

Does Exposure Timing Matter? Glycemic Indices and External Ventricular Drain–Associated Infection

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Research Article

Keywords: External ventricular drain, ventriculitis, healthcare-associated infection, hyperglycemia, hypoglycemia, competing risks, exposure timing

Posted Date: August 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10491158/v1>

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Abstract

Objective: To examine whether glycemic exposure is associated with external ventricular drain (EVD)-associated infection using analyses that distinguish exposures preceding infection from those following it.

Design: Retrospective cohort study.

Setting: Single tertiary academic hospital, January 2018 to July 2023.

Patients: One hundred seven consecutive patients undergoing EVD insertion for intracerebral or subarachnoid hemorrhage.

Interventions: None (observational study).

Measurements and Main Results: Infection was defined by 2015 CDC/NHSN criteria. Seven hyperglycemic indices were evaluated with conventional and equivalence analyses. Hypoglycemia (<70 mg/dL) was examined over three windows—whole admission, before infection diagnosis, and the first 72 hr—and as a time-varying covariate. Infection occurred in 21 patients (19.6%). No hyperglycemic index was associated with infection (odds ratios, 0.68–1.05 per 1 SD), and equivalence could not be established. Whole-admission hypoglycemia was more frequent in infected patients (47.6% vs 24.4%; OR, 2.74 [95% CI, 0.90–8.30]), but the association attenuated over the first 72 hr (OR, 1.14 [95% CI, 0.11–6.68]); the difference between exposure windows was not significant (ratio of odds ratios, 0.43; $p = 0.285$). Infected patients underwent approximately twice as many glucose measurements (median, 84 vs 40; $p = 0.009$). Hypoglycemia was associated with in-hospital mortality (adjusted OR, 2.68; 95% CI, 1.10–6.54). Among nine patients with hypoglycemia within 72 hr, before any infection, eight (88.9%) died versus 35.8% of the rest ($p = 0.003$).

Conclusions: No association was observed between glycemic indices and EVD-associated infection after accounting for exposure timing and differential glucose measurement, although the small number of infection events limits the range of effects that can be excluded. Hypoglycemia was more closely associated with mortality than infection, suggesting that it reflects illness severity rather than a cause of EVD-associated infection.

Key points

1. Seven glycemic indices were tested; none predicted EVD-associated infection in 107 patients.
2. Hypoglycemia looked linked to infection only because infected patients had their glucose checked twice as often (84 vs 40 measurements).
3. Hypoglycemia tracked with death, not infection—a sign of how sick the patient was, not a cause of ventriculitis.

4. Accounting for when exposures occur, and for competing deaths, separates real risk factors from consequences of infection.

Introduction

External ventricular drainage (EVD) is widely used in neurocritical care to divert cerebrospinal fluid (CSF) and control intracranial pressure after intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Its most serious complication is EVD-associated infection, including ventriculitis and meningitis, which prolongs intensive care, increases healthcare costs, and worsens neurological outcomes [1–3]. Reported infection rates vary from less than 5% to more than 30% [4, 5], making potentially modifiable risk factors an important focus of research.

Glucose is one such candidate. Hyperglycemia impairs neutrophil function [6], is associated with healthcare-associated infections in surgical and critically ill patients, and commonly occurs after ICH and SAH as part of the stress response [7, 8]. Hypoglycemia, in contrast, is a recognized marker of physiological deterioration and is consistently associated with mortality in critical illness [9]. Whether either is related to EVD-associated infection remains unclear, and previous studies have generally relied on isolated glucose measurements rather than glycemic exposure over time.

A major challenge in studying this relationship is preserving the temporal sequence between exposure and outcome. Several reported risk factors, including catheter duration, reinsertion, and CSF sampling, evolve during treatment and often increase once infection is suspected [4, 10]. Glucose measurements are subject to the same limitation. Values obtained after infection cannot have contributed to its development, and infected patients typically undergo more frequent glucose testing. Consequently, glycemic indices calculated over the entire admission may reflect differential measurement intensity rather than true glycemic exposure. Analyses should therefore distinguish glucose measured before infection from that recorded afterward.

Methods

Study design and setting

We conducted a single-center retrospective cohort study of consecutive patients who underwent EVD insertion at a tertiary academic hospital between January 2018 and July 2023. The institutional review board approved the study (No. 2024GR0350) and waived the requirement for informed consent because of the retrospective design. The study is reported in accordance with the STROBE statement.

Participants

Eligible patients underwent EVD insertion through Kocher's point for ICH or SAH. Patients were excluded if the EVD was placed for a pre-existing central nervous system infection, if craniotomy or craniectomy

was performed adjacent to the catheter tract, if another active infection was present at insertion, or if they were transferred before outcome assessment. Duplicate records and non-EVD procedures were removed before analysis. The unit of analysis was the patient, with catheter episodes from any reinsertion combined into a single patient-level record. Study flow is shown in Fig. 1. No formal sample size calculation was performed; all eligible consecutive patients were included.

Outcomes

The primary outcome was EVD-associated infection, defined according to the 2015 CDC/NHSN criteria for healthcare-associated meningitis or ventriculitis [11]. Final adjudication was performed by the infectious disease service. The infection date was defined as the earlier of the first abnormal CSF finding or first documented clinical suspicion. Patients were followed until discharge or death, including after EVD removal; infections after removal or reinsertion were attributed to the same patient. Patients without infection were censored at discharge or death.

Exposure definitions and the exposure-window framework

All exposure variables were derived from blood glucose measurements. CSF glucose values were not used in any exposure definition.

Glycemic exposures were evaluated over three windows: the whole admission, the period before infection diagnosis, and the first 72 hours after EVD insertion. The pre-diagnosis window extended from insertion to diagnosis in infected patients and to EVD removal in those without infection. Because no infection occurred within the first 72 hours (earliest, day 5), this fixed-length window was unaffected by the outcome and served as the primary analysis window to minimize reverse causation. Estimates across the three windows were compared to assess the effect of exposure timing.

We examined five glycemic measures, two of which were assessed in both exposure windows, yielding seven indices. Admission glucose was the first value after admission, and peak glucose the highest during hospitalization. Hyperglycemia burden was calculated over the whole admission only. Mean glucose and glucose coefficient of variation (CV; the SD divided by the mean, expressed as a percentage) were each calculated for the whole admission and the first 72 hours. The seven indices were admission glucose, peak glucose, whole-admission and 72-hour mean glucose, hyperglycemia burden, and whole-admission and 72-hour glucose CV.

Minimum glucose, defined as the lowest recorded value, was examined as an exploratory index in the whole-admission and pre-diagnosis windows. Because it is particularly susceptible to reverse causation and ascertainment bias from repeated measurement, it was treated as exploratory, and its findings should be considered hypothesis-generating only.

Hyperglycemia burden was defined as the proportion of glucose measurements exceeding 180 mg/dL [12]. Hypoglycemia was evaluated at two thresholds (< 70 and < 54 mg/dL), corresponding to American Diabetes Association Levels 1 and 2 [13]; patients were classified as exposed if any value fell below the threshold within the relevant window. Two additional measures characterized baseline glycemic status rather than study exposures: HbA1c, reflecting chronic glycemia, and the stress hyperglycemia ratio (SHR), calculated as admission glucose divided by estimated average glucose (eAG), where $\text{eAG (mg/dL)} = 28.7 \times \text{HbA1c (\%)} - 46.7$ [14, 15]. Because HbA1c was measured at the treating team's discretion, both variables were available only in the HbA1c subset and were summarized descriptively rather than modeled.

Baseline and post-insertion variables

Variables were classified as fixed at EVD insertion or time-varying. Baseline variables included insertion location, catheter type, chlorhexidine dressing, prophylactic antibiotic use, diabetes mellitus, hemorrhage subtype, and intraventricular hemorrhage, all considered potential infection risk factors.

Time-varying variables—catheter duration, EVD reinsertion, and CSF sampling frequency—were treated as descriptive because they may change in response to infection and were therefore excluded from infection models. They also increase opportunities for glucose measurement and CSF sampling, creating unequal chances to detect extreme glucose values and infection. Whole-admission glycemic indices are therefore susceptible to both ascertainment bias and reverse causation, motivating use of the fixed-length 72-hour window.

Statistical analysis

Continuous variables are presented as median (interquartile range) and categorical variables as number (percentage), and were compared using the Mann–Whitney U and Fisher's exact tests. Analyses were performed on complete cases; body mass index was missing in 23 patients, whereas HbA1c and SHR were available in 40. Associations of baseline variables and hypoglycemia with infection were estimated as odds ratios (ORs) with exact 95% CIs using conditional maximum-likelihood estimation (exact2x2 package).

For continuous glycemic indices, each measure was standardized to its sample standard deviation so that odds ratios represent the change per 1 SD and a common equivalence margin could be applied across indices. Conventional testing was complemented by two one-sided tests (TOST) against a post hoc odds ratio margin of 0.67–1.50, selected from published infection risk-factor effect sizes and not prespecified; margins of $\delta = 1.30, 1.50$, and 2.00 are shown in Supplementary Table 2. Bayes factors favoring the null (BF_{01}) were calculated using the Savage–Dickey density ratio with a normal prior on the log odds ratio (SD 0.5). Bonferroni- and Benjamini–Hochberg-adjusted P values are also reported. Odds ratios for hypoglycemia in the whole-admission and 72-hour windows were compared using a logistic generalized estimating equation (GEE) model with one observation per patient per window, a

hypoglycemia-by-window interaction, an independence working correlation, and clustering by patient. The interaction term estimated the ratio of odds ratios. The exploratory association between minimum glucose and infection probability was modeled using logistic regression with a restricted cubic spline (3 knots; rms package) over the 5th–95th percentile (43–130 mg/dL) (Supplementary Fig. 2).

To preserve the temporal sequence between exposure and outcome, hypoglycemia was also analyzed as a time-dependent covariate in a Cox proportional hazards model with counting-process formulation, contributing unexposed person-time until the first hypoglycemic episode and exposed person-time thereafter. Adjusted models included diabetes mellitus and hemorrhage subtype.

Because death before infection precludes infection, competing-risk analyses used the Fine–Gray subdistribution hazards model with pre-infection death as the competing event. Hypoglycemia was treated as a fixed baseline covariate, so the subdistribution hazard ratio reflects an association rather than a time-dependent effect. These models were not adjusted for admission severity because their purpose was to assess whether hypoglycemia precedes infection rather than estimate a severity-adjusted effect; severity was instead examined in the mortality models. As a sensitivity analysis, the time-dependent Cox model was additionally adjusted for admission Glasgow Coma Scale score.

Cumulative incidence of infection was estimated using the Aalen–Johansen estimator with death as the competing event. The complement of the Kaplan–Meier estimator ($1 - \text{KM}$) was calculated for comparison, and confidence intervals were derived using the Aalen-type variance implemented in the `*cuminc*` function.

All analyses were performed using R version 4.6.1. Statistical significance was defined as a two-sided $P < 0.05$, except for one-sided equivalence tests.

Results

Cohort characteristics

Of 107 patients, 21 (19.6%) developed EVD-associated infection. Baseline characteristics were similar between groups (Table 1), with no significant differences in age, sex, body mass index, admission Glasgow Coma Scale score, hemorrhage subtype, comorbidities, or EVD insertion factors (chlorhexidine dressing, antibiotic-impregnated catheter, operating-room insertion, and prophylactic antibiotics).

Table 1
Baseline characteristics by EVD-associated infection

Characteristic	Infection (n = 21)	No infection (n = 86)	P
Demographics			
Age, years	61 (48–69)	61 (52–77)	0.440
Female sex	13 (61.9)	45 (52.3)	0.473
Body mass index, kg/m ²	23.6 (22.7–25.8)	24.1 (21.6–25.7)	0.909
GCS at admission	9 (7–13)	9 (6–13)	0.651
Diagnosis			
Intracerebral hemorrhage	10 (47.6)	42 (48.8)	1.000
Intraventricular hemorrhage	10 (47.6)	36 (41.9)	0.633
Comorbidities			
Hypertension	6 (28.6)	36 (41.9)	0.324
Diabetes mellitus	5 (23.8)	13 (15.1)	0.341
Heart disease	3 (14.3)	14 (16.3)	1.000
Chronic kidney disease	2 (9.5)	9 (10.5)	1.000
Cancer	1 (4.8)	1 (1.2)	0.355
Liver disease	0 (0.0)	2 (2.3)	1.000
Dyslipidemia	1 (4.8)	8 (9.3)	0.685
Respiratory disease	0 (0.0)	2 (2.3)	1.000
Immune disease	1 (4.8)	2 (2.4)	0.488
Severity and glycemic management			
Hunt–Hess grade [‡]	4 (2.5–5)	3 (1–5)	0.486
Fisher grade [‡]	3 (3–4)	3 (3–3)	0.073
Values are median (IQR) or n (%). P values by Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. *Variables under the post-insertion course are recorded over the entire admission and may change after infection has occurred; they are shown for description only and are not interpretable as risk factors. Of 21 infections, 8 had the catheter retained beyond the day of diagnosis and 13 were diagnosed on or after the day of removal. Body mass index was missing in 23 patients. [‡]Hunt–Hess and Fisher grades apply to subarachnoid hemorrhage patients only (n = 55: 11 infection, 44 no infection). [§]HbA1c was measured in 40 patients (11 infection, 29 no infection). [¶]Stress hyperglycemia ratio was available in the same 40 patients as HbA1c; the overall median was 1.37 (IQR, 1.19–1.59).			

Characteristic	Infection (n = 21)	No infection (n = 86)	P
Demographics			
HbA1c, %	5.8 (5.4–5.9)	5.6 (5.2–6.1)	0.574
Stress hyperglycemia ratio	1.34 (0.97–1.48)	1.41 (1.24–1.61)	0.226
Steroid use	5 (23.8)	18 (20.9)	0.772
Intravenous insulin	6 (28.6)	17 (19.8)	0.385
EVD-related factors, fixed at insertion			
Chlorhexidine dressing	5 (23.8)	27 (31.4)	0.601
Antibiotic-impregnated catheter	4 (19.0)	11 (12.8)	0.488
Insertion in operating room	15 (71.4)	69 (80.2)	0.385
Prophylactic antibiotics	13 (61.9)	40 (46.5)	0.232
Post-insertion course, not baseline*			
EVD duration, days	11 (6–31)	6 (3–11)	0.002
EVD reinsertion	11 (52.4)	11 (12.8)	< 0.001
CSF sampling, times	3 (2–5)	2 (1–3)	0.001
Outcomes			
mRS at discharge	5 (4–6)	5 (4–6)	0.495
Length of stay, days	47 (26–89)	24 (7–44)	0.001
In-hospital mortality	6 (28.6)	37 (43.0)	0.321
Values are median (IQR) or n (%). P values by Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. *Variables under the post-insertion course are recorded over the entire admission and may change after infection has occurred; they are shown for description only and are not interpretable as risk factors. Of 21 infections, 8 had the catheter retained beyond the day of diagnosis and 13 were diagnosed on or after the day of removal. Body mass index was missing in 23 patients. †Hunt–Hess and Fisher grades apply to subarachnoid hemorrhage patients only (n = 55: 11 infection, 44 no infection). ‡HbA1c was measured in 40 patients (11 infection, 29 no infection). §Stress hyperglycemia ratio was available in the same 40 patients as HbA1c; the overall median was 1.37 (IQR, 1.19–1.59).			

Abbreviations: IQR, interquartile range; GCS, Glasgow Coma Scale; HbA1c, glycated hemoglobin; SHR, stress hyperglycemia ratio; EVD, external ventricular drain; CSF, cerebrospinal fluid; mRS, modified Rankin Scale.

Infected patients had longer EVD duration (median 11 vs 6 days; $*P^* = 0.002$), more frequent reinsertion (52.4% vs 12.8%; $*P^* < 0.001$), more CSF sampling (3 vs 2; $*P^* = 0.001$), more whole-admission glucose measurements (84 vs 40; $*P^* = 0.009$), and longer hospital stay (47 vs 24 days; $*P^* = 0.001$). The number of glucose measurements during the first 72 hours was similar (7 vs 10; $*P^* = 0.10$).

Hyperglycemic indices and infection

None of the seven indices was associated with infection (odds ratios, 0.68–1.05 per 1 SD; Supplementary Table 3; Fig. 2). Equivalence was not demonstrated: no 90% confidence interval lay within the post hoc margin (OR, 0.67–1.50), Bayes factors gave at most anecdotal support for the null, and only five indices met the criterion at $\delta = 2.00$ (Supplementary Table 2). These findings indicate no detectable association in an underpowered study rather than demonstrated equivalence. HbA1c and the stress hyperglycemia ratio (SHR) were available in 40 patients (37%), with median values of 5.7% and 1.37, respectively.

Hypoglycemia and exposure window

Whole-admission hypoglycemia (< 70 mg/dL) was more frequent in infected than uninfected patients (47.6% vs 24.4%; OR, 2.74; 95% CI, 0.90–8.30; $P = 0.059$). Restricting the analysis to the first 72 hours attenuated the estimate to 1.14 (95% CI, 0.11–6.68) (Table 2; Supplementary Fig. 1), although the difference between windows was not significant (ratio of odds ratios, 0.43; $P = 0.285$). In the pre-diagnosis window, the OR was 1.70 (95% CI, 0.41–6.06). Observation time remained longer in infected patients (median, 11 vs 7 days; $P < 0.001$), so the attenuation cannot be explained by shorter observation. The same pattern was observed for hypoglycemia < 54 mg/dL, and no infection occurred within the first 72 hours (earliest, day 5). Only whole-admission minimum glucose reached nominal significance (raw $P = 0.012$), but this did not persist after Bonferroni or Benjamini–Hochberg correction (Supplementary Table 1). Predicted infection probability decreased with higher minimum glucose (Supplementary Fig. 2), although confidence intervals were wide and the association did not remain significant after multiple-testing correction.

Table 2
Hypoglycemia and EVD-associated infection by exposure window

Exposure window	Infection (n = 21)	No infection (n = 86)	OR	95% CI	P
Hypoglycemia < 70 mg/dL					
Whole admission	10/21 (47.6)	21/86 (24.4)	2.74	0.90–8.30	0.059
Before infection diagnosis	5/21 (23.8)	13/86 (15.1)	1.70	0.41–6.06	0.350
First 72 hours	2/21 (9.5)	7/86 (8.1)	1.14	0.11–6.68	1.000
Hypoglycemia < 54 mg/dL					
Whole admission	5/21 (23.8)	9/86 (10.5)	2.61	0.60–10.15	0.146
First 72 hours	1/21 (4.8)	2/86 (2.3)	2.01	0.03–40.41	0.495
Values are the number exposed / group total (%), matching Tables 1 and 6. Odds ratios are conditional maximum-likelihood estimates with exact confidence limits; P values by Fisher's exact test. Point estimates attenuate as the exposure window narrows, but a formal interaction test does not establish that they differ (ratio of odds ratios 0.43, P = 0.285). No infection was diagnosed within the first 72 hours (earliest, day 5).					

Abbreviations: EVD, external ventricular drain; OR, odds ratio; CI, confidence interval.

Time-to-event analysis

Analyzed as a time-dependent exposure, hypoglycemia was not significantly associated with infection (unadjusted Cox HR, 2.01; adjusted for diabetes and hemorrhage subtype, 2.04; Supplementary Table 4). In the Fine–Gray model, treating hypoglycemia as a fixed baseline covariate and pre-infection death as the competing event, the subdistribution hazard ratio was 1.46 (95% CI, 0.64–3.31). Additional adjustment for admission Glasgow Coma Scale score yielded a similar estimate (HR, 2.28; *P* = 0.118).

Hypoglycemia and mortality

In-hospital mortality was higher in patients with whole-admission hypoglycemia (58.1% vs 32.0%; OR, 2.94; 95% CI, 1.24–6.97; *P* = 0.017) and remained significant after adjustment for admission Glasgow Coma Scale score and age (adjusted OR, 2.68; 95% CI, 1.10–6.54) (Table 3), and after further adjustment for intravenous insulin (adjusted OR, 2.66; 95% CI, 1.08–6.59). Hypoglycemia was not more frequent among insulin recipients (*P* = 0.12), and 21 of 31 hypoglycemic patients had not received insulin (n = 106). Within the first 72 hours, before any infection occurred, mortality was 88.9% (8/9) in patients with hypoglycemia versus 35.8% (34/95) in those without (*P* = 0.003; n = 104).

Table 3
Hypoglycemia as a marker of mortality

Outcome	Hypoglycemia (n = 31)	No hypoglycemia (n = 75)	P
EVD-associated infection	10/31 (32.3)	11/75 (14.7)	0.059
In-hospital mortality	18/31 (58.1)	24/75 (32.0)	0.017
Values are n/N (%). Hypoglycemia is defined over the whole admission (< 70 mg/dL); one patient without any glucose measurement in the window was excluded (n = 106). Hypoglycemia predicted death (OR 2.94, 1.24–6.97), persisting after adjustment for admission GCS and age (aOR 2.68, 1.10–6.54). In a separate analysis restricted to the first 72 hours after insertion, mortality among the 9 patients with early hypoglycemia – before any infection was diagnosed – was markedly higher (8/9, 88.9%) than among the 95 without early hypoglycemia (34/95, 35.8%; P = 0.003), which reverse causation cannot explain.			

Abbreviations: EVD, external ventricular drain; OR, odds ratio; aOR, adjusted odds ratio; GCS, Glasgow Coma Scale.

Baseline factors and infection

No baseline factor was associated with infection (Supplementary Table 5). All 95% confidence intervals for operating-room insertion, antibiotic-impregnated catheter, chlorhexidine dressing, prophylactic antibiotics, diabetes mellitus, intraventricular hemorrhage, and intracerebral hemorrhage crossed 1.0. With only 21 events, moderate associations could not be excluded.

Cumulative incidence of infection

The cumulative incidence of infection (Aalen–Johansen estimator; pre-infection death as the competing event) was 0.0% through day 3, 2.8% by day 7 (95% CI, 0.0–5.9), 9.4% by day 10 (3.8–15.0), 13.4% by day 14 (6.8–19.9), and 17.5% by day 21 (10.1–24.9) (Supplementary Table 6). Incidence remained low through day 7 and increased thereafter; the complement of the Kaplan–Meier estimator was consistently higher throughout follow-up (Fig. 3).

Discussion

We found no detectable association between any of the seven glycemic indices or baseline factors and EVD-associated infection. The apparent hypoglycemia–infection association attenuated when analyses were restricted to exposure windows preceding infection, whereas the mortality association persisted, suggesting that hypoglycemia reflects illness severity rather than susceptibility to infection, although the limited number of events warrants cautious interpretation.

The cohort was characterized predominantly by acute stress hyperglycemia rather than chronic diabetes: 88% of measured patients had HbA1c below the 6.5% diagnostic threshold [16], and 82% had a stress hyperglycemia ratio above 1.0 [14]. Stress hyperglycemia is generally considered a marker of

acute critical illness rather than an independent pathogenic exposure [14, 15]. Our findings therefore apply primarily to a largely non-diabetic population with acute stress hyperglycemia and may not generalize to cohorts with more chronic diabetes.

Whole-admission analyses of EVD-associated infection are susceptible to unequal ascertainment and reverse causation, potentially creating the appearance of causality. The apparent hypoglycemia–infection association illustrates this. Infected patients underwent about twice as many glucose measurements (median, 84 vs 40), increasing the likelihood of detecting an extreme low value, while glucose disturbances arising after infection are still included in whole-admission measures. Restricting exposure to the fixed 72-hour window attenuated the odds ratio from 2.74 to 1.14, and the time-dependent analysis likewise showed no association, suggesting that the whole-admission signal was partly driven by ascertainment and reverse causation, although limited events preclude firm conclusions. The same concern applies to hyperglycemia indices and other time-varying variables, including catheter duration, EVD reinsertion, and CSF sampling [4, 10]. We therefore limited risk-factor analyses to variables fixed at insertion and complemented them with exposure-window restriction, time-dependent modeling, and competing-risk analysis.

Hypoglycemia was associated with in-hospital mortality but not infection, and the mortality association persisted after adjustment for admission Glasgow Coma Scale score and age. It also remained in the first 72 hours, before any infection was diagnosed, making reverse causation less likely, although this small subgroup limits interpretation. These findings suggest that hypoglycemia reflects physiological deterioration rather than susceptibility to catheter-related infection, consistent with prior studies linking hypoglycemia to mortality without established causality [9].

None of the baseline factors reached significance, although prophylactic antibiotics (OR, 1.86), diabetes mellitus (OR, 1.74), and antibiotic-impregnated catheters (OR, 1.60) had point estimates above 1.0. With only 21 events, confidence intervals were wide. The associations with prophylactic antibiotics and antibiotic-impregnated catheters may reflect confounding by indication because both are preferentially used in higher-risk patients [4, 5].

Infection was uncommon during the first week and increased thereafter. As expected with competing events, the Kaplan–Meier estimator overestimated cumulative incidence relative to the Aalen–Johansen estimator [17]. Because catheter duration may increase after infection develops, cumulative incidence from insertion better describes infection risk than treating dwell time as a baseline covariate. These findings support removing the catheter once no longer clinically required, although they do not establish that earlier removal reduces infection.

Some reported risk factors and glycemic associations for EVD-associated infection may partly reflect exposure timing and ascertainment rather than true causal effects. Because many exposures evolve during EVD management, whole-admission analyses are susceptible to reverse causation and unequal ascertainment. Analyses that preserve temporal sequence may better distinguish antecedent risk factors from consequences of infection.

Limitations

This study has several limitations. First, only 21 infections limited statistical power; equivalence analyses showed that confidence intervals remained too wide to exclude clinically meaningful associations. Second, this retrospective single-center study relied on clinically indicated rather than protocolized glucose measurements, limiting generalizability and increasing unequal ascertainment. Third, restricting analyses to the first 72 hours minimized reverse causation but may have excluded exposures preceding later-onset infection. Fourth, in-hospital mortality was lower among infected than uninfected patients, likely reflecting immortal-time bias, because patients must survive long enough to receive an infection diagnosis [18]. Although competing-risk analyses accounted for pre-infection death, this bias cannot be fully eliminated. Finally, baseline glycemic status was incompletely characterized: HbA1c was available in only 40 patients, and information on diabetes duration, glycemic control, treatment, and inpatient glucose-modifying therapies was incomplete. Residual confounding by treatment and illness severity therefore cannot be excluded.

Conclusion

In patients undergoing EVD insertion for ICH or SAH, no detectable association was found between glycemic indices and EVD-associated infection after accounting for exposure timing and unequal ascertainment. Hypoglycemia was more closely associated with in-hospital mortality than infection, suggesting that it reflects illness severity rather than a determinant of EVD-associated infection. These findings provide little support for dysglycemia as a target for preventing EVD-associated infection. Larger prospective studies are warranted.

Declarations

1. Compliance with instructions to authors

The corresponding author confirms that this manuscript has been prepared in accordance with, and complies with, all Instructions for Authors of Neurocritical Care (updated February 2025), including the requirements for the title page, word count, references, figures and tables, and reporting checklists.

2. Author contributions

Hyo Jeong Kim conceived the study, collected the data, performed the statistical analysis, and drafted the manuscript. Hyunjun Jo contributed to the conception and refinement of the study concept, supervised the study, and served as corresponding author. Soo Yeon Jang and Jeonghwan Kim contributed to the statistical analysis and critically reviewed the manuscript. Hwamin Lee performed the extraction of clinical and glycemic data from the electronic medical record and critically reviewed the manuscript. Jinhoo Seok, Haewon Roh, Joonho Byun, Wonki Yoon, Jong Hyun Kim, and Taek-Hyun Kwon contributed to catheter insertion and patient management, to the adjudication of infection and interpretation of the results, and critically reviewed the manuscript for important intellectual content. All

authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

3. Authorship requirements

All authors meet the authorship criteria of the International Committee of Medical Journal Editors (ICMJE): each has made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; has drafted the article or revised it critically for important intellectual content; has given final approval of the version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The final version of the manuscript was reviewed and approved by all authors.

4. Prior publication

This manuscript has not been published elsewhere, in whole or in part, and is not under consideration by any other journal. No part of the data has been reported in a previous publication.

5. Ethical approval and informed consent

This retrospective study was approved by the Institutional Review Board of Korea University Guro Hospital (approval no. 2024GR0350). The requirement for written informed consent was waived by the Institutional Review Board owing to the retrospective design and the use of de-identified data. The study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. No identifying information of individual participants is included in this article.

6. Conflicts of interest

Hyo Jeong Kim, Soo Yeon Jang, Jeonghwan Kim, Jinhoo Seok, Haewon Roh, Joonho Byun, Wonki Yoon, Jong Hyun Kim, Taek-Hyun Kwon, Hwamin Lee, and Hyunjun Jo declare that they have no financial or non-financial conflicts of interest relevant to this work.

7. Reporting checklist

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies. The completed STROBE checklist is provided as Supplemental Digital Content.

8. Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

9. Artificial intelligence statement

During the final preparation of this manuscript, the authors used [tool name, developer] solely for English language editing of the completed draft, to improve grammar, word choice, and readability. AI-assisted technologies were not used for the study design, data collection, statistical analysis, interpretation of the results, generation or selection of references, or the creation of any tables or figures. All AI-edited text was subsequently reviewed and revised by the authors, who take full responsibility for the accuracy, integrity, and originality of the content, including the absence of plagiarism and the appropriate attribution and citation of all quoted material.

Acknowledgements

Hwamin Lee is supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (RS-2026-25477844). The funder had no role in the design or conduct of this study, in the collection, analysis, or interpretation of the data, or in the preparation of the manuscript.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available because they contain information that could compromise participant privacy, but are available from the corresponding author on reasonable request.

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Figures

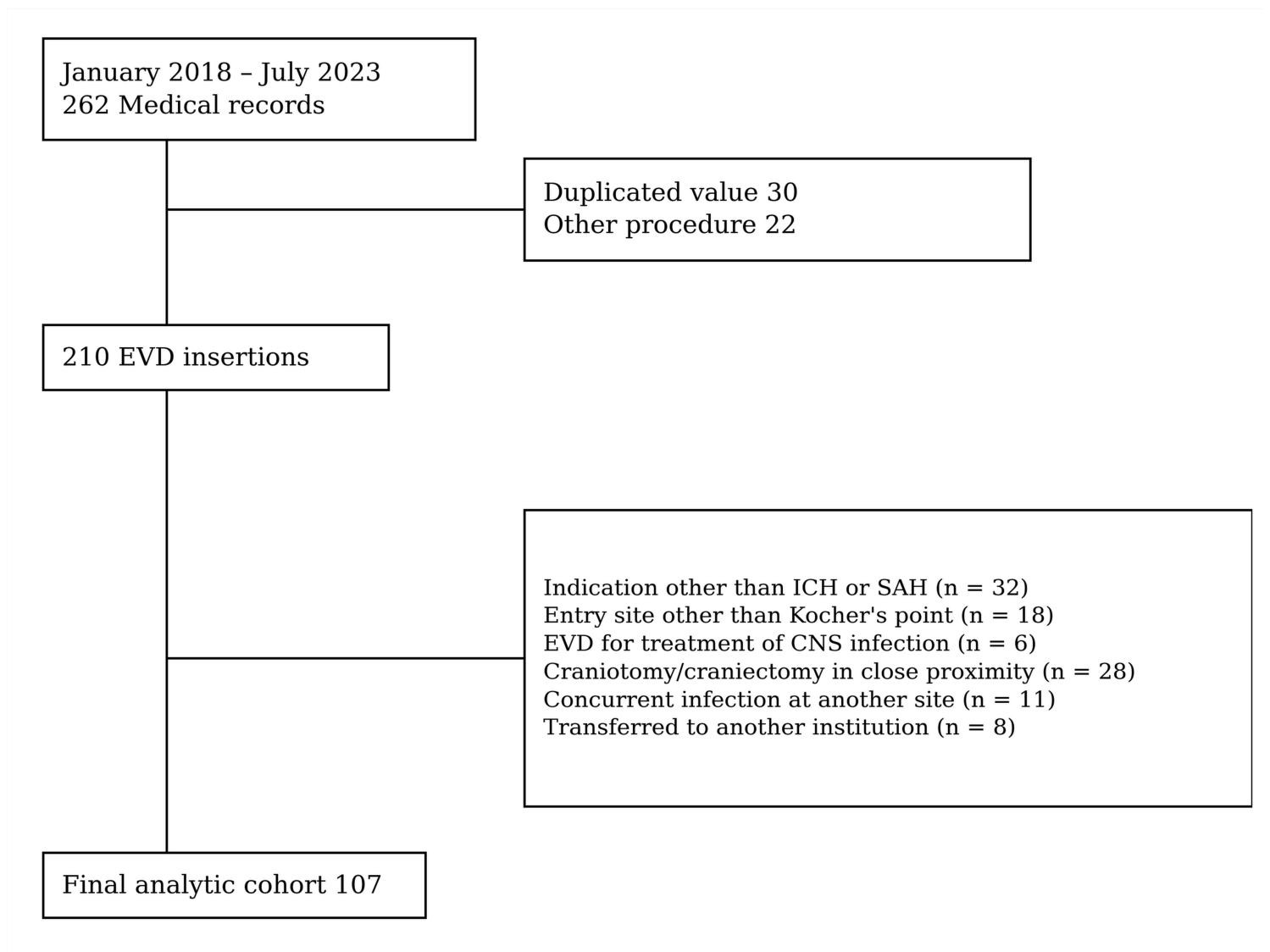


Figure 1

Study flow. Of 262 medical records screened between January 2018 and July 2023, 52 were removed before eligibility assessment (30 duplicate records and 22 procedures other than EVD insertion), leaving 210 EVD insertions. A further 103 were excluded for the reasons shown, yielding a final analytic cohort of 107 patients. EVD, external ventricular drain; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; CNS, central nervous system.

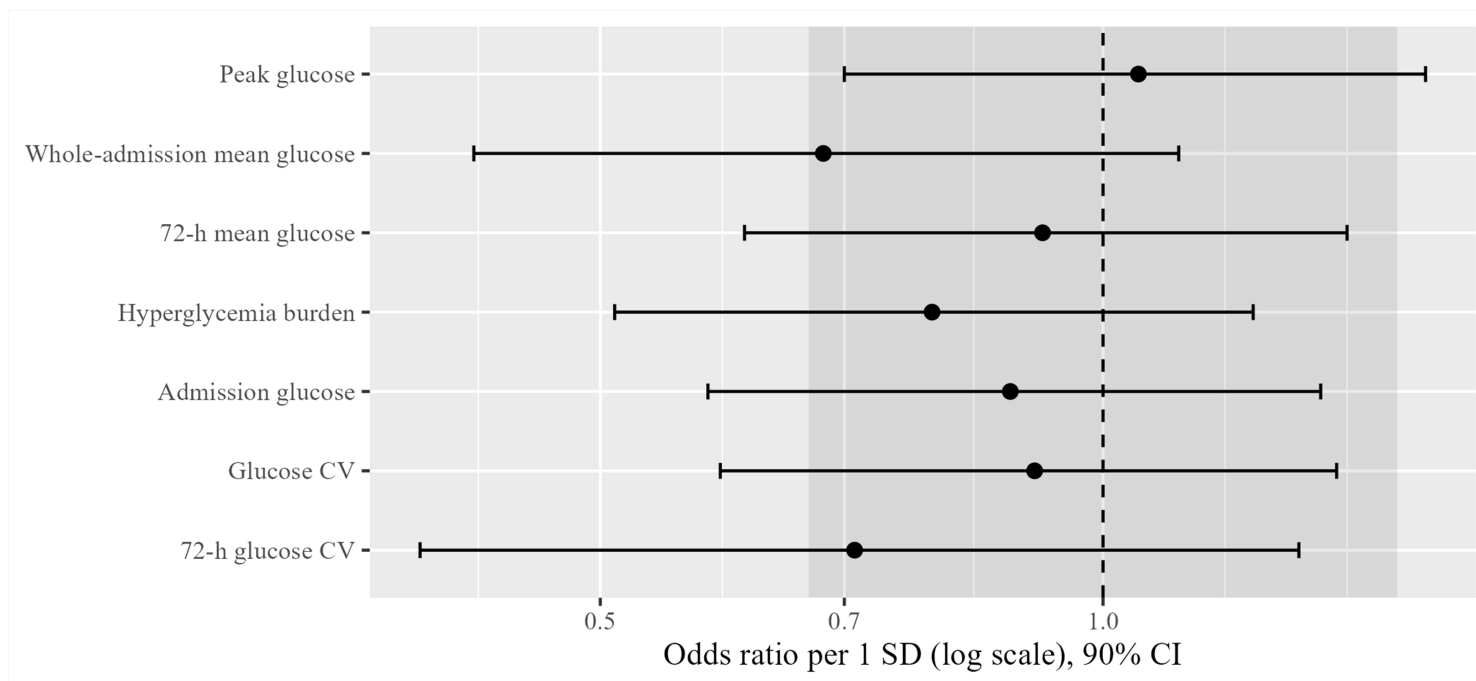


Figure 2

Equivalence testing of the seven prespecified hyperglycemic indices. Points are odds ratios per 1 standard deviation increase with 90% confidence intervals, plotted on a logarithmic scale; the shaded band marks the post hoc equivalence margin (odds ratio 0.67–1.50) and the dashed line the null value. Each index was standardized to its sample standard deviation so that a single margin is comparable across indices. No index has a confidence interval lying entirely within the margin: point estimates cluster near the null, but with 21 infection events the intervals are too wide to establish equivalence. CV, coefficient of variation.

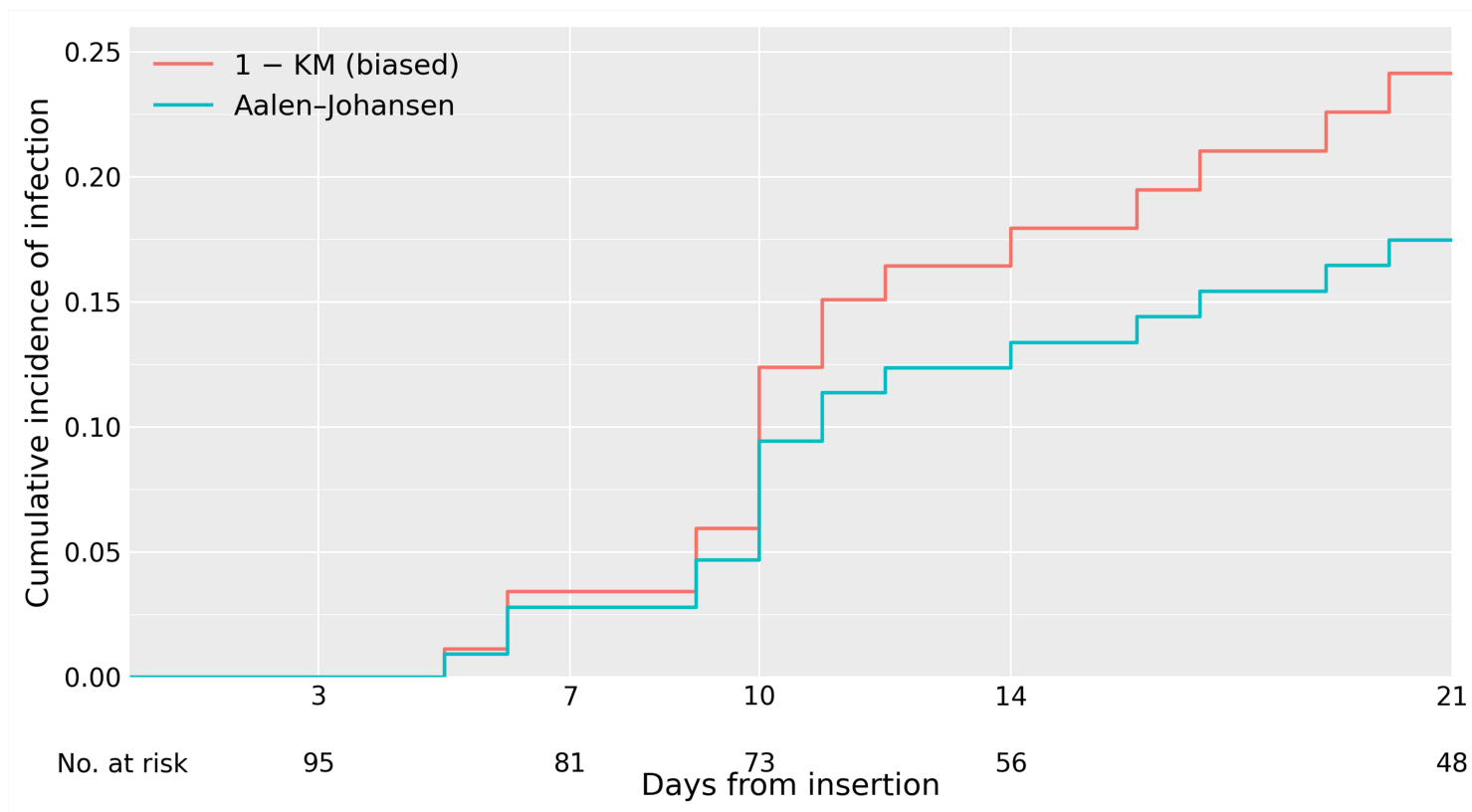


Figure 3

Cumulative incidence of EVD-associated infection from the time of catheter insertion, estimated with the Aalen–Johansen method treating pre-infection death as a competing event, compared with the complement of the Kaplan–Meier estimator ($1 - \text{KM}$), which ignores competing death and consequently overestimates incidence. The number of patients remaining at risk is shown below the x-axis. The plot is truncated at day 21, by which time 18 of the 21 infections had occurred. KM, Kaplan–Meier.

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