Supplemental Digital Content

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

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STROBE Statement—checklist of items that should be included in reports of cohort studies

Manuscript: "Does Exposure Timing Matter? Glycemic Indices and External Ventricular Drain–Associated Infection" (retrospective cohort study). Locations refer to the section of the manuscript; page numbers to be inserted before submission.

	Item	Recommendation	Reported in
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Abstract, Methods ("single-center retrospective cohort study"). Page 3-4
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract. Page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, paragraphs 1–3. Page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, paragraphs 2–3 (aim: whether dysglycemia is associated with EVD-associated infection using analyses that preserve exposure–outcome timing). Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Methods — Study design and setting (retrospective single-center cohort). Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods — Study design and setting (single tertiary center; January 2018–July 2023). Page 6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods — Participants; Outcomes (followed to discharge or death); Figure 1. Page 6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable (unmatched cohort).
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods — Outcomes (2015 CDC/NHSN criteria); Exposure definitions and the exposure-window framework; Baseline and post-insertion variables. Page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods — Exposure definitions (blood glucose from the electronic medical record; CSF glucose not used). Page 7-8
Bias	9	Describe any efforts to address potential sources of bias	Methods — Exposure-window framework (fixed 72-hour window to limit reverse causation); Baseline vs post-insertion variables (ascertainment bias); competing-risk analysis for pre-infection death. Page 7
Study size	10	Explain how the study size was arrived at	Methods — Participants (final sentence): no formal sample size calculation; all consecutive eligible patients were included. Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods — Statistical analysis (continuous glycemic indices standardized to 1 SD; hypoglycemia dichotomized at <70 and <54 mg/dL; hyperglycemia burden at >180 mg/dL). Page 9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods — Statistical analysis. Page 9
		(b) Describe any methods used to examine subgroups and interactions	Methods — Statistical analysis: the whole-admission vs 72-hour exposure windows were compared with a hypoglycemia-by-window interaction term in a logistic GEE model (ratio of odds ratios). Page 9
		(c) Explain how missing data were addressed	Methods — Statistical analysis: complete-case analysis; body mass index missing in 23, HbA1c and SHR available in 40. Page 9
		(d) If applicable, explain how loss to follow-up was addressed	Methods — Participants (transfer before outcome assessment excluded); Outcomes (followed to discharge or death); pre-infection death handled as a competing event. Page 7
		(e) Describe any sensitivity analyses	Methods — Statistical analysis (equivalence-margin sensitivity; time-dependent Cox additionally adjusted for admission GCS; adjustment for intravenous insulin in the mortality analysis). Page 10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study	Results — Cohort characteristics; Figure 1 (262 records → 210 insertions → 107 analysed). Page 11
		(b) Give reasons for non-participation at each stage	Figure 1 (exclusion reasons with numbers).
		(c) Consider use of a flow diagram	Figure 1.
Descriptive data	14*	(a) Give characteristics of study participants and information on exposures and	Table 1. Page 11

		potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	Table 1 footnotes (BMI missing in 23; HbA1c and SHR in 40; Hunt–Hess and Fisher grades in the 55 SAH patients). Page 9
		(c) Summarise follow-up time	Results — Hypoglycemia and exposure window (pre-diagnosis observation: median 11 vs 7 days); Table 1 (EVD duration, length of stay).
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results — Cohort characteristics (21 infections, 19.6%); Cumulative incidence of infection; Table 7. Page 11
Main results	16	(a) Give unadjusted and, if applicable, confounder-adjusted estimates and their precision. Make clear which confounders were adjusted for and why	Tables 2–6; Results — Hyperglycemic indices; Hypoglycemia and exposure window; Time-to-event analysis (adjusted for diabetes and hemorrhage subtype; sensitivity adjustment for GCS); Hypoglycemia and mortality (adjusted for GCS and age). Page 11
		(b) Report category boundaries when continuous variables were categorized	Methods — Exposure definitions (hypoglycemia <70 and <54 mg/dL; hyperglycemia burden >180 mg/dL). Page 8
		(c) If relevant, consider translating estimates of relative risk into absolute risk	Table 7 / Figure 3 (absolute cumulative incidence by day 7, 10, 14, 21). Page14
Other analyses	17	Report other analyses done—eg subgroups, interactions, sensitivity analyses	Results — Time-to-event analysis (severity-adjusted sensitivity, HR 2.28); Hypoglycemia and mortality (insulin-adjusted sensitivity); Supplementary Tables 1–2. Page 13
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion, opening paragraph. Page14
Limitations	19	Discuss limitations, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion — Limitations (21 events limit power; retrospective single-center design; non-standardized glucose sampling; immortal-time bias; coarse characterization of baseline glycemic status). Page 17
Interpretation	20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, and other evidence	Discussion; Limitations (no association detected rather than none exists); Conclusion. Page 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion — Limitations (single-center design; findings apply to acute stress hyperglycemia in a largely non-diabetic cohort). Page 14
Other information			
Funding	22	Give the source of funding and the role of the funders	None. This study received no specific funding.

**Give information separately for exposed and unexposed groups.*

Supplementary Table 1. Multiple comparisons across glycemic hypotheses

Exposure	Raw P	Bonferroni	BH-FDR
Minimum glucose (whole)	**0.012**	**0.169**	**0.169**
Hypoglycemia < 70 (whole)	0.059	0.826	0.377
Minimum glucose (pre-dx)	0.081	1.000	0.377
Hypoglycemia < 54 (whole)	0.146	1.000	0.512
Glucose CV (72 h)	0.192	1.000	0.537
Mean glucose (whole)	0.314	1.000	0.612
Hyperglycemia burden (whole)	0.322	1.000	0.612
Hypoglycemia < 70 (pre-dx)	0.350	1.000	0.612
Admission glucose	0.483	1.000	0.694
Hypoglycemia < 54 (72 h)	0.495	1.000	0.694
Mean glucose (pre-dx)	0.586	1.000	0.746
Glucose CV (whole)	0.777	1.000	0.906
Peak glucose (whole)	0.972	1.000	1.000
Hypoglycemia < 70 (72 h)	1.000	1.000	1.000

Of the glycemic hypotheses examined, the single nominally significant result — minimum glucose over the whole admission — is precisely the exposure most vulnerable to reverse causation. None survived Bonferroni or Benjamini–Hochberg correction.

Abbreviations: pre-dx, before infection diagnosis; CV, coefficient of variation; BH-FDR, Benjamini–Hochberg false discovery rate.

Supplementary Table 2. Sensitivity of the equivalence margin

Index	δ = 1.30	δ = 1.50	δ = 2.00
Admission glucose	**No**	**No**	**Yes**
72-h mean glucose	No	No	Yes
Whole-admission mean glucose	No	No	No
Peak glucose	No	No	Yes
Hyperglycemia burden	No	No	Yes
Glucose CV	No	No	Yes
72-h glucose CV	No	No	No

Odds ratios per 1 SD. Equivalence under three candidate margins (δ = upper OR bound; lower bound 1/δ). No index is equivalent at the reference δ = 1.50, and none is equivalent at the stricter δ = 1.30. Equivalence appears for five indices only when the margin is widened to δ = 2.00 (OR 0.50–2.00), a range that permits effects large enough to be clinically important; two indices are not equivalent even then. The finding is therefore best described as an absence of detectable association under an underpowered design, not as demonstrated equivalence.

Abbreviations: SD, standard deviation; OR, odds ratio; CV, coefficient of variation.

Supplementary Table 3. Hyperglycemia indices — equivalence testing

Index	OR	90% CI	TOST P	BF_{01}	Within margin
Admission glucose	**0.88**	**0.58–1.35**	**0.141**	**2.0**	**No**
72-h mean glucose	0.92	0.61–1.40	0.102	2.1	No
Whole-admission mean glucose	0.68	0.42–1.11	0.469	1.1	No
Peak glucose	1.05	0.70–1.56	0.068	2.3	No
Hyperglycemia burden	0.79	0.51–1.23	0.260	1.6	No
Glucose CV	0.91	0.59–1.38	0.116	2.1	No
72-h glucose CV	0.71	0.39–1.31	0.426	1.3	No

Odds ratios are per 1 standard deviation increase in each index, so that a single equivalence margin is comparable across indices. Equivalence margin OR 0.67 to 1.50, chosen post hoc with reference to effect sizes reported for established infection risk factors; this margin was not registered in advance. No index has a 90% confidence interval lying entirely within the margin: point estimates sit near the null, but with 21 events the intervals are too wide to establish equivalence. These data therefore do not demonstrate that hyperglycemia is unrelated to infection; they show only that no meaningful association was detected and that the study is underpowered to exclude one. Two one-sided tests (TOST) were conducted against the margin; margin sensitivity is shown in Supplementary Table 2. BF_{01} quantifies evidence favouring the null (Savage–Dickey density ratio, normal prior on the log odds ratio, SD 0.5); all values are below 3, i.e. no more than anecdotal evidence for the null.

Abbreviations: SD, standard deviation; OR, odds ratio; CI, confidence interval; TOST, two one-sided tests; BF_{01}, Bayes factor for the null; CV, coefficient of variation.

Supplementary Table 4. Time-to-event analysis of hypoglycemia

Model	Estimate	95% CI	P
Time-dependent Cox, unadjusted	**HR 2.01**	**0.75–5.44**	**0.167**
Time-dependent Cox, adjusted	HR 2.04	0.69–6.04	0.199
Time-dependent Cox, severity-adjusted[a]	HR 2.28	0.81–6.42	0.118
Fine–Gray subdistribution hazard	sHR 1.46	0.64–3.31	0.370

Abbreviations: HR, hazard ratio; sHR, subdistribution hazard ratio; CI, confidence interval; GCS, Glasgow Coma Scale.

Supplementary Table 5. Baseline factors and infection

Factor	Infection (n = 21)	No infection (n = 86)	OR	95% CI	P
Insertion in operating room	**15/21 (71.4)**	**69/86 (80.2)**	**0.62**	**0.19–2.24**	**0.385**
Antibiotic-impregnated catheter	4/21 (19.0)	11/86 (12.8)	1.60	0.33–6.29	0.488
Chlorhexidine dressing	5/21 (23.8)	27/86 (31.4)	0.69	0.18–2.23	0.601
Prophylactic antibiotics	13/21 (61.9)	40/86 (46.5)	1.86	0.64–5.74	0.232
Diabetes mellitus	5/21 (23.8)	13/86 (15.1)	1.74	0.43–6.22	0.341
Intraventricular hemorrhage	10/21 (47.6)	36/86 (41.9)	1.26	0.43–3.67	0.633
Intracerebral hemorrhage	10/21 (47.6)	42/86 (48.8)	0.95	0.33–2.76	1.000

Only variables fixed at the time of insertion are shown. Values are the number exposed / group total (%). Odds ratios are conditional maximum-likelihood estimates with exact confidence limits; P values by Fisher's exact test. No factor reached significance, but intervals are wide and moderate effects cannot be excluded. Total dwell time, reinsertion, and CSF sampling frequency are excluded because each continues to change after infection has occurred.

Abbreviations: OR, odds ratio; CI, confidence interval; CSF, cerebrospinal fluid.

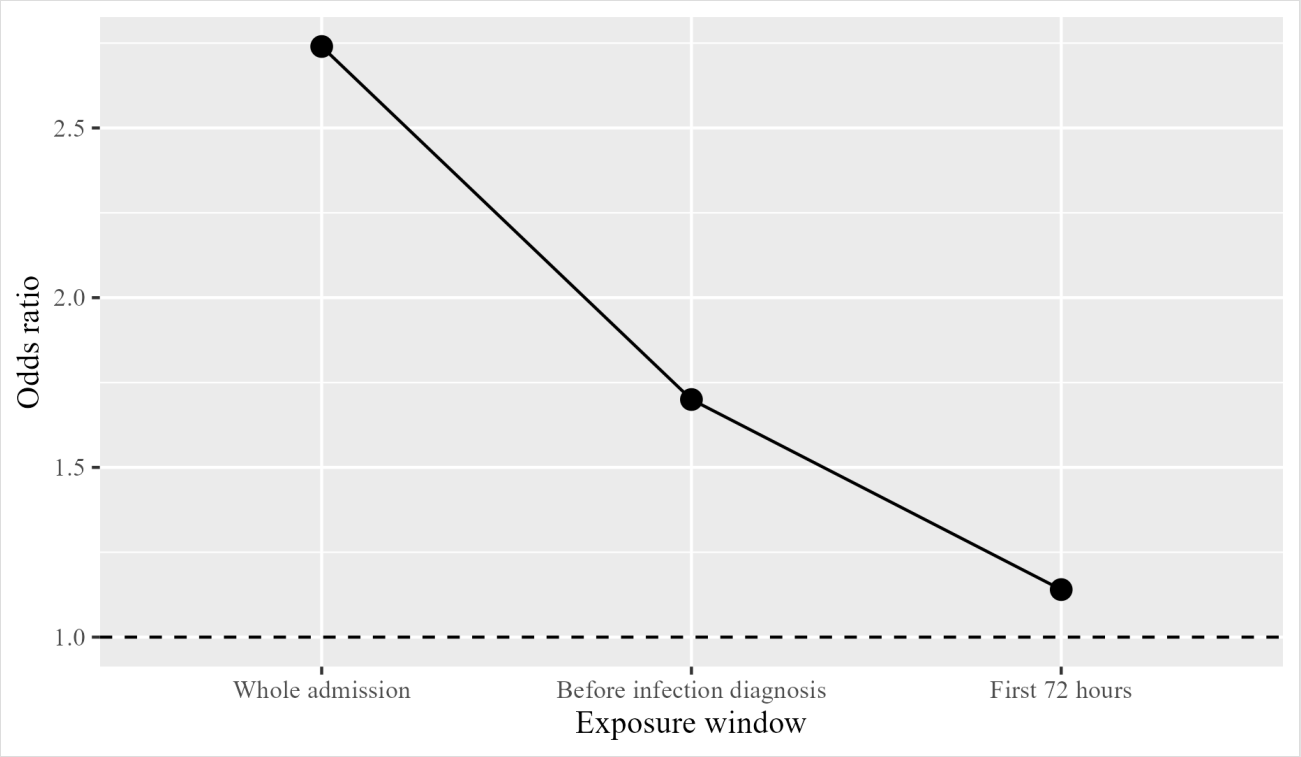
Supplementary Table 6. Cumulative incidence of EVD-associated infection over time

Time	Patients at risk	Cumulative incidence (%)	95% CI (%)
Day 3	**95**	**0.0**	**—**
Day 7	81	2.8	0.0–5.9
Day 10	73	9.4	3.8–15.0
Day 14	56	13.4	6.8–19.9
Day 21	48	17.5	10.1–24.9

Aalen–Johansen estimator, accounting for death before infection as a competing event. The time scale is days from insertion, not days of catheter retention. Consistent with the study protocol, patients were followed for infection until hospital discharge or death, including the period after EVD removal; Figure 3 is truncated at day 21, by which time 18 of the 21 infections had occurred. Risk remains low through the first week and rises thereafter; because this describes the timing of infection risk from insertion rather than an effect of catheter dwell time, it characterizes when infections occur but cannot establish that earlier removal reduces infection.

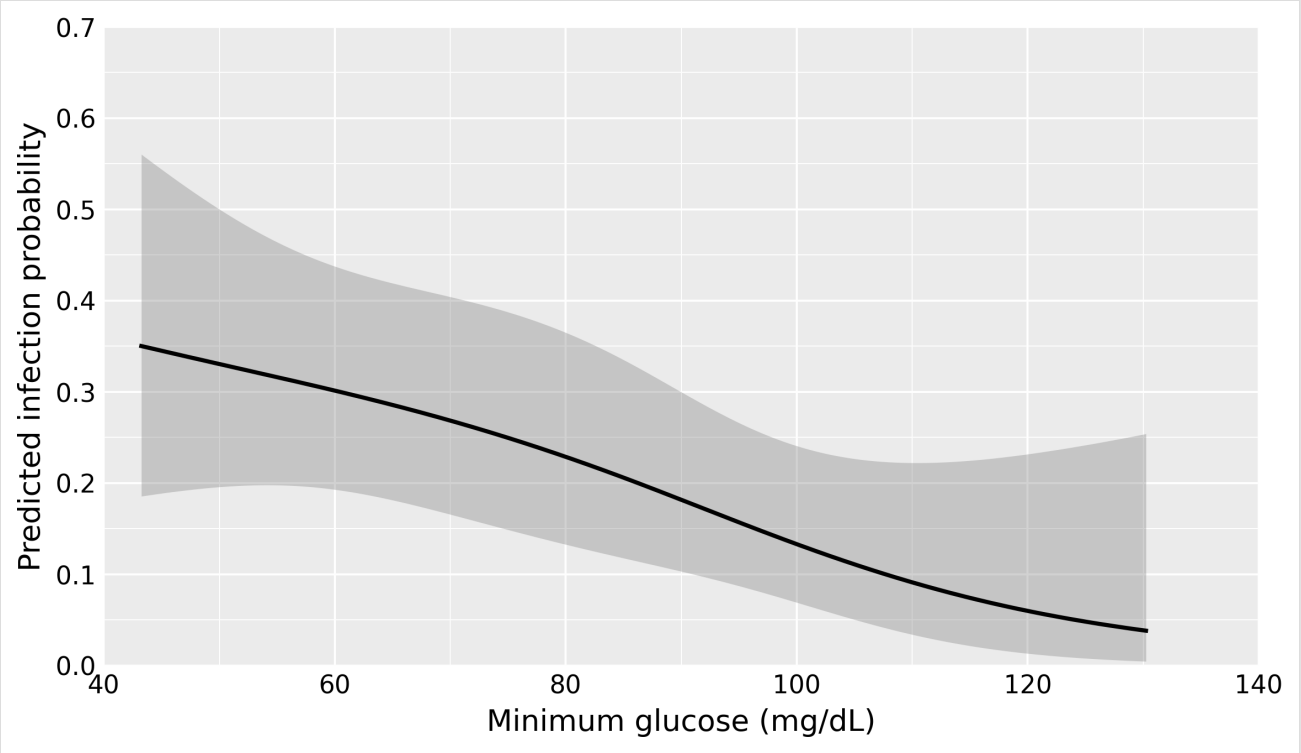
Abbreviations: EVD, external ventricular drain; CI, confidence interval.

Supplementary Figure 1. Odds ratio for hypoglycemia across exposure windows



Odds ratio for hypoglycemia (<70 mg/dL) and EVD-associated infection across three exposure windows: the whole admission, the period before infection diagnosis, and the first 72 hours after insertion. The dashed line marks the null value. The point estimate attenuates as the window narrows; the whole-admission and 72-hour estimates were not formally distinguishable (ratio of odds ratios 0.43, P = 0.285). Confidence intervals are omitted for clarity (see Table 2).

Supplementary Figure 2. Predicted infection probability by minimum glucose



Predicted probability of EVD-associated infection as a function of minimum glucose over the whole admission, estimated by logistic regression with a restricted cubic spline (three knots at the 10th, 50th, and 90th percentiles). The shaded area is the 95% confidence band. The curve is plotted across the 5th–95th percentile of minimum glucose (43–130 mg/dL). The curve is hypothesis-generating and should not be interpreted as a dose–response relationship.