REVIEW

Risk Factors for External Ventricular Drainage–Related Infection

A Systematic Review and Meta-analysis

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Abstract

Background and Objectives

External ventricular drainage (EVD) is one of the most commonly performed neurosurgical procedures, but EVD-related infection constitutes a significant health concern. Yet, little consensus identifies the risk factors for the development of EVD-related infection. Therefore, we performed a meta-analysis to systematically summarize existing evidence on the incidence and risk factors for EVD-related infection.

Methods

PubMed, Embase, and the Cochrane Library databases from database inception to February 28, 2022, were searched for all studies investigating the incidence and risk factors for EVD-related infection. Data were assessed by R-4.2.0 software. The meta-analysis was used to calculate pooled odds ratios (OR) and 95% confidence intervals (CI).

Results

A total of 48 studies were included. Among the 29 factors analyzed, statistically significant risk factors were subarachnoid hemorrhage(SAH)/intraventricular hemorrhage(IVH) (OR = 1.48, 95% CI = 1.20–1.82, $p < 0.001$), concomitant systemic infection (OR = 1.90, 95% CI = 1.34–2.70, $p < 0.001$), other neurosurgical procedures (OR = 1.76, 95% CI = 1.02–3.04, $p = 0.041$), change of catheter (OR = 5.05, 95% CI = 3.67–6.96, $p < 0.001$), bilateral EVDs (OR = 2.25, 95% CI = 1.03–4.89, $p = 0.041$), (cerebrospinal fluid) CSF leak (OR = 3.19, 95% CI = 2.12–4.81, $p < 0.001$) and duration of EVD >7 days (OR = 4.62, 95% CI = 2.26–9.43, $p < 0.001$). The use of silver-coated catheters (OR = 0.57, 95% CI = 0.38–0.87, $p = 0.008$) and antibiotic-impregnated catheters (OR = 0.60, 95% CI = 0.41–0.88, $p = 0.009$) might help reduce the risk of infection. No significant difference was indicated in studies evaluating factors like diabetes mellitus (OR = 1.25, 95% CI = 0.90–1.75, $p = 0.178$), steroids used (OR = 1.52, 95% CI = 0.96–2.4, $p = 0.074$), prophylactic antibiotics(OR = 0.87, 95% CI = 0.66–1.14, $p = 0.308$).

Discussion

The meta-analysis of various relevant factors in the onset of EVD-related infection in patients submitted to EVD enabled us to establish a more probable profile of the patients who are more likely to develop it during the treatment.

External ventricular drainage (EVD) is one of the most commonly performed neurosurgical procedures for monitoring intracranial pressure and temporarily diverting CSF.[1] EVD placement can be a lifesaving procedure in patients with neurologic decline caused by subarachnoid hemorrhage (SAH), intraventricular hemorrhage (IVH), intraparenchymal hemorrhage (IPH),

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traumatic brain injury (TBI), intracranial infection, brain tumor, or shunt failure.[2-4] As the "gold standard" among the array of methods used to monitor intracranial pressure, the number of EVD placements has increased.[5-7] However, there are concerns regarding the high rate of complications such as malposition, hemorrhage, and, the most common, EVD-related infections.[5,8-12] The incidence of EVD-related infections, including meningitis and ventriculitis, varies from <5% to 20% depending on the criteria of diagnosis.[13] EVD-related infections lead to prolonged hospital stay, increased costs, and higher mortality.[14] Thus, it is essential to identify the risk and associated factors of these infections to develop preventive interventions.

EVD-related infections may arise from catheter colonization by inoculation of skin flora during insertion or manipulation of the drainage system during the postoperative period.[15] Therefore, risk factors believed to be associated with EVD-related infection include previous craniotomy, systemic infection, duration of EVD, catheter irrigation, site leaks, and frequency of CSF sampling.[16] However, most of these factors have not been carefully adjusted. To inform the creation of evidence-based care bundles, we performed a meta-analysis to identify the real risk factors.

Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. As our study was based on published data, ethical approval or patient consent was not required. In addition, only studies that reported ethical approval or patient consent were included in the meta-analysis.

Search Strategy

Two investigators performed a systematic study search using keywords "External ventricular drainage," "External ventricular drain," "EVD," "infection," "infestation," and all related free search terms in PubMed, Embase, and the Cochrane Library databases from database inception to February 28, 2022. To avoid omissions, we manually searched the reference lists of all the relevant articles.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) study type: observational and interventional studies; (2) population: patients older than 18 years; (3) articles had to have a case-control, longitudinal, or case-crossover design; (4) studies mentioning a specific definition of EVD-related infection; and (5) studies reporting crude or adjusted effect estimates with corresponding 95% confidence intervals (CIs) or results that allowed the calculation of risk ratios (RRs) or odds ratios (ORs).

The exclusion criteria were as follows: (1) unavailability of sufficient data that are studied in this meta-analysis; (2) unclear definition of EVD-related infection; (3) reviews, letters, meeting abstracts, supplements, and case reports; and (3) studies not differentiating EVD from lumbar drainage (LD).

Data Extraction

Two investigators extracted the following data from the included studies: first author, year, country, sample size, study design, patient demographics, and the presence of risk factors. They recorded the data using a dedicated data extraction form.

Quality Assessment

We evaluated the quality of cohort studies according to the Newcastle-Ottawa Scale (NOS), which is a commonly used tool to assess the quality of observational studies in meta-analyses.[17] We assessed each study using 8 items categorized into 3 domains: selection of the study groups, comparability of the groups, and ascertainment of either exposure or outcome of interest for cohort studies. Stars (ranging from zero to 9 stars) were assigned to items of good quality.

Statistical Analysis

Data were assessed using R-4.2.0. We obtained ORs with 95% CIs for various risk factors for EVD-related infections. ORs greater than 1 indicate an increased risk of infection, whereas ORs less than 1 indicate a decreased risk. We assessed statistical significance using 95% confidence intervals (CIs). If the 95% CI did not include a neutral value of 1, we considered the risk to be statistically significant. Heterogeneity was classified as moderate (I^2 = 25%–50%), substantial (I^2 = 50%–75%), or considerable ($I^2 \geq 75\%$).[18] A random-effect or fixed-effect model was used according to the degree of heterogeneity found.[19] To determine the source of heterogeneity and assess the influence of each study on the final results, we excluded 1 study in sequence through a sensitivity analysis. Considering the extensive placement of antibiotic-impregnated catheters, a subgroup analysis was performed to investigate the stability of the consolidated results. Based on the study design, the subgroups were classified as observational studies and randomized control trials (RCTs).

Results

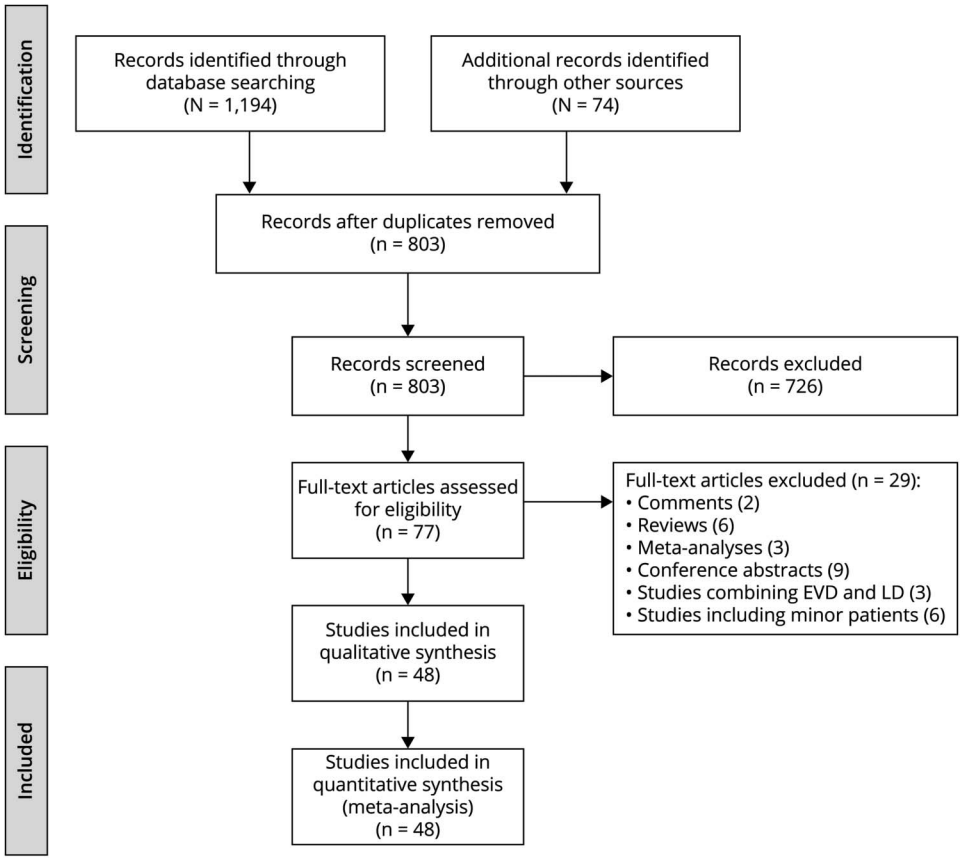
Study Selection

A total of 1268 articles were identified from PubMed, Embase, and Cochrane Library databases. A total of 1192 records were removed because of duplication (465 records) or irrelevance to the study (726 records). Twenty-nine other records were excluded because they were comments (2 records), reviews (6 records), meta-analyses (3 records), conference abstracts (9 records), studies not differentiating EVD and LD (3 records), and studies including minor patients (6 records). Forty-eight studies were included in this meta-analysis. The entire process of study search, selection, and inclusion is presented in Figure 1.

Study Characteristics

The details of the included studies are presented in eTable 1 (links.lww.com/CPJ/A438). The 48 included studies were published between 1986 and 2022.[7,16,20-60,e1-e5] The median

Figure 1 Study Flowchart (as per PRISMA Guideline)



EVD-related infection rate was 10.7% (IQR 7.3%–20.9%), and the median number of patients included was 207 (IQR 119.25–335). Most studies included defined EVD-related infections by considering pathologic CSF findings, microbiology, and clinical signs based on US Centers for Disease Control and Infection/National Healthcare Safety Network (CDC/NHSN) surveillance definitions.[e6]

Quality Assessment

Forty-four studies were evaluated according to the NOS. Thirty-eight studies were assessed as having 3 or more stars for the appraisal of the selection domain in the NOS checklist. Most of the included studies had 1 of 2 stars in the comparability domain. For the outcome domain, 36 studies were appraised as having 3 stars (eTable 2, links.lww.com/CPJ/A438).

Risk and Associated Factors

In total, we analyzed 29 different factors and divided them into 3 categories based on timing, including 17 preoperative factors, 7 intraoperative factors, and 5 postoperative factors. A summary of the results of the meta-analysis is presented in Table.

Preoperative risk factors for EVD-related infection found in our meta-analysis included SAH/IVH (OR = 1.48, 95% CI 1.20–1.82, $p < 0.001$), concomitant systemic infection (OR = 1.90, 95% CI 1.34–2.70, $p < 0.001$), and other neurosurgical procedures (OR = 1.76, 95% CI 1.02–3.04, $p = 0.041$). However, factors including male (OR = 0.98, 95% CI 0.89–1.08, $p = 0.664$), ICH (OR = 0.86, 95% CI 0.66–1.12, $p = 0.249$), brain tumor (OR = 1.11, 95% CI 0.84–1.47, $p = 0.459$), brain trauma (OR = 0.83, 95% CI 0.61–1.13, $p = 0.240$), hydrocephalus (OR = 1.34, 95% CI 0.69–2.60, $p = 0.388$), cerebrovascular accidents (OR = 1.57, 95% CI 0.75–3.28, $p = 0.226$), ischemic stroke (OR = 1.03, 95% CI 0.45–2.33, $p = 0.947$), diabetes mellitus (OR = 1.25, 95% CI 0.90–1.75, $p = 0.178$), steroids used (OR = 1.52, 95% CI 0.96–2.4, $p = 0.074$), nonintracranial tumors (OR = 0.93, 95% CI 0.51–1.70, $p = 0.821$), hypertension (OR = 1.01, 95% CI 0.78–1.32, $p = 0.935$), cardiovascular disease (OR = 0.77, 95% CI 0.37–1.59, $p = 0.473$), Charlson score > 2 (OR = 1.39, 95% CI 0.84–2.30, $p = 0.200$), and Glasgow Coma Scale (GCS) < 9 (OR = 1.16, 95% CI 0.68–1.99, $p = 0.587$) were not significantly associated with infection (eFigures 1–3, links.lww.com/CPJ/A438).

Changes in catheter (OR = 5.05, 95% CI 3.67–6.96, $p < 0.001$), bilateral EVDs (OR = 2.25, 95% CI 1.03–4.89, $p = 0.041$), CSF leak (OR = 3.19, 95% CI 2.12–4.81, $p < 0.001$), and duration of EVD >7 days (OR = 4.62, 95% CI 2.26–9.43, $p < 0.001$) were risk factors during or after the procedures. In addition, the use

Table Summary of Meta-analysis Results

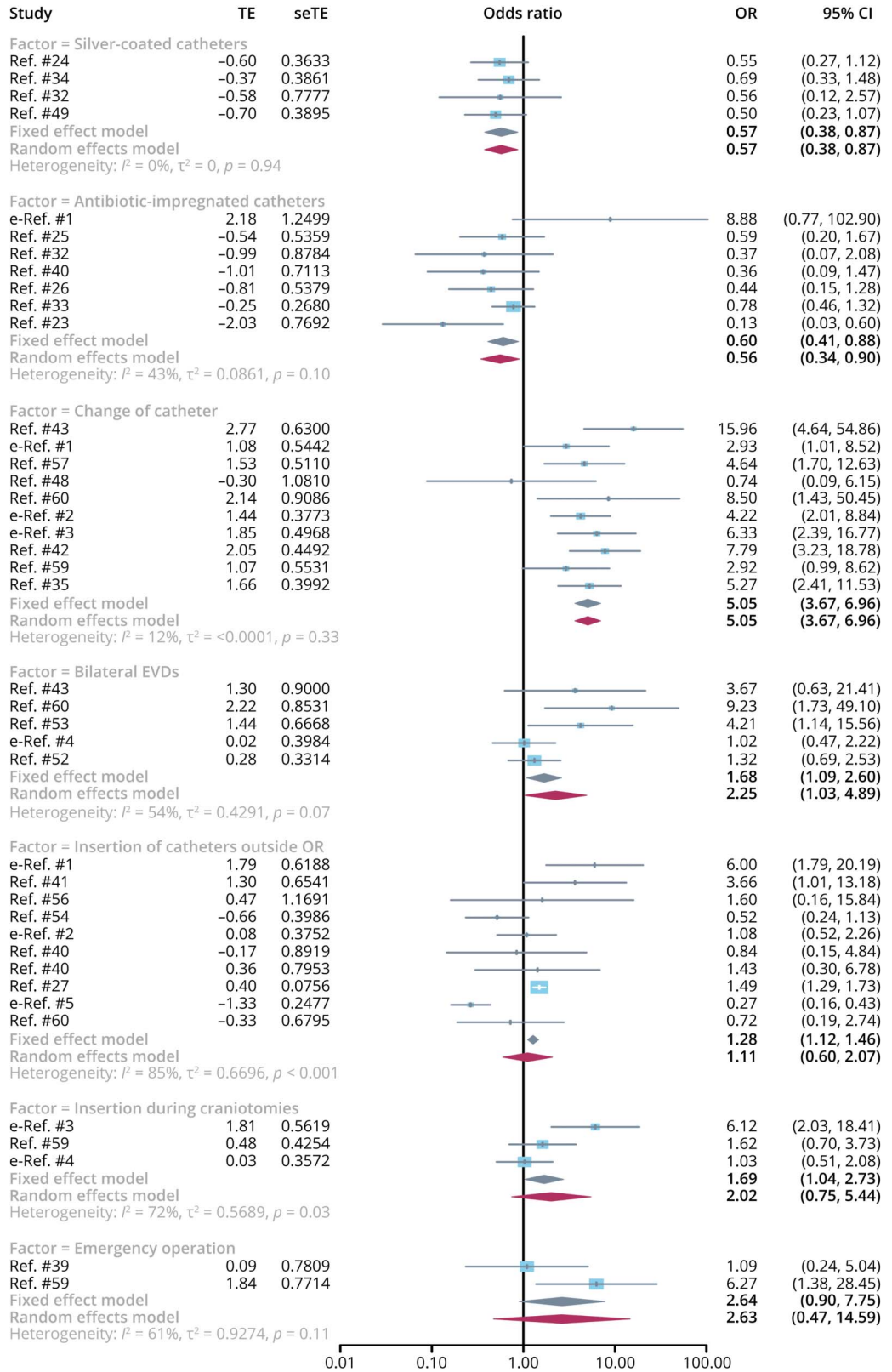
Factors	Number of studies	OR (95% CI)	*p* Value	Methods (I^2)
Preoperative risk factors: admission diagnosis				
SAH/IVH	21	1.48 (1.20–1.82)	<0.001	Fixed (28%)
ICH	14	0.86 (0.66–1.12)	0.249	Fixed (0%)
Brain tumor	17	1.11 (0.84–1.47)	0.459	Fixed (0%)
Brain trauma	15	0.83 (0.61–1.13)	0.240	Fixed (39%)
Hydrocephalus	5	1.34 (0.69–2.60)	0.388	Fixed (23%)
Cerebrovascular accidents	3	1.57 (0.75–3.28)	0.226	Random (51%)
Ischemic stroke	2	1.03 (0.45–2.33)	0.947	Fixed (0%)
Preoperative risk factors: Others				
Male	30	0.98 (0.89–1.08)	0.664	Fixed (15%)
Concomitant systemic infection	6	1.90 (1.34–2.70)	<0.001	Fixed (0%)
Diabetes mellitus	11	1.25 (0.90–1.75)	0.178	Fixed (0%)
Steroids used	7	1.52 (0.96–2.41)	0.074	Fixed (0%)
Nonintracranial tumors	5	0.93 (0.51–1.70)	0.821	Fixed (0%)
Hypertension	5	1.01 (0.78–1.32)	0.935	Fixed (18%)
Cardiovascular disease	3	0.77 (0.37–1.59)	0.473	Fixed (22%)
Other neurosurgical procedures	7	1.76 (1.02,3.04)	0.041	Random (65%)
Charlson score >2	2	1.39 (0.84–2.30)	0.200	Fixed (0%)
GCS <9	3	1.16 (0.68–1.99)	0.587	Fixed (0%)
Intraoperative risk factors				
Silver-coated catheters	4	0.57 (0.38–0.87)	0.008	Fixed (0%)
Antibiotic-impregnated catheters	7	0.60 (0.41–0.88)	0.009	Fixed (43%)
Change of catheter	10	5.05 (3.67–6.96)	0.000	Fixed (12%)
Bilateral EVDs	5	2.25 (1.03–4.89)	0.041	Random (54%)
Insertion of catheters outside the OR	10	1.11 (0.60–2.07)	0.736	Random (85%)
Insertion during craniotomy	3	2.02 (0.75–5.44)	0.166	Random (72%)
Emergency operation	2	2.63 (0.47–14.59)	0.269	Random (61%)
Postoperative risk factors				
CSF leak	8	3.19 (2.12–4.81)	<0.001	Fixed (37%)
Duration of EVD >7 d	3	4.62 (2.26–9.43)	<0.001	Fixed (0.0%)
Prophylactic antibiotics	14	0.87 (0.66–1.14)	0.309	Fixed (24%)
Artificial ventilation	2	1.58 (0.65–3.84)	0.308	Random (67%)
Single room	2	1.95 (0.76–4.97)	0.163	Fixed (0%)

Abbreviation: EVD = external ventricular drainage.

of silver-coated (OR = 0.57, 95% CI 0.38–0.87, p = 0.008) and antibiotic-impregnated (OR = 0.60, 95% CI 0.41–0.88, p = 0.009) catheters might help reduce the risk of infection (Figures 2 and 3).

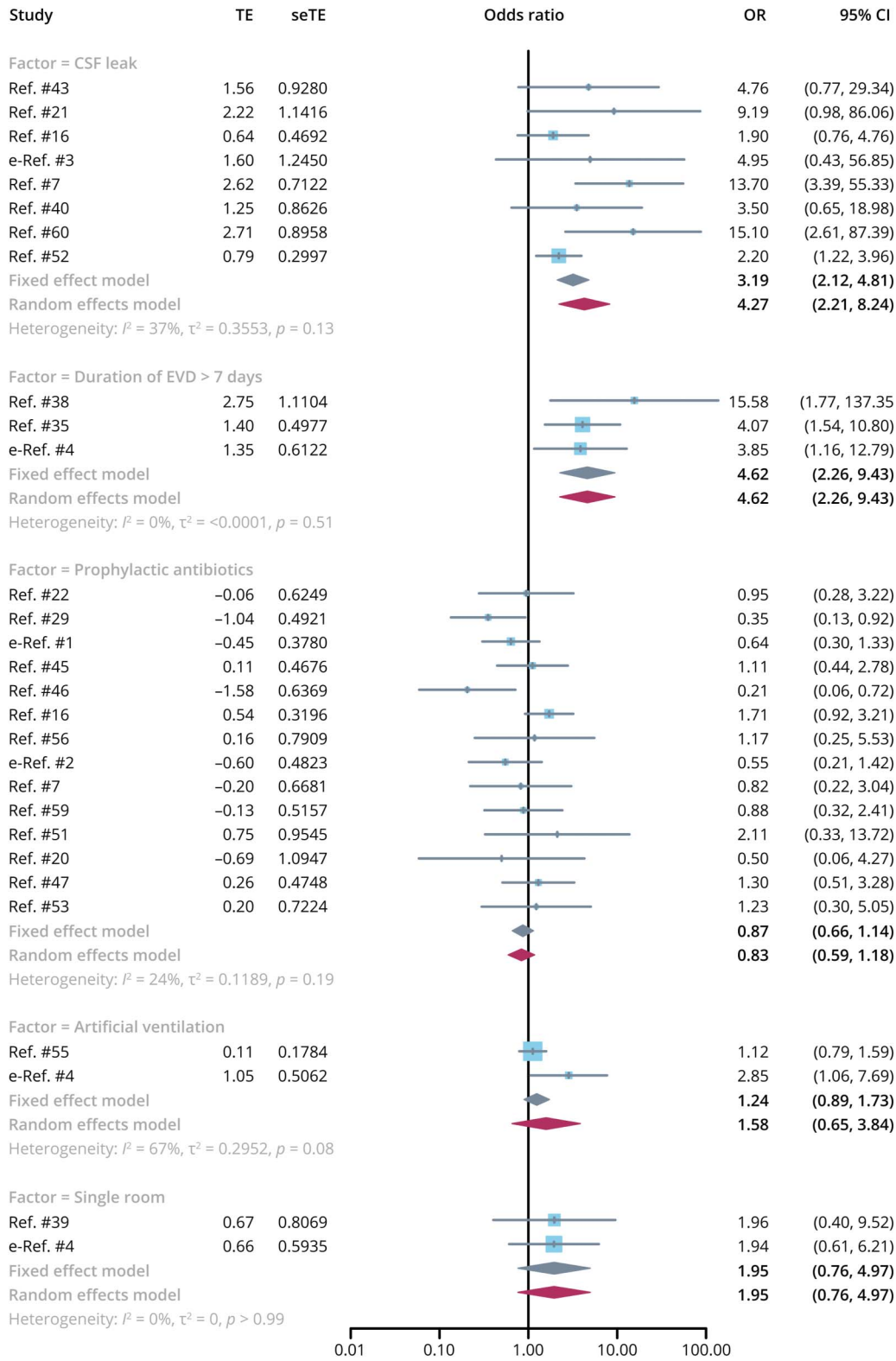
We found no significant relationship between the following factors and EVD-related infection: insertion of catheters outside the OR (OR = 1.11, 95% CI 0.60–2.07, p = 0.736), insertion during craniotomy (OR = 2.02, 95% CI 0.75–5.44, p = 0.166),

Figure 2 Forest Plot Summarizing the Meta-analysis of Studies Reporting Intraoperative Risk and Associated Factors



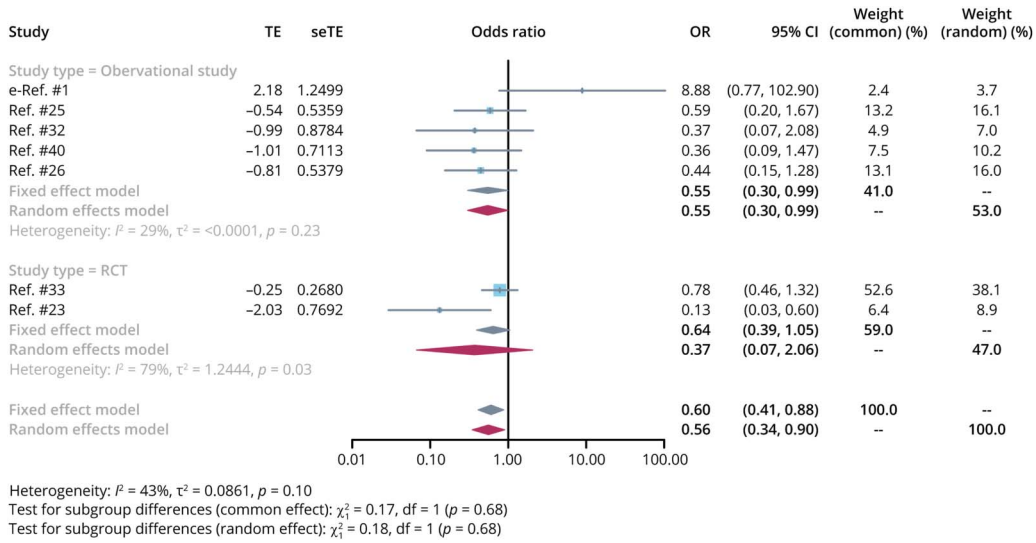
Both fixed-effect and random-effect models were used. Notes: The light gray spots indicate the estimated odds ratio for each study, with the extending lines indicating the estimated 95% CI; the blue square indicates the weights of each study; and the light gray and maroon rhombuses indicate the estimated odds ratio (95% CI) calculated using the fixed-effect model and random-effect model, respectively, for all patients included. Insertion of catheters outside the OR = Insertion of catheters outside the operating room; TE = treatment estimate; seTE = standard error of treatment estimate.

Figure 3 Forest Plot Summarizing the Meta-analysis of Studies Reporting Postoperative Risk and Associated Factors



Both fixed-effect and random-effect models were used. Notes: The light gray spots indicate the estimated odds ratio for each study, with the extending lines indicating the estimated 95% CI; the blue square indicates the weights of each study; and the light gray and maroon rhombuses indicate the estimated odds ratio (95% CI) calculated using the fixed-effect model and random-effect model, respectively, for all patients included. EVD = external ventricular drainage; TE = treatment estimate; seTE = standard error of treatment estimate.

Figure 4 Forest Plot Summarizing the Subgroup Analysis of Studies Reporting the Effect of Antibiotic-Impregnated Catheters on Reduction of EVD-Related Infection Rate



Both fixed-effect and random-effect models were used. Notes: The light gray spots indicate the estimated odds ratio for each study, with the extending lines indicating the estimated 95% CI; the blue square indicates the weights of each study; and the light gray and maroon rhombuses indicate the estimated odds ratio (95% CI) calculated using the fixed-effect model and random-effect model, respectively, for all patients included in each subgroup. EVD = external ventricular drainage; TE = treatment estimate; seTE = standard error of treatment estimate; RCT = randomized control trial.

emergency operation (OR = 2.63, 95% CI 0.47–14.59, p = 0.269), prophylactic antibiotics (OR = 0.87, 95% CI 0.66–1.14, p = 0.308), artificial ventilation (OR = 1.58, 95% CI 0.65–3.84, p = 0.308), and single room (OR = 1.95, 95% CI 0.76–4.97, p = 0.163) (Figures 2 and 3).

The results of "leave-one-out" sensitivity analysis are presented in eFigures 4–32 (links.lww.com/CPJ/A438).

Subgroup Analysis

Finally, we performed a subgroup analysis on the effect of antibiotic-impregnated catheters on the reduction of EVD-related infection rates. Subgroup analysis was performed according to study type. The fixed-effect and random-effect models were applied according to heterogeneity. As shown in Figure 4, we found that the use of antibiotic-impregnated catheters could reduce EVD-related infections, but without statistical significance in RCTs (OR = 0.37, 95% CI 0.07–2.06, p = 0.257). However, observational studies (OR = 0.55, 95% CI 0.30–0.99, p = 0.047) and consolidated results (OR = 0.60, 95% CI 0.41–0.88, p = 0.009) support the use of antibiotic-impregnated catheters.

Study Bias Assessment

The study-wise odds ratio estimates were plotted against their corresponding standard errors (eFigures 33–61, links.lww.com/CPJ/A438). Funnel plot analysis for studies of sex (male) revealed that 2 of 30 studies fell out of the 95% confidence bounds, but there was no funnel plot asymmetry (that is, no systematic relationship between risk ratios and associated study precision). Funnel plot analysis for SAH/IVH (3 of 21 studies), brain trauma (2 of 15 studies), other neurosurgical procedures (1 of 7 studies), bilateral EVDs (1 of 5 studies), insertion of catheters outside the OR (4 of 10 studies), insertion during craniotomy (1 of 3 studies), CSF leak (1 of 8 studies), and prophylactic antibiotics (2 of 14 studies) showed similar results. Funnel plot asymmetry has been found in studies on diabetes mellitus. However, we detected no indication of publication bias using the Duval trim-and-fill method (no new studies added).[e7]

Discussion

Previously, a few meta-analyses have identified risk factors for the development of EVD-related infections. The meta-analysis of various relevant factors in the onset of EVD-related infection in patients who underwent EVD enabled us to establish a more probable profile for patients who are more likely to develop it during treatment. Overall, 7 potential risk factors (SAH/IVH, concomitant systemic infection, other neurosurgical procedures, change of catheter, bilateral EVDs, CSF leak, and duration of EVD >7 days) and 2 protective factors (use of silver-coated and antibiotic-impregnated catheters) were identified. With the change in diagnosis criteria and the stringent placement and maintenance protocols applied, the overall EVD-related infection rate was 2.2%–36.2% in the included studies.

We found that SAH and IVH were associated with a high risk of EVD-related infections. One possible explanation being that intraventricular blood could form a culture medium for bacterial growth. Moreover, the inflammatory response and impaired systemic immunity may contribute to the high

infection rate. In a study by Sweid et al., 45% of patients were diagnosed with subarachnoid hemorrhage and intracerebral hemorrhage, and these patients were often bedridden and immunocompromised.[60] In addition, patients with blood in the CSF had a longer duration of EVD and more manipulations of the drainage system, such as CSF sampling. Infected patients may have other potential risk factors, and further studies are needed to confirm this. By contrast, intracranial hemorrhage, another important indication for EVD, was not associated with a higher rate of EVD-related infections in our study (OR = 0.86, 95% CI 0.66–1.12, $p = 0.249$). This could be attributed to the initial heterogeneous alteration in CSF parameters after ICH or SAH because CSF values might show abnormal results even in the absence of an EVD-associated infection.[e2] However, ICH may extend into intraventricular areas, denoted as IVH; it happens in 40%–60% of patients with ICH and is associated with complications and poor outcomes.[e8–e10] Therefore, there was also a possibility that the different results between EVD/IVH and ICH were due to the fact that some studies might categorize patients with ICH with SAH/IVH extension as having SAH/IVH. However, detailed classification criteria were not provided for most of the included studies. Thus, more attention should be paid to patients with ICH who have a potential risk of hemorrhage expansion.

Several studies have found a trend toward the development of EVD-related infections in patients with concomitant systemic infections, but the relationship was not statistically significant.[31,45,e2] However, we demonstrated in our meta-analysis that patients with concomitant systemic infection had almost double the risk of EVD-related infection (OR = 1.90, 95% CI 1.34–2.70, $p < 0.001$). Microorganisms found in the CSF were also found in samples from other parts of the body in 17% of cases in the study by Thompson et al.[52] and in 50% of cases in the study by Kim et al.[31] This might be explained by hematogenous seeding. This finding emphasizes the need to investigate and treat systemic infections. The increasing use of prophylactic antibiotics might also contribute to the concordance rates of microorganisms found in CSF and systemic cultures. Interestingly, diabetes (OR = 1.25, 95% CI 0.90–1.75, $p = 0.178$) and steroid use (OR = 1.52, 95% CI 0.96–2.41, $p = 0.074$) were not significant risk factors. This suggests that EVD-related infections do not share the same patient-related risk factors as other infections, such as surgical site infections. Steroids are recommended for patients with tumor-related cerebral edema. However, an updated meta-analysis conducted by Wintzer et al. indicated a lack of clear evidence of the beneficial or adverse effects of steroids.[e11] This finding is consistent with the results of our study.

EVD insertion with other neurosurgical procedures was associated with a high risk of infection (OR = 1.76, 95% CI 1.02–3.04, $p = 0.041$). However, significant heterogeneity was observed among the included studies. Both studies reporting significant relationships defined the specific period of neurosurgical procedures recorded (Kirmani et al. recorded other neurosurgical procedures performed within 2 weeks of EVD insertion or any time in the duration of ventriculostomy, and Kim et al. recorded all craniotomy operations performed in patients with a catheter).[42,e3] This phenomenon was also reported by Holloway et al. and Mayhall et al.[e12,e13]. We considered that this was due to immunosuppression accompanying the trauma and the operative procedure. However, the "leave-one-out" sensitivity analysis we conducted showed that the overall OR was 1.29 (95% CI 0.95–1.76, $I^2 = 24\%$) when excluding the study by Kirmani et al. from the meta-analysis of studies reporting the relationship between EVD-related infection and other neurosurgical procedures (eFigure 16, links.lww.com/CPJ/A438). Considering that EVD is often performed in neurosurgery, it is hoped that more related studies can be conducted in the future.

Considering that EVD-related infection is closely associated with colonization and biofilm formation on catheters, catheters with antibacterial effects were introduced to reduce the infection rate. The first study on antibiotic-impregnated catheters was conducted by Gower et al., and a reduction of 54% of *Staphylococcus epidermidis* adherence to the catheter surface was found with catheters soaked in Bacitracin A for half an hour.[e14] The Bactiseal® EVD Catheter system (Codman, Raynham, MA) impregnated with 0.15% clindamycin and 0.054% rifampicin was used more often. It allows for the release of antibiotics into the lumen of the EVD for up to 50 days after insertion.[e15] The EVD-related infection rate was significantly reduced (OR = 0.60, 95% CI 0.41–0.88, $p = 0.009$) with the application of antibiotic-impregnated catheters in our meta-analysis. However, the effect is not reliable under sensitivity analysis, and it might be caused by the different definitions of infection. Silver is another choice for EVD catheters because of its broad antimicrobial spectrum.[e16] In our meta-analysis, the use of silver-coated catheters significantly reduced the rate of EVD-related infections (OR = 0.57, 95% CI 0.38–0.87, $p = 0.008$). Similar results were obtained in a network meta-analysis conducted by Goda et al.[e17] Large amounts of Ag have been reported to result in organ accumulation and toxicity.[e18] However, no toxic effects were observed in the studies included in our meta-analysis. We found that silver-coated catheters seemed to have a more convincing effect on the reduction in EVD-related infection rates. However, antibiotic-impregnated catheters demonstrated a statistically significant lower rate of infection than silver-coated catheters (RR = 0.47, 95% CI 0.25–0.87) in a network meta-analysis including 7 trials.[e17] Apart from the antibacterial and adverse effects of different catheters, cost implications should also be taken into consideration.

A change in catheter is usually required for infection, blockage, or inadvertent dislodgment. A higher infection rate associated with catheter replacement was observed in our meta-analysis (OR = 5.05, 95% CI 3.67–6.96, $p < 0.001$). A previous study demonstrated that previous ventriculostomy did not increase the risk of infection with subsequent procedures.[e13] Mayhall et al. believed that prophylactic

replacement of catheters every 5 days could reduce EVD-related infections by reducing the duration of EVDs. Based on the results obtained in our meta-analysis, we suggest that catheters should not be changed, unless necessary. In addition, avoiding dislodging of EVDs might be an effective procedure to reduce the infection rate, owing to the high risk of EVDs replacement. Using image guidance, meticulous securing of the catheters and reinforcement with medical and nursing staff might help achieve this target. Bilateral EVD was another significant risk factor in our meta-analysis (OR = 2.25, 95% CI 1.03–4.89, $p = 0.041$). Bilateral EVDs can accelerate blood drainage, which can shorten the duration of drainage. This might be beneficial in severe IVH because of the more pronounced IVH reduction in patients treated with bilateral EVDs. However, it is clear that the placement of additional catheters could lead to a higher risk of infection. In addition, patients with bilateral EVDs usually have more severe conditions, which could increase the infection rate. Therefore, enhanced surveillance and control of infection are required when neurosurgeons use bilateral EVD. More studies are required to demonstrate the relationship between bilateral EVDs and EVD-related infections. In our study, insertion of catheters in the emergency department/intensive care unit was not associated with a higher rate of EVD-related infection (OR = 1.11, 95% CI 0.60–2.07, $p = 0.736$) compared with the operating room. This is beyond our expectations because placement in the operating room provides the advantages of a sterile environment, irrigation, and suction. We believe that the increasing use of standardized techniques may be an explanation. Optimized antiseptic and insertion techniques are of great importance considering that placement outside the operating room is necessary for urgent indications.

CSF leakage is considered a major risk factor for EVD-related infection.[50] We also find CSF leak to be a significant contributor (OR = 3.19, 95% CI 2.12–4.81, $p < 0.001$). Poor wound healing, high intracranial pressure, and surgical factors may contribute to leakage. Extraluminal progression of pathogens initially colonizing the skin site where CSF leaks might cause EVD-related infection. The relationship between the duration of EVD >7 days and higher infection rate was confirmed in most studies, although the cause-and-effect relationship has not been determined.[16,29,30,45,49,e3,e4] The possibility of infection drastically increased when the catheters were inserted for 7 days or more (OR = 4.62, 95% CI 2.26–9.43, $p < 0.001$). Stroknik et al. mentioned similar results.[35] Bacteria might be difficult to eradicate without catheter removal because they can form a biofilm along the lumen of the catheter. Therefore, we recommend careful consideration of whether to insert the catheters for >7 days, depending on the patient's condition. The 2017 IDSA guidelines for Healthcare-Associated Ventriculitis and Meningitis recommended periprocedural prophylactic antimicrobial administration for patients undergoing placement of EVD.[e19] However, our meta-analysis showed that the use of prophylactic antibiotics did not significantly decrease the rate of EVD-related infections (OR = 0.87, 95% CI 0.66–1.14, $p = 0.309$). Furthermore, indiscriminate use may cause infections with resistant germs, anaphylactic reactions, prolonged bleeding times, and systemic toxicity. The selection of resistant microbial species could occur even at subminimum inhibitory concentration levels.[e20] Considering these aspects, we recommend not using prophylactic antibiotics. Therefore, it would be more effective to use antibiotic-impregnated catheters to prevent EVD-related infections.

As mentioned in a statement from the Neurocritical Care Society,[2] care bundles including attention to sterile techniques, tunneling of the catheter, periprocedural antibiotic use only, use of an impregnated catheter, use of a closed system, no routine CSF sampling, use of a sterile dressing, and no site changes after placement are recommended for reduction in EVD-related infection rates.[7,e21,e22] However, most of the approaches used individually did not significantly change the infection rates in our meta-analysis, which is consistent with this statement. Owing to the different elements of care bundles, it is not certain which parts were effective in reducing EVD-related infection rates. We also analyzed other factors, such as hypertension, insertion during surgery, and artificial ventilation. However, none of the differences were statistically significant.

Statistically significant heterogeneity was found in some analyses, most of which were caused by differences in study design, especially in the definition of risk factors. Other studies reported factors such as skull fracture,[20] smoking,[52] and flushing catheters.[60] However, the number of studies investigating these factors was small, and the studies were largely heterogeneous. Therefore, it was impossible to conduct a meta-analysis. We hope that more studies with unified diagnostic criteria and a prospective design could be conducted to help identify the risk factors for EVD-related infection.

One of the limitations of our study was that most of the included studies had cohort designs and most were retrospective studies. In addition, there were 2 CDC criteria for the diagnosis of meningitis/ventriculitis (eTable 3, links.lww.com/CPJ/A438). The exclusive use of criterion one might lead to artificially low infection rates. The adoption of different diagnostic criteria might cause unavoidable heterogeneity, especially when studies mention new techniques.

External ventricular drainage is a vital tool in neurosurgery and carries a non-negligible risk of EVD-related infections. We demonstrated some potential risk factors, including SAH/IVH, concomitant systemic infection, other neurosurgical procedures, change of catheter, bilateral EVDs, CSF leak, and duration of EVD > 7 days in our meta-analysis. The use of silver-coated and antibiotic-impregnated catheters may help reduce the risk of infection. However, some controversial factors such as diabetes mellitus, steroid use, and prophylactic antibiotics were not associated with an increased or decreased risk of an EVD-related infection. More studies with unified diagnostic criteria and a prospective design are warranted to clarify the cause-and-effect relationship.

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