 6 variables (age, craniotomy history, EVD history, prothrombin time, location of shunt, and presence of brain edema around catheter) were consequently selected for the multivariate analysis. The variables in the logistic regression multivariate model that were significantly different were EVD history and presence of brain edema around the catheter.

A history of EVD was regarded as an independent risk factor for DICH in our study, which was first reported and not found in previous studies. We also found that the presence of brain edema around the catheter on the first postoperative CT scan increased the risk of DICH, which corresponded with the report by Guo et al[15]. An EVD and VP shunts are inserted using the same frontal approach, which is an invasive brain procedure that may cause neural injury in patients[21]. Some authors have proposed that catheter insertion may lead to a disturbance in venous return or hemostasis of a cortical vein and then contribute to subcortical hemorrhage[15,17,22]. Brain edema around the catheter is regarded as a radiographic sign of vascular erosion and could be used to predict DICH.

Fragile cerebral tissue is considered another underlying mechanism of DICH. Cerebral fragility is not easy to detect and the standard diagnosis is based on features of the fragile arteries surrounding the microbleeds in histological analysis after surgical resection[23]. The microbleed that was confirmed on T2-weighted MR imaging, reflected hemosiderin deposits and could be considered an imaging sign related to fragile cerebral tissue[8,24,25]. In Kwon and Jang[20,26]’s study, two neural tracts (cortico-
### Table 1 Demographical characteristics and clinical data of the patients

| Variables                        | DICH group (n = 26) | Non-DICH group (n = 133) | P value |
|----------------------------------|---------------------|--------------------------|---------|
| Age (yr)                         | 51.35 ± 12.08       | 53.89 ± 15.17            | 0.422   |
| Male gender, n (%)               | 17 (65.38)          | 66 (49.62)               | 0.141   |
| Primary intracranial lesion, n (%) |                     |                          | 0.679   |
| Traumatic brain injury           | 6 (23.07)           | 43 (17.29)               |         |
| Intracranial hemorrhage          | 5 (19.23)           | 30 (22.56)               |         |
| SAH (aneurysm rupture)           | 10 (38.46)          | 29 (21.80)               |         |
| SAH (AVM rupture)                | 0 (0)               | 0 (0)                    |         |
| Cerebral infarction              | 0 (0)               | 0 (0)                    |         |
| Tumor                            | 2 (7.69)            | 8 (6.02)                 |         |
| Infection                        | 0 (0)               | 4 (3.01)                 |         |
| Primary hydrocephalus            | 3 (11.54)           | 19 (14.29)               |         |
| Pre-Craniotomy, n (%)            | 9 (34.62)           | 56 (42.11)               | 0.477   |
| Pre-Decompression, n (%)         | 8 (30.77)           | 50 (37.59)               | 0.508   |
| Pre-EVD, n (%)                   | 16 (61.54)          | 42 (31.58)               | 0.004*  |
| Pre-Cranioplasty, n (%)          | 2 (7.69)            | 23 (17.29)               | 0.350   |
| LP pressure (mmH2O)              | 141.54 ± 60.93      | 139.42 ± 64.94           | 0.878   |
| CSF protein (g/L)                | 0.56 ± 0.46         | 0.64 ± 0.60              | 0.509   |
| CSF glucose (mmol/L)             | 3.87 ± 1.45         | 3.88 ± 1.35              | 0.980   |
| CSF nucleated cells (10⁶/L)      | 16.31 ± 20.16       | 11.68 ± 17.15            | 0.223   |
| WBC (10⁹/L)                      | 8.37 ± 3.10         | 7.97 ± 2.82              | 0.512   |
| Neutrophils (10⁹/L)              | 5.55 ± 2.97         | 5.41 ± 2.63              | 0.810   |
| Lymphocyte (10⁹/L)               | 1.89 ± 0.55         | 1.75 ± 0.59              | 0.237   |
| NLR                              | 3.40 ± 2.79         | 3.48 ± 2.20              | 0.869   |
| RBC (10⁹²/L)                     | 4.04 ± 1.54         | 3.88 ± 0.69              | 0.407   |
| HGB (g/L)                        | 112.88 ± 15.44      | 114.71 ± 18.15           | 0.631   |
| PLT (10⁹/L)                      | 276.31 ± 68.61      | 280.92 ± 102.98          | 0.827   |
| PLR                              | 160.46 ± 69.01      | 184.02 ± 105.17          | 0.275   |
| PT(s)                            | 11.64 ± 1.24        | 11.40±1.26               | 0.374   |
| INR                              | 1.01 ± 0.11         | 0.99 ± 0.11              | 0.382   |
| Fib (g/L)                        | 4.88 ± 7.40         | 3.67 ± 1.60              | 0.416   |
| Potassium (mmol/L)               | 3.85 ± 0.42         | 3.81 ± 0.43              | 0.680   |
| Sodium (mmol/L)                  | 136.68 ± 5.19       | 138.34 ± 5.30            | 0.144   |
| Calcium (mmol/L)                 | 2.23 ± 0.12         | 2.22 ± 0.17              | 0.796   |
| Blood glucose (mmol/L)           | 5.92 ± 1.45         | 6.17 ± 2.34              | 0.591   |
| SBP (mmHg)                       | 137.46 ± 21.35      | 140.14 ± 24.84           | 0.609   |
| DBP (mmHg)                       | 86.50 ± 13.22       | 85.71 ± 14.08            | 0.791   |
| Hypertension, n (%)              | 10 (38.46)          | 49 (36.84)               | 0.876   |
| Other basic disease, n (%)       | 3 (11.54)           | 16 (12.03)               | 1.000   |
| Smoker, n (%)                    | 7 (26.92)           | 31 (23.31)               | 0.693   |
| Prior Blood transfusion, n (%)   | 6 (23.08)           | 48 (36.09)               | 0.200   |
| Operation time (min)             | 73.46 ± 34.58       | 74.35 ± 26.86            | 0.883   |
Location of VP shunt, n (%)  

| Location       | n   | %   |
|----------------|-----|-----|
| Frontal        | 23  | (88.46) |
| Occipital      | 3   | (11.54) |

Other VP Complications, n (%)  

| Other Complications | n   | %   |
|---------------------|-----|-----|
| Brain edema around catheter | 15  | (57.69) |

Pre-mRS, n (%)  

| Pre-mRS | n   | %   |
|---------|-----|-----|
| Low     | 8   | (30.77) |
| High    | 18  | (69.23) |

Post-mRS, n (%)  

| Post-mRS | n   | %   |
|----------|-----|-----|
| Low      | 9   | 77  |
| High     | 17  | 55  |

p < 0.05.

AVM: Arteriovenous malformation; CSF: Cerebrospinal fluid; DBP: Diastolic blood pressure; DICH: Delayed intracranial hemorrhage; EVD: External ventricular drain; HGB: Hemoglobin; LP: Lumbar puncture; INR: International normalized ratio; NLR: Neutrophil to lymphocyte ratio; mRS: Modified Rankin Scale; PLR: Platelet to lymphocyte ratio; PLT: Platelet; PT: Prothrombin time; RBC: Red blood cell; SAH: Subarachnoid hemorrhage; SBP: Systolic blood pressure; VP: Ventriculoperitoneal; WBC: White blood cell.

Figure 2 Computed tomography images of the delayed intracranial hemorrhages in our study. A: A postoperative computed tomography (CT) scan showed subdural hematoma in patient 23; B: A CT scan indicated intracranial hematoma along the path of the catheter in patient 7.

DOI: 10.12998/wjcc.v10.i21.7302  Copyright ©The Author(s) 2022.

ticular pathway and cingulum) were damaged by an EVD and were confirmed by diffusion tensor imaging parameters (fractional anisotropy and fiber number) and the configuration of the neural tracts [20,26]. The fractional anisotropy value refers to the degree of directionality of water diffusion and represents white matter organization, including the degree of directionality and integrity of white matter microstructures such as axons, myelins, and microtubules[21,27]. This evidence provides an anatomical mechanism to explain cerebral tissue fragility after EVD. Neural injury supposedly occurred in a considerable number of patients with an EVD history[21]. Notably, a history of craniotomy was considered an independent risk factor for DICH in some previous studies[15,16]. The possible mechanism is that craniotomy could contribute to brain fragility and the adhesive arachnoid with small cerebral vessels, which is prone to bleeding after the insertion of a catheter[15,16]. However, a history of craniotomy did not increase the risk of DICH in our research.

Other variables were not risk factors in our study but had statistical significance in other retrospective studies (Table 5). Guo et al[15] pointed out that advanced age might contribute to the high incidence of DICH because of present complications such as hypertension and cerebral amyloid angiopathy. Coagulation dysfunction, antiplatelet therapy, and the use of LMWH are associated with an increased risk of DICH[14,18,19]. Cerebral amyloid angiopathy was believed to contribute to DICH secondary to
Table 2 Univariate analysis of variable relating to delayed intracranial hemorrhage in ventriculoperitoneal shunt patients

| Variables                                  | DICH group (n = 26) | Non-DICH group (n = 133) | P value |
|--------------------------------------------|---------------------|--------------------------|---------|
| Demographics                               |                     |                          |         |
| Age (yr)                                   | 51.35 ± 12.08       | 53.89 ± 15.17            | 0.420   |
| Male gender, n (%)                         | 17 (65.38)          | 66 (49.62)               | 0.145   |
| Primary clinical diagnosis, n (%)          |                     |                          |         |
| Traumatic brain injury                     | 6 (23.07)           | 43 (17.29)               |         |
| Intracranial hemorrhage                    | 5 (19.23)           | 30 (22.56)               |         |
| SAH (aneurysm rupture)                     | 10 (38.46)          | 29 (21.80)               |         |
| SAH (AVM rupture)                          | 0 (0)               | 0 (0)                    |         |
| Cerebral infarction                        | 0 (0)               | 0 (0)                    |         |
| Tumor                                      | 2 (7.69)            | 8 (6.02)                 |         |
| Infection                                  | 0 (0)               | 4 (3.01)                 |         |
| Primary hydrocephalus                      | 3 (11.54)           | 19 (14.29)               |         |
| Pre-Craniotomy, n (%)                      | 9 (34.62)           | 56 (42.11)               | 0.479   |
| Pre-Decompression, n (%)                   | 8 (30.77)           | 50 (37.59)               | 0.510   |
| Pre-EVD, n (%)                             | 16 (61.54)          | 42 (31.58)               | 0.005*  |
| Pre-Cranioplasty, n (%)                    | 2 (7.69)            | 23 (17.29)               | 0.233   |
| LP pressure (mmH2O)                        | 141.54 ± 60.94      | 139.42 ± 64.94           | 0.877   |
| CSF protein (g/L)                          | 0.56 ± 0.46         | 0.64 ± 0.60              | 0.509   |
| CSF glucose (mmol/L)                       | 3.87 ± 1.45         | 3.88 ± 1.35              | 0.980   |
| CSF nucleated cells (10^6/L)               | 16.31 ± 20.16       | 11.68 ± 17.15            | 0.229   |
| WBC (10^9/L)                               | 8.37 ± 3.10         | 7.97 ± 2.82              | 0.510   |
| Neutrophils (10^9/L)                       | 5.55 ± 2.97         | 5.41 ± 2.63              | 0.808   |
| Lymphocyte (10^9/L)                        | 1.89 ± 0.55         | 1.75 ± 0.59              | 0.237   |
| NLR                                        | 3.40 ± 2.79         | 3.48 ± 2.20              | 0.868   |
| RBC (10^12/L)                              | 4.04 ± 1.54         | 3.88 ± 0.69              | 0.415   |
| HCB (g/L)                                  | 112.88 ± 15.44      | 114.71 ± 18.15           | 0.629   |
| PLT (10^9/L)                               | 276.31 ± 68.61      | 280.92 ± 102.97          | 0.826   |
| PLR                                        | 160.46 ± 69.01      | 184.02 ± 105.17          | 0.276   |
| PT(s)                                      | 11.64 ± 1.24        | 11.40 ± 1.26             | 0.373   |
| INR                                        | 1.01 ± 0.11         | 0.99 ± 0.11              | 0.381   |
| Fib (g/L)                                  | 4.88 ± 7.40         | 3.67 ± 1.60              | 0.183   |
| Potassium (mmol/L)                         | 3.85 ± 0.42         | 3.81 ± 0.43              | 0.678   |
| Sodium (mmol/L)                            | 136.68 ± 5.19       | 138.34 ± 5.30            | 0.145   |
| Calcium (mmol/L)                           | 2.23 ± 0.12         | 2.2238 ± 0.17            | 0.795   |
| Blood glucose (mmol/L)                     | 5.92 ± 1.45         | 6.17 ± 2.34              | 0.589   |
| SBP (mmHg)                                 | 137.46 ± 21.35      | 140.14 ± 24.84           | 0.607   |
| DBP (mmHg)                                 | 86.50 ± 13.22       | 85.71 ± 14.08            | 0.790   |
| Hypertension, n (%)                        | 10 (38.46)          | 49 (36.84)               | 0.876   |
| Other basic disease, n (%)                 | 5 (19.23)           | 16 (12.03)               | 0.944   |
| Smoker, n (%)                              | 7 (26.92)           | 31 (23.31)               | 0.693   |
| Prior Blood transfusion, n (%)             | 6 (23.08)           | 48 (36.09)               | 0.205   |
### Table 3 Multivariate analysis of variable relating to delayed intracranial hemorrhage in ventriculoperitoneal shunt patients

| Variable                  | P value | OR    | 95%CI          |
|---------------------------|---------|-------|----------------|
| Age (yr)                  | 0.162   | 0.975 | 0.942-1.010    |
| Pre-Craniotomy            | 0.548   | 0.723 | 0.250-2.085    |
| Pre-EVD                   | 0.045   | 2.814 | 1.024-7.730    |
| PT(s)                     | 0.224   | 1.268 | 0.865-1.859    |
| Location of VP shunt      | 0.153   | 2.775 | 0.685-11.249   |
| Brain edema around catheter | 0.000 | 8.397 | 3.043-23.171   |

CI: Confidence interval; EVD: External ventricular drain; OR: Odds ratio; PT: Prothrombin time; VP: Ventriculoperitoneal.

VP shunt in elderly patients in Wang et al's research. The discrepancy might be related to the inclusion and exclusion criteria in our study[28]. We included patients aged 18-75 years and excluded patients with coagulation dysfunction to control for confounders and achieve a balanced baseline.

In contrast to the preoperative mRS scores, the postoperative mRS scores for both the DICH group and the non-DICH group were significant in the statistical analysis in our study. Sixty-five percent of DICH patients were involved in the higher postoperative mRS group, which was higher than that of non-DICH patients (41%). This indicates that VP shunt patients with DICH might have worse clinical outcomes. DICH may contribute to severe neurological function deterioration and secondary surgical intervention should be performed in patients with large volume hematoma and intractable intracranial pressure. The average hematoma volume of DICH is 10.92 mL. Only 2 patients with hematomas exceeding 50 mL in volume in our study underwent surgery, and the other 24 patients received conservative treatment. Most DICH patients treated conservatively are asymptomatic due to the low hematoma volume. These observations collectively demonstrate that DICH increases the length of hospital stay and is related to poor clinical outcomes.

Several limitations should be noted in the present study. First, this was a retrospective study that used a multivariate analysis to minimize bias in patient selection. Some confounders mentioned in other studies, such as manipulation of the valve system and same-sided approach as EVD, were not recorded. Second, the low statistical power (0.63) and the small sample size in our study may overestimate the effect measure. The low statistical power increases the likelihood of a false positive result. The small sample was solely comprised of Chinese individuals in a single center. The number of DICH patients was much smaller than that of the non-DICH group. Logistic regression overestimates the OR in studies with small to moderate sample sizes[29]. More samples from different populations and centers should be included in future studies. Third, the follow-up evaluation needs to be replaced by a more objective method to verify the prognosis.
Table 4 Summary of 26 patients with delayed intracranial hemorrhage after ventriculoperitoneal shunt

| No. | Age/sex | Primary intracranial lesion | History of EVD | Location of VP shunt | DICH type | Onsetday | Treatment | Pre-mRS | Post-mRS |
|-----|---------|------------------------------|----------------|---------------------|-----------|----------|-----------|---------|----------|
| 1   | 50/F    | Aneurysm                     | Y              | Frontal             | IVH       | 2        | Conservative | 1       | 1        |
| 2   | 67/M    | ICH                           | Y              | Frontal             | ICH around catheter | 3        | Conservative | 3       | 1        |
| 3   | 64/M    | Aneurysm                     | Y              | Frontal             | IVH       | 1        | Conservative | 1       | 1        |
| 4   | 37/F    | Tumor                        | N              | Occipital           | ICH around catheter | 11       | Conservative | 5       | 4        |
| 5   | 56/M    | TBI                           | Y              | Frontal             | ICH around catheter | 3        | Conservative | 5       | 5        |
| 6   | 23/M    | TBI                           | N              | Frontal             | ICH around catheter | 4        | Conservative | 5       | 5        |
| 7   | 63/F    | Aneurysm                     | N              | Frontal             | ICH around catheter | 7        | Surgery     | 4       | 5        |
| 8   | 54/M    | Aneurysm                     | Y              | Frontal             | ICH around catheter | 3        | Conservative | 5       | 5        |
| 9   | 61/M    | Aneurysm                     | Y              | Occipital           | ICH around catheter | 5        | Conservative | 2       | 1        |
| 10  | 47/M    | ICH                           | Y              | Frontal             | ICH around catheter | 7        | Conservative | 5       | 5        |
| 11  | 58/M    | Aneurysm                     | Y              | Frontal             | IVH       | 7        | Conservative | 2       | 2        |
| 12  | 51/F    | Aneurysm                     | N              | Frontal             | ICH around catheter | 3        | Conservative | 1       | 1        |
| 13  | 58/M    | Tumor                        | N              | Frontal             | ICH around catheter | 2        | Conservative | 5       | 5        |
| 14  | 58/F    | Primary hydrocephalus        | N              | Frontal             | Subdural hematoma | 7        | Conservative | 5       | 5        |
| 15  | 47/M    | Primary hydrocephalus        | N              | Frontal             | ICH around catheter | 5        | Conservative | 4       | 4        |
| 16  | 53/M    | TBI                           | Y              | Frontal             | IVH       | 2        | Conservative | 5       | 3        |
| 17  | 42/M    | Aneurysm                     | Y              | Frontal             | ICH around catheter | 9        | Conservative | 5       | 5        |
| 18  | 32/M    | Aneurysm                     | Y              | Occipital           | IVH       | 1        | Conservative | 2       | 2        |
| 19  | 45/M    | TBI                           | Y              | Frontal             | ICH around catheter | 1        | Conservative | 5       | 5        |
| 20  | 62/M    | ICH                           | Y              | Frontal             | Subdural hematoma | 2        | Conservative | 5       | 5        |
| 21  | 47/F    | TBI                           | Y              | Frontal             | ICH around catheter | 2        | Conservative | 4       | 4        |
| 22  | 56/M    | ICH                           | N              | Frontal             | IVH       | 7        | Conservative | 5       | 4        |
| 23  | 47/M    | ICH                           | N              | Frontal             | Subdural hematoma | 4        | Surgery     | 5       | 5        |
| 24  | 26/F    | Primary hydrocephalus        | Y              | Frontal             | IVH       | 8        | Conservative | 2       | 2        |
| 25  | 72/F    | Aneurysm                     | Y              | Frontal             | IVH       | 1        | Conservative | 1       | 1        |
| 26  | 59/F    | TBI                           | N              | Frontal             | IVH       | 1        | Conservative | 5       | 5        |

EVD: External ventricular drain; F: Female; ICH: Intracranial hemorrhage; IVH: Intraventricular hemorrhage; M: Male; mRS: Modified Rankin Scale; N: No; TBI: Traumatic brain injury; VP: Ventriculoperitoneal; Y: Yes.

CONCLUSION

In summary, the incidence of DICH would be more accurate with careful surveillance that includes
Table 5 Summary of the previous studies of delayed intracranial hemorrhage after ventriculoperitoneal shunt

| Ref.          | Year | DICH | Non-DICH | Number of variables | Proposed risk factors                                                                                     |
|---------------|------|------|----------|--------------------|----------------------------------------------------------------------------------------------------------|
| Hudson et al  | 2018 | 8    | 72       | 10                 | DAPT ($P = 0.0001$, OR = 31.23, 95%CI: 2.98-327.32)                                                      |
| Guo et al     | 2017 | 20   | 512      | 8                  | Advanced age ($P = 0.027$, OR = 1.048, 95%CI: 1.005-1.092), craniotomy history ($P = 0.025$, OR = 3.874, 95%CI: 1.183-12.693), brain edema around the catheter ($P < 0.001$, OR = 9.056, 95%CI: 3.194-25.675) |
| Gong et al    | 2017 | 12   | 742      | 9                  | Age ≥ 60 yr ($P = 0.0008$), prior craniotomy operation ($P = 0.0001$) and manipulation of the valve system ($P = 0.0017$) |
| Qian et al    | 2017 | 11   | 140      | 18                 | Postoperative LMWH therapy ($P = 0.026$, relative ratio = 4.8, 95%CI: 1.4-17.1)                           |
| Jang et al    | 2018 | 34   | 104      | 9                  | Old age ($P = 0.037$) and delayed PTT ($P = 0.032$)                                                      |
| Li et al      | 2021 | 29   | 101      | 21                 | Elevated NLRR ($P < 0.001$, OR = 2.792, 95%CI: 1.747-4.460); history of craniotomy ($P = 0.010$, OR = 3.394, 95%CI: 1.060-10.869) |

DAPT: Dual antiplatelet therapy; NLRR: A ratio of postoperative neutrophil-to-lymphocyte ratio to preoperative neutrophil-to-lymphocyte ratio; LMWH: Low-molecular-weight heparin; OR: Odds ratio; PTT: Partial thromboplastin time; DICH: Delayed intracranial hemorrhage.

imaging and unified standards. Our results indicate that a history of EVD and postoperative brain edema around the catheter are associated with a high risk of DICH in VP shunt patients. DICH patients with a high mRS score are vulnerable to poor clinical outcomes.

ARTICLE HIGHLIGHTS

Research background
Delayed intracranial hemorrhage (DICH), one of the high mortality complications in ventriculoperitoneal (VP) shunt patients, has not been fully recognized.

Research motivation
To explore the risk factors of delay intracranial hemorrhage and reduce the incidence of this complication in VP shunt patients.

Research objectives
To explore the potential risk factors and mechanisms of delay intracranial hemorrhage in VP shunt patients.

Research methods
We collected the demographic and clinical characteristics data of VP shunt patients between January 2016 and December 2020. DICH group and Non-DICH group were compared in a retrospective study.

Research results
A history of an external ventricular drain and postoperative brain edema around the catheter were related to a high risk for DICH statistically. There was a significant difference in the postoperative modified Rankin Scale scores at the 3-mo follow-up in these two groups.

Research conclusions
A history of an EVD and postoperative brain edema around the catheter were risk factors of DICH VP shunt patients. DICH patients are vulnerable to poor clinical outcomes with a high mRS score.

Research perspectives
More samples from different populations and centers should be included in future studies. The follow-up evaluation needs to be replaced by a more objective method to verify the prognosis.
FOOTNOTES

Author contributions: Chen JC was considered as first author; Chen JC, Xue ZB, Yang SY, Li Y, Lai RL and Tan DH participated in the patient treatment; Chen JC, Xue ZB and Yang SY collected the clinical data and performed the literature; Chen JC and Duan SX wrote the manuscript; Tan DH helped to design and revise the paper.

Supported by Shantou Medical Healthcare Science and Technology Program, No. [mant]-[70]; Natural Science Foundation of Guangdong Province of China, No. 2022A155010407; and Guangdong Provincial Science and Technology Fund ("major special project + Task list") for high-level hospital construction, No. STKJ2021119.

Institutional review board statement: This retrospective study was reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Shantou University Medical College, No. 2019034.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Jun-Chen Chen 0000-0001-9922-1986; Shou-Xing Duan 0000-0002-3539-6741; Ze-Bin Xue 0000-0002-2171-7743; Sen-Yuan Yang 0000-0002-8968-2874; Yong Li 0000-0002-6640-883X; Run-Long Lai 0000-0002-5656-2358; Dian-Hui Tan 0000-0002-5624-3170.

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES

1 Katiyar V, Sharma R, Tandon V, Garg K, Narwal P, Chandra PS, Suri A, Kale SS. Comparison of Programmable and Non-Programmable Shunts for Normal Pressure Hydrocephalus: A Meta-Analysis and Trial Sequential Analysis. *Neuro India* 2021; 69: S413-S419 [PMID: 35102997 DOI: 10.4103/0028-3886.332277]

2 Mallucci CL, Jenkinson MD, Conroy EJ, Hartley JC, Brown M, Dalton J, Kearns T, Moitt T, Griffiths MJ, Culeddu G, Solomon T, Hughes D, Gamble C. BASICS Study collaborators. Antibiotic or silver vs standard ventriculoperitoneal shunts (BASICS): a multicentre, single-blind, randomised trial and economic evaluation. *Lancet* 2019; 394: 1530-1539 [PMID: 31228346 DOI: 10.1016/S0140-6736(19)31603-4]

3 Reddy GK, Bollam P, Caldito G. Long-term outcomes of ventriculoperitoneal shunt surgery in patients with hydrocephalus. *World Neurosurg* 2014; 81: 404-410 [PMID: 23380280 DOI: 10.1016/j.wneu.2013.01.096]

4 Sun T, Cui W, Yang J, Yuan Y, Li X, Yu H, Zhou Y, You C, Guan J. Shunting outcomes in communicating hydrocephalus: protocol for a multicentre, open-label, randomised controlled trial. *BMJ Open* 2021; 11: e051127 [PMID: 34446499 DOI: 10.1136/bmjopen-2021-051127]

5 Wu Y, Green NL, Wrensch MR, Zhao S, Gupta N. Ventriculoperitoneal shunt complications in California: 1990 to 2000. *Neurosurgery* 2007; 61: 557-62; discussion 562 [PMID: 17881969 DOI: 10.1227/01.NEU.0000290903.07943.AF]

6 Li S, Wang H, Li F, Chen M, Chen P. A new inflammatory parameter can predict delayed intracranial hemorrhage following ventriculoperitoneal shunt. *Sci Rep* 2021; 11: 13763 [PMID: 34215820 DOI: 10.1038/s41598-021-93315-4]

7 Matsumura A, Shinohara A, Munekata K, Maki Y. Delayed intracerebral hemorrhage after ventriculoperitoneal shunt. *Surg Neurol* 1985; 24: 503-506 [PMID: 4049225]

8 Gold MM, Shiffert K, Valdberg S, Lombard J, Lipton ML. Brain injury due to ventricular shunt placement delineated by diffusion tensor imaging (DTI) tractography. *Neurologist* 2008; 14: 252-254 [PMID: 18617852 DOI: 10.1097/NRL.0b013e31816b73e4]

9 Musali SR, Manne S, Beniwai HK, Butkuri N, Gollapudi PR, Nandigama PK. Delayed Intracerebral Hemorrhage after Placement of a Ventriculoperitoneal Shunt in a Case of Hydrocephalus: A Rare Case Report and Review of Literature. *J Neurosci Rural Pract* 2019; 10: 533-536 [PMID: 31595129 DOI: 10.1055/s-0039-1697769]

10 Ma L, Chen YL, Yang SX, Wang YR. Delayed Intracerebral Hemorrhage Secondary to Ventriculoperitoneal Shunt: A Case Report and Literature Review. *Medicine (Baltimore)* 2015; 94: e2029 [PMID: 26632700 DOI: 10.1097/MD.0000000000002029]

11 Couilhaly O, Dama M, Diálo O, Li G, Sogoba Y, Kanikomo D. Delayed intracerebral and subdural hematomas after
ventriculo-peritoneal shunt in a child: A case report and review of the literature. *Neurochirurgie* 2016; 62: 105-107 [PMID: 27133380 DOI: 10.1016/j.neuchi.2016.01.003]

12 Alcázar L, Alfaro R, Tamait M, Gómez-Angulo JC, Ortega JM, Aragonés P, Jere P, Salazar F, del Pozo JM. Delayed intracerebral hemorrhage after ventriculoperitoneal shunt insertion. Case report and literature review. *Neurochirurgia (Astr)* 2007; 18: 128-133 [PMID: 17497059]

13 Zhou F, Liu Q, Ying G, Zhu X. Delayed intracerebral hemorrhage secondary to ventriculoperitoneal shunt: two case reports and a literature review. *Int J Med Sci* 2012; 9: 65-67 [PMID: 22219712]

14 Qian Z, Gao L, Wang K, Pandey S. Delayed Catheter-Related Intracranial Hemorrhage After a Ventriculoperitoneal or Ventriculoatrial Shunt in Hydrocephalus. *World Neurosurg* 2017; 107: 846-851 [PMID: 28847553 DOI: 10.1016/j.wneu.2017.08.098]

15 Guo L, Chen X, Yu B, Shen L, Zhang X. Delayed Intracerebral Hemorrhage Secondary to Ventriculoperitoneal Shunt: A Retrospective Study. *World Neurosurg.* 2017; 107: 160-167 [PMID: 28765020 DOI: 10.1016/j.wneu.2017.07.133]

16 Gong W, Xu L, Yang P, Yu Z, Wang Z, Chen G, Zhang S, Wu J. Characteristics of delayed intracerebral hemorrhage after ventriculoperitoneal shunt insertion. *Oncotarget* 2017; 8: 42693-42699 [PMID: 28496010 DOI: 10.18632/oncotarget.17444]

17 Jang SY, Kim CH, Cheong JH, Kim JM. Risk Factors of Delayed Intracerebral Hemorrhage Following Ventriculoperitoneal Shunt. *Korean J Neurotrauma* 2018; 14: 112-117 [PMID: 30402428 DOI: 10.13004/kjnt.2018.14.2.112]

18 Hudson JS, Nagahama Y, Nakagawa D, Starke RM, Dlouhy BJ, Torner JC, Jabbour P, Allan L, Derdeyn CP, Greenlee JDW, Hasan D. Hemorrhage associated with ventriculoperitoneal shunt placement in aneurysmal subarachnoid hemorrhage patients on a regimen of dual antiplatelet therapy: a retrospective analysis. *J Neurosurg* 2018; 129: 916-921 [PMID: 29125410 DOI: 10.3171/2017.5.JNS17642]

19 Calayag M, Paul AR, Adamo MA. Intraventricular hemorrhage after ventriculoperitoneal shunt revision: a retrospective review. *J Neurosurg Pediatr* 2015; 16: 42-45 [PMID: 25860981 DOI: 10.3171/2014.11.PEDS14246]

20 Kwon YM, Jang SH. Neural injury by frontal approach of external ventricular drainage in stroke patients. *Int J Neurosci* 2015; 125: 742-746 [PMID: 26000521 DOI: 10.3109/00207454.2015.1012665]

21 Misaki K, Uchiyama N, Hayashi Y, Hamada J. Intracerebral hemorrhage secondary to ventriculoperitoneal shunt insertion—four case reports. *Neur Med Chir (Tokyo)* 2010; 50: 76-79 [PMID: 2098034]

22 Maivridis IN, Mitropoulos A, Mantas C, Karagianni A, Vlachos K. Delayed Intraventricular Hemorrhage following a Ventriculoperitoneal Shunt Placement: Exploring the Surgical Anatomy of a Rare Complication. *Resp Med* 2017; 128-133 [PMID: 20098034]

23 Imaiuzumi T, Homma T, Horita Y, Kawamura M, Kohama I, Miyata K, Niyoi KS, Niwa J. The number of microbleeds on gradient T2*-weighted magnetic resonance image at the onset of intracerebral hemorrhage. *J Stroke Cerebrovasc Dis* 2008; 17: 30-34 [PMID: 18190819 DOI: 10.1016/j.jstrokecerebrovasdis.2007.11.001]

24 Kikuta K, Takagi Y, Nozaki K, Okada T, Hashimoto N. Histological analysis of microbleed after surgical resection in a patient with moyamoya disease. *Neur Med Chir (Tokyo)* 2007; 47: 564-567 [PMID: 18191942 DOI: 10.2176/nmc.47.564]

25 Naka H, Nomura E, Takahashi T, Wakabayashi S, Mimori Y, Kajikawa H, Kohriyama T, Matsumoto M. Combinations of the presence or absence of cerebral microbleeds and advanced white matter hyperintensity as predictors of subsequent stroke types. *AJNR Am J Neuroradiol* 2006; 27: 830-835 [PMID: 16617773]

26 Kwon HG, Jang SH. Cingulum injury by external ventricular drainage procedure: diffusion tensor tractography study. *Clin Neuroradiol* 2015; 25: 65-67 [PMID: 24221532 DOI: 10.1007/s00062-013-0269-z]

27 Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. *J Mol Neurosci* 2008; 34: 51-61 [PMID: 18157658 DOI: 10.1007/s12031-007-0029-0]

28 Wang XT, Zhang LY, Lv HT, Liu J, Xu YH. Delayed intracerebral hemorrhage after ventriculo-peritoneal shunt procedure: two case reports and a review of literature. *Eur Rev Med Pharmacol Sci* 2021; 25: 6093-6100 [PMID: 34661269 DOI: 10.26355/eurev_202110_26887]

29 Nemes S, Jonasson JM, Genell A, Steineck G. Bias in odds ratios by logistic regression modelling and sample size. *BMC Med Res Methodol* 2009; 9: 56 [PMID: 19635144 DOI: 10.1186/1471-2288-9-56]
