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Prehospital Delay and the Care Cascade in Intracranial Suppurative Infections: An Exploratory Mediation Analysis of In-Hospital Prognosis in a Resource-Limited Ivorian Cohort

Running title: Prehospital delay and care cascade in intracranial suppurative infections

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Abstract

Background. In our cohort of intracranial suppurative infections (ISI), the median delay between symptom onset and admission was 19 days. We hypothesised that a longer prehospital delay is associated with higher in-hospital mortality, partly through impaired consciousness on admission, measured by the Glasgow Coma Scale (GCS).

Methods. Single-centre secondary analysis of 150 admissions (148 patients; 16 deaths; mortality 10.7%) at Bouaké University Hospital, Côte d'Ivoire, 2016–2026. The care cascade distinguished the prehospital phase (symptom onset to admission; n = 150) from the in-hospital phase (admission to surgery; n = 125 operated patients). Associations between delay, severity and lesion characteristics were estimated with Spearman's coefficient and models adjusted for age

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and sex. A counterfactual mediation analysis (natural direct and indirect effects expressed as odds ratios; non-parametric percentile bootstrap, 2000 resamples) followed a causal framework defined before model estimation (directed acyclic graph). Firth penalised regression, sensitivity analyses (adjustment for rurality and referral, exclusion of scalp involvement and of postoperative forms, one admission per patient, risk-scale g-formula) and the E-value assessed robustness. Given 16 deaths, all analyses are exploratory.

Results. The median prehospital delay (19 days; IQR 15–25) was about nine to ten times the admission-to-surgery delay (2 days; IQR 1–3). A prolonged delay (>19 days) was associated with rural residence (aOR 2.27; 95% CI 1.16–4.43) and, borderline, with referral from another facility (aOR 1.88; 95% CI 0.96–3.67). A longer delay was associated with a lower admission GCS ($\rho = -0.25$; $p = 0.002$; −0.67 point per 10 days after adjustment). The total effect of delay on death was imprecise and compatible with no effect (OR 1.79 per +10 days; 95% CI 0.85–4.52). The proportion mediated through the GCS was about 19% (95% CI −48 to 105%); the indirect effect (OR 1.11; 95% CI 0.99–1.39) did not reach significance. Adjustment for rurality and referral modestly attenuated the direct effect (OR 1.49; 95% CI 0.73–3.19).

Conclusion. Delay was mainly prehospital and associated with structural access factors and with a lower GCS on admission; its effect on mortality remained imprecise. Prehospital delay is a potential target for organisational interventions, whose effectiveness must be evaluated prospectively.

Keywords: intracranial suppurative infection; prehospital delay; care cascade; mediation analysis; Glasgow Coma Scale; global neurosurgery; sub-Saharan Africa.

This work uses the Ivorian cohort of intracranial suppurative infections (Bouaké University Hospital, 2016–2026) to understand how the delay before admission relates to mortality. This delay runs from symptom onset to admission to the hospital, not to diagnosis: in this sense we call it "prehospital delay".

Abbreviations

ISI: intracranial suppurative infection · GCS: Glasgow Coma Scale · IQR: interquartile range · OR: odds ratio · aOR: adjusted OR · 95% CI: 95% confidence interval · NDE: natural direct effect · NIE: natural indirect effect · DAG: directed acyclic graph · STROBE / AGReMA: reporting guidelines for, respectively, observational studies and mediation analyses.

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Research in context

- **What is already known.** Delayed care is associated with a poorer prognosis in ISI, but few studies separate its prehospital and in-hospital components, and, to our knowledge, none in sub-Saharan Africa has decomposed its effect on mortality.
- **What this study adds.** To our knowledge, this is the first decomposition of the care cascade coupled with a mediation analysis in a West African cohort. The delay is almost entirely prehospital, and an exploratory share of its association with death is compatible with mediation by the GCS.
- **Implications.** Improvement efforts could first target the prehospital phase and referral pathways, subject to prospective evaluation.

1. Introduction

Intracranial suppurative infections (ISI) are neurosurgical emergencies in which every day counts: prognosis depends on the speed of diagnosis and drainage [1–4]. In our Ivorian cohort, patients arrived a median of 19 days after symptom onset. A Danish series reports 7 days between first symptoms and antibiotic therapy; this interval is close to ours, without being identical [5]. Unlike the biology of the infection, this delay can be reduced through the organisation of care. It belongs to global neurosurgery: the Lancet Commission on Global Surgery and the work that followed show that a large share of the population of low- and middle-income countries, especially in sub-Saharan Africa, lacks timely access to safe surgery [6–7].
In the prognostic component of this series, a GCS < 9 on admission was the factor most strongly associated with death (aOR 3.79; 95% CI 1.11–12.92: an imprecise estimate, and only 5 of the 16 deaths occurred at GCS < 9). Delay appeared to be an upstream determinant of it. Here we wanted to go beyond simply measuring the delay and to understand by which path it might lead to death. We first decomposed the care cascade to identify the longest segment. We then tested, by a mediation analysis [8–11], whether the link between delay and death is compatible with a passage through clinical severity on admission.

Hypothesis. A longer prehospital delay would increase in-hospital mortality, in part by worsening consciousness on admission (GCS). To our knowledge, no study from sub-Saharan Africa has yet combined care-cascade decomposition and causal mediation in ISI.

2. Patients and methods

2.1. Population, statistical unit and selection

Secondary analysis of the database described in the previous components (Bouaké University Hospital, 2016–2026), reported according to STROBE [12]. The **statistical unit** was the admission: 150 admissions, 148 patients. Two patients had two admissions, corresponding to distinct infectious episodes, retained as independent observations. An analysis with one admission per patient (n = 148) checks that this slight dependence does not change the results.

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None of the 150 admissions was excluded: age, sex, delay, GCS and vital status were recorded in all cases. The primary outcome was in-hospital mortality (16 deaths; 10.7%). Missing data were not imputed (complete-case analysis; numbers in Table 1). The flow diagram is shown in Figure 1.

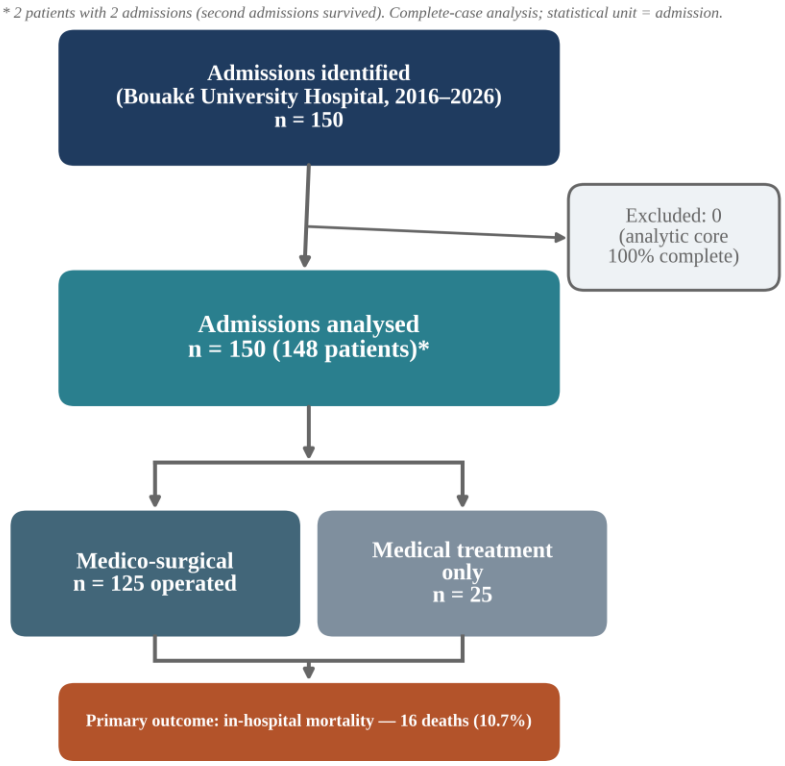


Figure 1. Flow diagram (STROBE). No admission was excluded; the statistical unit is the admission.

2.2. Definition of the cascade and delays

The exposure, which we call "prehospital delay", is the interval between **symptom onset** and **admission to the university hospital**. It does not measure the delay to radiological diagnosis, the time of which is not reliably recorded in the files. The in-hospital phase is the admission → surgery interval, available for the 125 operated patients. To describe the access pathway, we used referral status, place of residence and mode of transport. The time of first medical contact was not available: referral status is the only indirect indicator. In the 77 referred patients, the delay therefore includes the time spent in the first-line facility. "Prehospital" here means "before admission to the university hospital": patient delay cannot be separated from health-system delay. This breakdown is inspired by the "three delays" model [13], the prehospital phase grouping the decision to seek care and access to an appropriate facility.

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2.3. Causal framework and adjustment variables

The directed acyclic graph (DAG; Figure 6) [14] was defined before the models were estimated. Age and sex, confounders of the relationship between delay, GCS and death, are included in all models. Rurality and referral status lie upstream of the delay: we studied them as determinants of the delay, without including them in the main mediation model, because 16 deaths do not allow additional covariates to be added without major instability. They therefore remain possible confounders of the delay–death relationship (crude mortality: 10/78 in rural versus 6/72 in urban areas); a sensitivity analysis that includes them is reported in § 3.5. The graph contains only measured variables. Immunosuppression, type of suppuration, ventricular rupture and hydrocephalus are plausible common causes of the GCS and of death (the last two may also result from the delay); they are not in the main model and limit the causal interpretation of the natural effects (§ 4.4). Adjustment variables were chosen on clinical and causal reasoning, not on their significance.

2.4. Statistical analysis and mediation

Delays are described by their median and IQR, and compared between subgroups with the Mann–Whitney test. Determinants of a prolonged delay were sought by adjusted logistic regression, with a threshold of 19 days (the median), also used for the sensitivity analyses; the mediation treats the delay as continuous. The delay–GCS association was quantified by Spearman's coefficient, then by a linear regression adjusted for age and sex (residual diagnostics in § 3.6).

The mediation follows the counterfactual framework of natural effects [9–10], reported according to AGReMA [11]. The exposure is the delay (contrast of +10 days), the mediator the continuous GCS and the outcome death; age and sex are included. A linear model relates the delay to the GCS (path a), and a logistic model the GCS to death, at a given delay (path b). The natural direct (NDE) and indirect (NIE) effects are expressed as ORs, assuming no exposure–mediator interaction and a rare event. With 10.7% of deaths, close to the usual 10% threshold, these natural ORs remain approximations. The proportion mediated is calculated on the log-OR scale.

Confidence intervals come from a non-parametric percentile bootstrap: 2,000 replications, seed fixed at 20261003, resampling admissions with replacement (patients for the one-admission-per-patient analysis); all 2,000 replications of the main analysis were valid. We checked their agreement with bias-corrected and accelerated (BCa) intervals [15], as well as the stability of estimates across subsamples. With 16 deaths (about 3 events per variable in the outcome model), the models are deliberately parsimonious [16–17], and a Firth logistic regression [18–19] was added as a sensitivity analysis to limit small-sample bias and the risk of separation. The E-value [20] assesses sensitivity to unmeasured confounding. We examined the residuals of the linear model (normality, homoscedasticity), influential observations (Cook's distance), collinearity (variance inflation factors) and the linearity of the delay (restricted cubic splines). As the analytic

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core (delay, GCS, death) was complete, no imputation was performed: the analysis is a complete-case analysis. The results are exploratory. The analyses used Python 3.12 (statsmodels 0.14, SciPy 1.17, NumPy 2.4, pandas) and a Firth implementation developed for the study.

Mediation assumptions. The causal interpretation of natural effects assumes no unmeasured confounding (between exposure and mediator, mediator and outcome, exposure and outcome), correct chronology and measurement without systematic error. A retrospective study cannot guarantee these conditions; we discuss the consequences in the limitations.

Sensitivity analyses. We varied the delay (continuous, or thresholds > 14, > 19, > 21 days), the mediator (GCS < 9), the method (Firth regression), the shape of the delay (splines), the covariates (Firth mediation additionally adjusted for rurality and referral), the population (without scalp involvement, 14 observations, then without postoperative forms, 27 observations; one admission per patient, n = 148, with resampling by patient) and the scale (g-formula on the risk scale, for a standardised contrast from 19 to 29 days, preferable here since 10.7% of patients died). The determinants of the delay were also studied by linear regression of its logarithm.

3. Results

3.1. Time is lost before the hospital

Time was lost before arrival at the hospital: 19 days in median for the prehospital phase (IQR 15–25; n = 150), versus 2 days (IQR 1–3) between admission and surgery in the 125 operated patients. The ratio, about 9 to 10, remains descriptive: it compares different numbers of patients, without adjustment (Figure 2, Table 1). The main delay segment is therefore upstream of the referral centre.

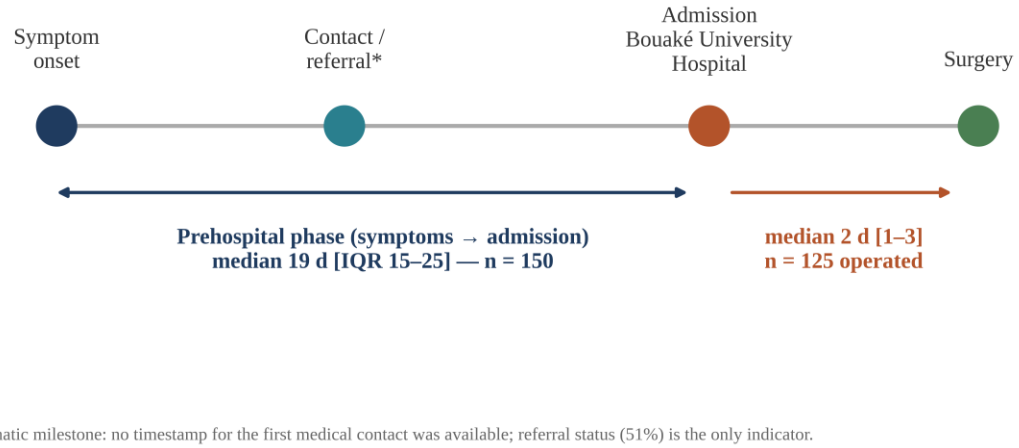


Figure 2. Care cascade. The prehospital phase (symptoms → admission; n = 150) concentrates most of the delay; the in-hospital phase (admission → surgery) is measured only in the 125 operated patients. The first medical contact was not timestamped.

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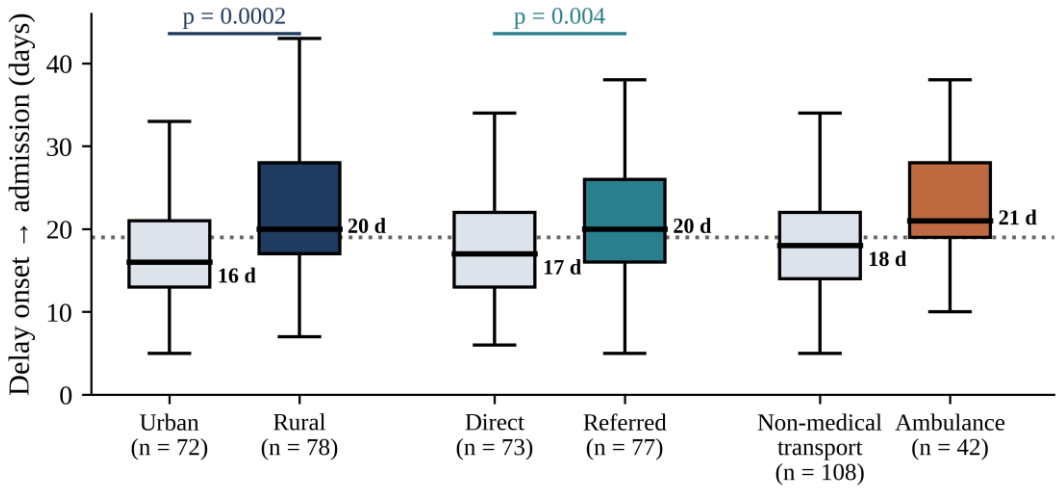
Table 1. Analytic numbers, completeness and delays of the cascade segments.

Variable / segment	n available	Missing	Median (d)	IQR
Delay symptoms → admission	150	0%	19	15–25
Delay admission → surgery (operated)	125	—*	2	1–3
GCS on admission	150	0%	13	10–15
Maximum lesion size	144	4%	36	30–44
Mass effect (presence)	150	0%	—	—

* The operative delay concerns only the 125 operated patients; the other 25 received medical treatment only. The "portal of entry → suppuration" delay (infectious-disease estimate; n = 129, median 17 d) does not belong to the care cascade and is not reported here. The mortality and mediation analyses cover the 150 admissions (16 deaths).

3.2. A delay linked to access to care

The prehospital delay was not randomly distributed. It was longer in rural patients (n = 78; median 20 d versus 16 d for the 72 urban patients; p = 0.0002) and in referred patients (n = 77; 20 d versus 17 d for the 73 non-referred; p = 0.004). It also tended to lengthen with ambulance transport (21 d versus 18 d; descriptive comparison, no test) (Figure 3). Among referred patients, medians varied little according to the facility of origin (19–21 d; description without formal test).



Boxes: median (black line, value shown) and IQR; whiskers: minimum–maximum; dotted line: overall median (19 d). No individual data are shown.

Figure 3. Prehospital delay by place of residence, referral status and mode of transport. Boxes: median and IQR; whiskers: minimum–maximum; dotted line: overall median (19 days).

In multivariable analysis (Table 2), rural residence increased the probability of a delay > 19 days, after adjustment for age and referral status (aOR 2.27; 95% CI 1.16–4.43; p = 0.017); referral

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status did so borderline (aOR 1.88; 95% CI 0.96–3.67; p = 0.065). These associations are compatible with the weight of inequalities in access, without excluding that of the natural history of the infection (subacute forms inherently last longer). The delay treated as continuous (linear regression of its logarithm) gives the same results: rurality multiplies the geometric mean of the delay by 1.23 (95% CI 1.11–1.36; p < 0.001), referral status by 1.16 (1.05–1.28; p = 0.004) and each 10-year age increment by 1.01 (0.98–1.04; p = 0.52).

Table 2. Determinants of a prolonged prehospital delay (> 19 days): logistic regression.

Factor	aOR [95% CI]	p
Rural residence (vs urban)	2.27 [1.16–4.43]	0.017
Referred patient (vs direct)	1.88 [0.96–3.67]	0.065

Logistic regression of delay > 19 days, mutually adjusted for rurality and referral, and for age; the outcome is the prolonged delay, not death. aOR: adjusted odds ratio. For descriptive purposes, crude mortality was 10/78 in rural versus 6/72 in urban areas, and 9/77 in referred versus 7/73 in non-referred patients.

3.3. Delay and severity on admission

The longer the delay, the lower the admission GCS: Spearman ρ = −0.25 (p = 0.002; n = 150), i.e. −0.67 GCS point per 10-day increment after adjustment for age and sex (95% CI −1.26 to −0.08; p = 0.027) (Figure 4). By delay tertile (≤ 16 d, n = 55; 17–21 d, n = 45; ≥ 22 d, n = 50), the proportion with GCS < 9 was 5%, 20% and 14%: higher in the two long tertiles than in the first, without a regular progression. Mortality, for its part, increased steadily (5%, 11%, 16%).
In contrast, the delay was not linked to the radiological lesion burden: neither to the maximum size of the collection (ρ = 0.10; p = 0.23; n = 144), nor to the presence of a mass effect (median delay 19 d versus 17 d; p = 0.23). The absence of significance does not prove the absence of an effect: it may come from a lack of power or imperfect measurement. It nevertheless suggests that the time-related deterioration is read more in the clinical picture than in these morphological markers.

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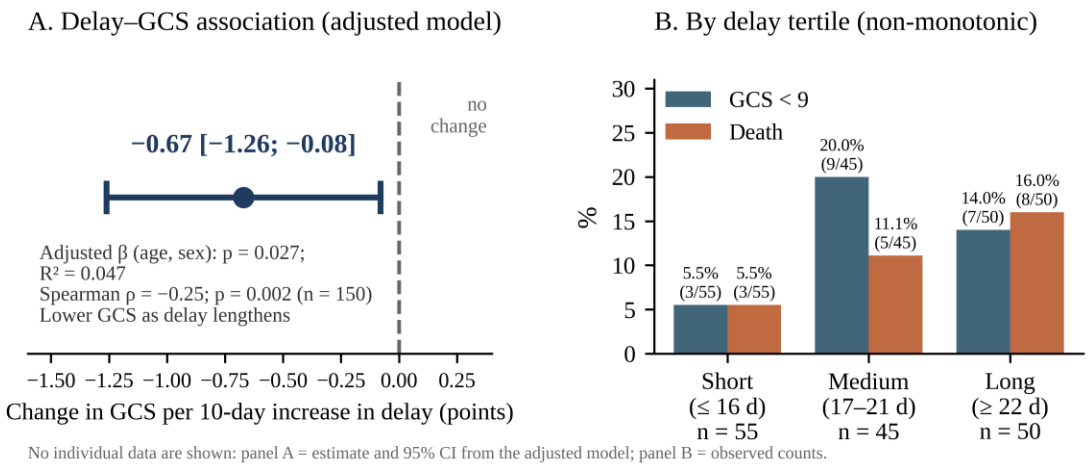


Figure 4. A. Association between prehospital delay and admission GCS: change in GCS per 10-day increment, adjusted for age and sex, with its 95% CI. B. Proportion with GCS < 9 and mortality by delay tertile (numbers: 55, 45, 50; GCS < 9: 3, 9 and 7; deaths: 3, 5 and 8). No individual data are shown.

3.4. Exploratory mediation analysis

For 10 additional days of delay, the total effect on death was imprecise and compatible with no effect (OR 1.79; 95% CI 0.85–4.52; n = 150, 16 deaths). It decomposes into a direct effect, outside the GCS, of OR 1.61 (95% CI 0.81–3.66) and an indirect effect, through the GCS, of OR 1.11 (95% CI 0.99–1.39) (Figure 5, Table 3). The proportion mediated is estimated at about 19%, with a very wide interval (−48 to 105%). Path b (GCS → death, adjusted for delay, age and sex) is 0.85 per GCS point (95% CI 0.74–0.97; p = 0.018). These results are exploratory and hypothesis-generating: they are compatible with a partial role of the GCS, without demonstrating it. The total effect of 1.79 is the product of the two natural effects; direct logistic regression of death on delay gives 1.68 (95% CI 0.89–3.18; Table 4). The difference is due to the non-collapsibility of the OR and to the approximations of the mediation model; both estimates are read in the same way.

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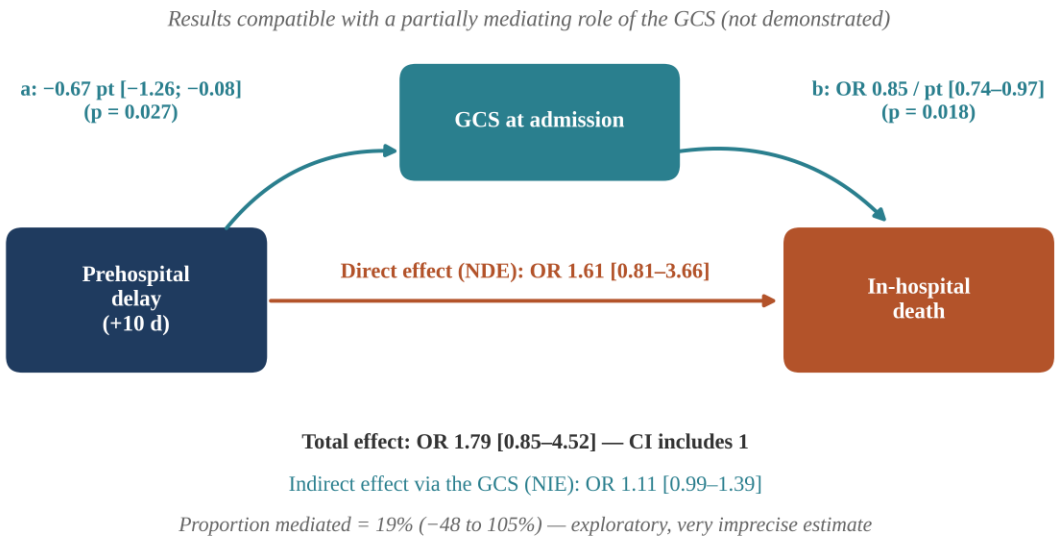


Figure 5. Mediation decomposition. The total effect of the delay on death is imprecise (CI including 1). The indirect effect through the GCS and the proportion mediated are exploratory, with very wide intervals.

Table 3. Decomposition of the prehospital delay (+10 days) – death association (OR scale; n = 150; 16 deaths).

Effect	OR [95% percentile CI]	Interpretation
Total effect	1.79 [0.85–4.52]	CI including 1
Direct effect (NDE)	1.61 [0.81–3.66]	outside the GCS
Indirect effect (NIE)	1.11 [0.99–1.39]	via the GCS
Proportion mediated	≈ 19% [−48 to 105%]	very imprecise

Natural effects under the assumption of no interaction and a rare event; percentile bootstrap, 2,000 replications, age/sex adjustment. The total effect is the product of the natural effects (1.61 × 1.11); direct logistic regression gives 1.68 (95% CI 0.89–3.18; Table 4). The small number of deaths explains the low precision and requires an exploratory reading.

3.5. Sensitivity analyses

The sensitivity analyses went in the same direction as the main analysis, without gaining precision (Table 4). Depending on the delay threshold, the aOR for death ranged from 1.49 (> 14 d) to 2.36 (> 21 d), all intervals including 1; with the delay as continuous, it was 1.68 per +10 days (95% CI 0.89–3.18). With GCS < 9 as mediator, the proportion mediated rose to ~42%, but unstably (quasi-separation due to the small sample). No variant changed the message: same direction, insufficient precision to conclude an effect.

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Table 4. Sensitivity analyses of the delay – death association (adjusted for age and sex).

Delay definition	Mortality	OR [95% CI]	p	Method
> 14 days (n = 116)	11% vs 9%	1.49 [0.39–5.74]	0.56	Logistic
> 19 days (n = 66)	15% vs 7%	2.26 [0.77–6.67]	0.14	Logistic
> 21 days (n = 50)	16% vs 8%	2.36 [0.81–6.85]	0.12	Logistic
Continuous (+10 d)	—	1.68 [0.89–3.18]	0.11	Logistic
Continuous (+10 d)	—	1.67 [0.90–3.10]	—	Firth

All estimates are compatible with no effect (CI including 1). Their robustness lies in the consistency of direction, not in significance. Firth regression gives an almost identical estimate to the standard model.

Adjustment for rurality and referral status. In a Firth model without interaction, adjusted for delay, GCS, age, sex, rurality and referral, the total effect was 1.65 (95% CI 0.80–3.63), the direct effect 1.49 (0.73–3.19) and the indirect effect 1.11 (0.98–1.35); the proportion mediated was 21% (−52 to 111%). The direct effect decreased moderately (1.49 versus 1.61), without changing the reading: a very imprecise mediation. **Exclusions.** Without scalp involvement (n = 136; 15 deaths, 11.0%), the total effect was 1.76 (0.82–4.40), the direct effect 1.58 (0.77–3.54) and the indirect effect 1.11 (0.99–1.40). Without postoperative forms (n = 123; 14 deaths, 11.4%, i.e. 2 deaths among the 27 postoperative forms), they were 1.84 (0.85–4.55), 1.64 (0.79–3.68) and 1.12 (0.99–1.41). These exclusions, which address the heterogeneity of the forms included, did not change the estimates. **One admission per patient.** Keeping only one admission per patient (n = 148; 16 deaths, 10.8%; the two admissions removed concerned survivors), with resampling at patient level, the main results were found again: total effect 1.80 (0.85–4.56), direct effect 1.62 (0.81–3.70), indirect effect 1.11 (0.99–1.39) and proportion mediated 19% (−49 to 106%).

Decomposition on the risk scale. For a standardised contrast from 19 to 29 days (g-formula), the risk of death was 9.8% at 19 days, 14.9% with the direct effect alone and 16.1% at 29 days. The total effect was +6.3 points (95% CI −1.3 to +14.8), the direct effect +5.1 points (−1.9 to +13.5) and the indirect effect, through the GCS, +1.2 points (−0.2 to +3.6), i.e. a proportion mediated of 19% on the additive scale (−47 to 103%). This scale suits a mortality of 10.7% better than an OR; it leads to the same conclusion: a small indirect effect, whose interval includes zero.

3.6. Robustness and model diagnostics

Firth regression. With Firth penalisation, estimates were superimposable on the standard analysis: total effect OR 1.67 (95% CI 0.90–3.10); in the outcome model of the mediation, direct effect OR 1.59 and indirect effect OR 1.11 (mediated share ≈ 18%; their product, 1.76, departs

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slightly from the total effect estimated directly, 1.67, for the same reasons of approximation); determinants of prolonged delay: rurality OR 2.22 (1.13–4.32), referral OR 1.85 (0.95–3.60). Penalisation changed neither the direction nor the magnitude of the associations, which rules out separation bias despite the 16 deaths.

Agreement of bootstrap intervals. Percentile and BCa intervals agreed (indirect effect: percentile 0.99–1.39 versus BCa 1.00–1.41; direct effect: 0.81–3.66 versus 0.76–3.49), and estimates were stable across subsamples; we therefore retained the percentile interval. The BCa lower bound of the indirect effect, rounded to 1.00, places this effect at the borderline of significance.

Model diagnostics. The linear delay → GCS model explained little variance ($R^2 = 0.047$; adjusted $R^2 = 0.028$), which is expected for a single determinant of a multifactorial clinical score. Residuals departed from normality (Shapiro $W = 0.92$; $p < 0.001$), as is common for a bounded, discrete score. Homoscedasticity was respected (Breusch–Pagan $p = 0.87$), no observation was influential to a worrying degree (maximum Cook's distance 0.06) and no collinearity was detected (variance inflation factors ≈ 1.0). As inference does not rest on normality alone, Spearman's coefficient, independent of the distribution, confirmed the association ($\rho = -0.25$; $p = 0.002$).

Linearity. Restricted cubic splines suggested a moderate departure from linearity of the delay → GCS relationship (likelihood-ratio test $p = 0.028$), without reversing its direction; a logarithmic transformation of the delay did not change the correlation. The linear coefficient (−0.67 point/10 d) is therefore read as an average slope. Splines were not feasible for the death model (singular matrix) with 16 events, which supports the choice of parsimonious models.

Unmeasured confounding. The E-value of the total effect (risk ratio approximated by the square root of the OR, the outcome not being rare) was 2.01 (2.98 if the risk ratio is equated with the OR): to explain the point estimate alone, an unmeasured confounder would have to be associated with both the delay and death by a risk ratio of at least 2.0. As the confidence interval already includes no effect, the corresponding E-value was 1.0: no confounding is needed to make the result compatible with no effect.

Discrimination. For descriptive purposes (prediction was not the objective), the outcome model (death ~ delay + GCS + age + sex) had moderate discrimination (apparent AUC 0.71; bootstrap 95% CI 0.60–0.88; optimism-corrected 0.64 [21]) and a Brier score of 0.09, versus 0.096 for a model without covariates at this prevalence: the gain, of about 6%, is modest. Detailed calibration (intercept, slope, curve) and the decision curve are in the prognostic component (component 2).

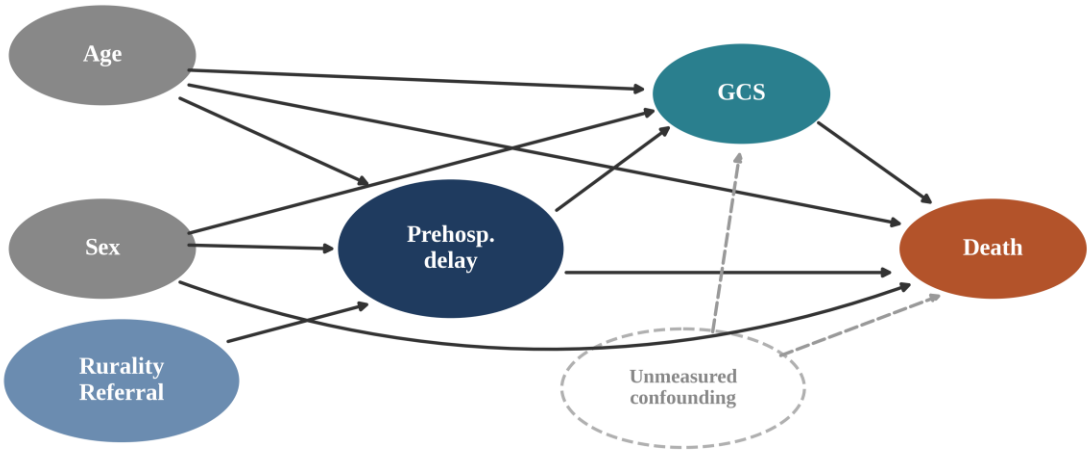
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Table 5. Summary of multivariable models (n = 150; age and sex adjustment).

Model	Main association	Estimate [95% CI]	Method
Delay determinant	Rurality → delay > 19 d	aOR 2.27 [1.16–4.43]	Logistic
Mediator (path a)	Delay (+10 d) → GCS	β −0.67 [−1.26; −0.08]	Linear
Outcome (path b)	GCS → death (/point)	OR 0.85 [0.74–0.97]	Logistic
Total effect	Delay (+10 d) → death	OR 1.79 [0.85–4.52]	Mediation
Direct effect (NDE)	outside the GCS	OR 1.61 [0.81–3.66]	Mediation
Indirect effect (NIE)	via the GCS	OR 1.11 [0.99–1.39]	Mediation

Summary of the detailed estimates in Tables 2–4 and Figure 5 (DAG: Figure 6). NDE/NIE: natural direct/indirect effects; 95% CI by bootstrap for the mediation. Apparent AUC of the outcome model 0.71 (Brier 0.09).



Adjustment for age and sex (confounders). Rurality/referral: upstream determinants, not included in the main mediation model.
Dashed: unmeasured confounding, not excluded.

Figure 6. Directed acyclic graph (DAG) fixing the presumed causal structure before model estimation and justifying the adjustments (age and sex: confounders; rurality and referral: upstream determinants, not included in the main mediation model).

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4. Discussion

Four questions guide this discussion: where is time lost, how might it act on prognosis, what follows from this, and what remains to be demonstrated?

4.1. Where the delay lies

The delay was concentrated in the prehospital phase (median of 19 days, versus 2 days to surgery; IQR 1–3), therefore upstream of the referral centre. The operative delay is nevertheless not negligible for urgent lesions: in the TRIAGE-ISI component of the series, only 41 patients (27% of the cohort) were operated within 24 hours. We did not analyse its effect on GCS or death (non-operated patients and early deaths expose to immortal-time bias). The in-hospital segment therefore remains a possible lever [6–7].

4.2. How the delay might act

The delay appears mainly linked to structural access factors: it lengthens with rural residence and referred status, independently of age, which ties ISI to global neurosurgery, whose deficit is marked in sub-Saharan Africa [6–7]. As for the mechanism, a longer delay went with a lower GCS on admission (path a, the most consistent). In the prognostic component, the GCS was also the factor most strongly associated with death (imprecise estimate); but 11 of the 16 deaths occurred at GCS $\geq$ 9, so that the GCS explains only part of the mortality. Our results are therefore compatible with a partial role of severity on admission, without demonstrating it: the mediated share (~19%) is very imprecise and the total effect remains compatible with no effect. The most consistent links are delay–rurality and delay–GCS, more than delay–mortality; even so, the delay–GCS association is of small magnitude (−0.67 point per 10 days; lower bound of the CI at −0.08; $R^2 = 0.047$).

In pathophysiological terms, several mechanisms make this link plausible. Over time, cerebritis evolves into an organised abscess and the collection extends; perilesional oedema, intracranial pressure and mass effect increase, with a risk of herniation. Complications are added (ventriculitis, hydrocephalus, seizures, sepsis) which impair alertness independently of lesion volume [1–3]. The GCS clinically summarises this cascade: it is the most measurable intermediate link between lost time and outcome.

The absence of a link between delay and radiological markers (size, mass effect) deserves comment. Imaging freezes a moment and does not reflect the whole dynamics of the infection; clinical severity also depends on lesion site, oedema, sepsis or comorbidities; consciousness may finally drop without the collection clearly growing. A long delay could therefore harm through pathways that these markers do not capture, which is consistent with the weight of the direct effect in the decomposition.

Our cohort resembles African series. Its mortality (10.7%) is of the same order as that reported in South Africa (13.4% at discharge, in a series of 973 abscesses [22]), Cameroon (17.1%, i.e. 6

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deaths among 35 operated children [23]) and Nigeria (16.3% in a series of 49 subdural empyemas [24]; Chikani's series of 18 patients reports no mortality [25]). But these series differ in population, endpoints and size: the comparison remains descriptive. Our mortality exceeds that of the Danish national cohort (6% in hospital, 12% six months after discharge) [4]. Recent West African series, a review of 201 cases in Guinea [26] and a Togolese series [27], find a male predominance, ENT portals of entry and CT-centred management; an African systematic review underlines the heterogeneity of definitions and the scarcity of structured prognostic analyses [28]. The Danish series cited above reports a median of 7 days between symptoms and antibiotic therapy [5]; this interval is not strictly comparable with ours (symptoms → admission), and 81% of those patients had first been admitted to a peripheral hospital. The gap with our 19 days nevertheless gives the measure of the access delay in our context. The European ESCMID guidelines codify reference management [29]; their adaptation to resource-limited settings remains to be done.

4.3. What this implies

Our data cannot tell whether the in-hospital phase compensates for the time lost upstream. Mortality comparisons with other series, including meta-analyses [30], are not adjusted for patient profile, and survival bias (patients who died before transfer are not represented) calls for caution. The prehospital delay potentially acts upstream of the factor most strongly associated with death: this is a lead to be evaluated.

These findings tie ISI to global neurosurgery. The Lancet Commission on Global Surgery established that a large part of the population of low- and middle-income countries lacks timely access to safe surgery [6,31–32], and the neurosurgical deficit is particularly marked there [7,33]. Health-system strengthening and resilience are now recognised as the main route to close it [34–35]. The delay we describe is a local expression of it: resources concentrated in a single centre, poorly structured referral pathways, unequal access to imaging, financial barriers that may cause catastrophic expenditure. Unlike age or comorbidities, it is potentially modifiable and can serve as an indicator of the quality of care organisation. Its link with rurality is less a matter of equality (theoretical availability of services) than of equity of access (real ability to benefit from them) [36], a central question for universal health coverage [37] and for integrating essential neurosurgery into national surgical plans (NSOAP) [38]. Work applying the “three delays” model to surgery in sub-Saharan Africa shows that in-hospital delay weighs on operative mortality [39]. The question goes beyond ISI: in ischaemic stroke (“time is brain” [40]) or severe head injury [41], the loss of chance is also largely built before arrival at the expert centre.

Care pathways have been much studied in stroke, trauma or cancer, rarely in ISI. This work shifts the question from “why this delay?” to “how to reduce it?”, which belongs to implementation science [42–45]. Identifying a modifiable factor does not, however, guarantee that acting on it will produce the expected benefit: interventional studies will have to test it. The framework used here (cascade, DAG, mediation, Firth, bootstrap) is transposable to other time-

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dependent neurosurgical emergencies, and the prehospital phase can serve as a measurable indicator of the performance of a neurosurgical system in a resource-limited context.

The following avenues stem from our observations; they are not universal recommendations. For the patient and first-line care: learn to recognise ISI early in any infectious syndrome with neurological expression. For the network: regional transfer protocols, first-line brain imaging, neurosurgical tele-expertise between peripheral centres and the referral centre. For steering: track simple indicators that break down the pathway (symptoms → first contact, first contact → referral, referral → admission, admission → imaging, admission → surgery), in order to target the most contributory segment.

Multicentre validation in West Africa will now be needed, together with a prospective, timestamped measurement of each component of the delay, a multiple-mediator mediation (GCS, sepsis, size and multiloculated character of the collection), then the evaluation of organisational interventions that shorten the prehospital phase. Only this last step can establish a causal relationship, which the present analysis cannot do.

Level of evidence. The most consistent results are a long prehospital delay and its links with rurality and with a lower GCS on admission. A partial role of the GCS between delay and death is plausible, but imprecise. The magnitude of the effect of delay on mortality remains to be confirmed: its estimate is compatible with no effect.

Table 6. Avenues for action by level of the care system: to be evaluated prospectively; these are not recommendations.

Level	Avenue for action	Support in this study
Community	Awareness of neurological warning signs	Not measured (decision to seek care not timestamped)
Peripheral hospital	Early recognition and referral protocol	Not measured (first contact not timestamped; 51% of patients referred)
Region	Rapid access to imaging; tele-expertise	Not measured (delay to imaging access not timestamped)
University hospital	Standardisation of the operative circuit and delays	Median delay of 2 d; effect on outcome not analysed
National system	Neurosurgical networks; delay indicators	Research/policy

These avenues come from the literature and clinical reasoning, not from measurements in this study: only the overall symptoms → admission delay and the operative delay were measured. These data do not rank the levels; the avenues must be evaluated before any generalisation.

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Messages for practice

- **Neurosurgeon:** a low GCS on admission may reflect time already lost upstream (association of small magnitude in this series); prognosis is not decided only in the operating theatre.
- **Emergency physician / first line:** think of ISI in an infectious syndrome with neurological expression and refer without waiting.
- **Radiologist:** the delay to access to brain imaging was not timestamped in this study; this link remains to be measured.
- **Decision-maker:** track simple delays, from first contact to surgery, to identify the segment that weighs most; these data do not rank either the prehospital phase or the operative circuit.

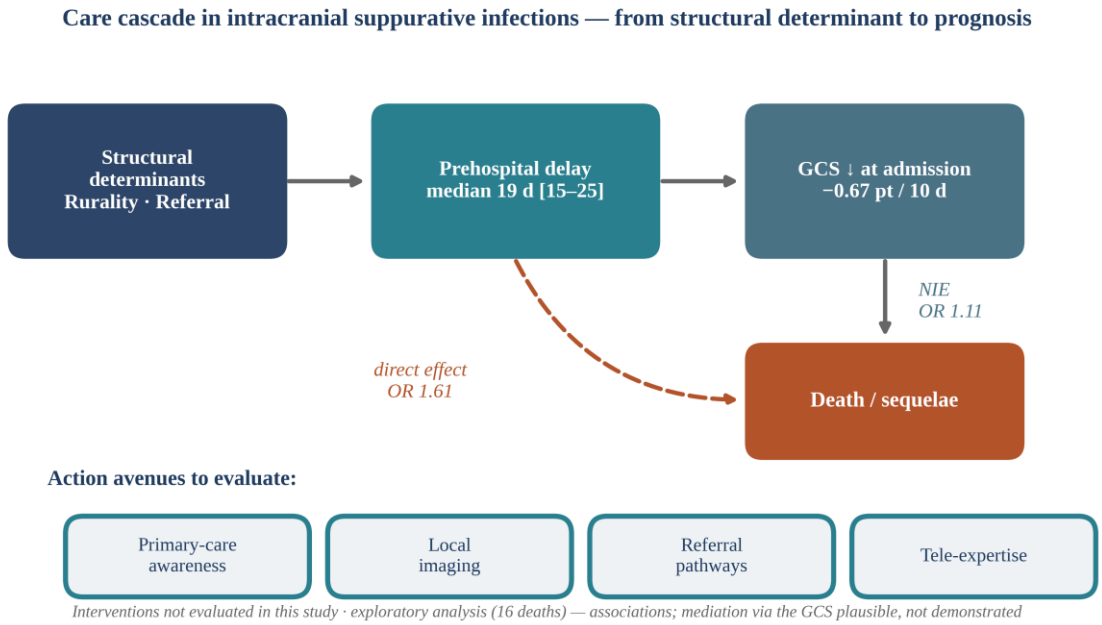


Figure 7. Summary. From structural determinants (rurality, referral) to prehospital delay, then to the fall in GCS and prognosis, with the avenues for action to be evaluated. This diagram summarises observed associations and potential avenues; these data establish no hierarchy of intervention. Mediation by the GCS is plausible, not demonstrated.

4.4. Strengths and limitations

Strengths: homogeneous West African cohort over ten years, explicitly defined delays, causal framework made explicit by a DAG, adjusted analyses, bootstrap intervals and, to our knowledge, the first mediation–cascade decomposition in this context.

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Limitations: with 16 deaths, power is limited, especially for the mediation, whose indirect effect remains imprecise; the risk of over-adjustment requires parsimonious models and an exploratory reading. The study is single-centre, largely retrospective (selection, information and referral bias), without external validation. Imaging was not standardised (CT most often, MRI variable), microbiology rested on a single sample, and the university hospital probably receives mostly the most severe forms. The symptom onset date, self-reported, exposes to recall bias, and the delay measured (symptoms → admission) is not the diagnostic delay. Patients who died before transfer are absent (survival bias). Without a timestamp for the first medical contact, the prehospital phase (decision, journey, orientation) cannot be broken down; for the 51% of referred patients, it includes the time spent in first-line care and does not distinguish patient delay from health-system delay. The mediation rests on assumptions that cannot be verified in observational data (no unmeasured confounding between exposure and mediator and between mediator and outcome, chronology, no measurement error): residual confounding remains possible, the causal graph has not been externally validated and the mediation demonstrates no causality. This graph contains only measured variables: immunosuppression, type of suppuration, ventricular rupture and hydrocephalus, plausible common causes of the GCS and of death, are not in the main model (adjustment for rurality and referral attenuates the direct effect only moderately, § 3.5); the last two may result from the delay, which makes the natural effects non-identifiable: the decomposition is descriptive. The cohort mixes heterogeneous forms (14 observations with scalp involvement, 27 postoperative forms), for which the delay does not have the same meaning; the sensitivity analyses that exclude them (§ 3.5) do not change the estimates. Resampling of the main model is at the admission level; restriction to one admission per patient, with resampling by patient, gives superimposable results. Bootstrap intervals reflect only sampling uncertainty, not the biases of retrospective collection. The operative delay (median of 2 days) was not related to the outcome. These analyses generate hypotheses; they do not confirm them.

4.5. Foreseeable methodological objections

Several objections are foreseeable; here they are, with our answers. **(i) The small number of deaths (16).** It reflects the mortality observed; it limits power and does not allow judging the quality of in-hospital care. We contained the risk of over-adjustment with parsimonious models, Firth regression and bootstrap. **(ii) A mediation despite this power.** We were not trying to prove a mechanism but to explore a pathophysiological hypothesis formulated before the analysis, reporting estimates and precision rather than significance thresholds. AGReMA guided the transparency of the report, not the interpretation.

(iii) The GCS as the sole mediator. Other intermediates are plausible (sepsis, intracranial hypertension, hydrocephalus, ventriculitis, extension of the collection), but the GCS was the only mediator available in all patients in a complete, standardised and chronologically consistent way, and it was already the factor most strongly associated with death in component 2 (imprecise estimate). **(iv) No multiple-mediator model.** Such a model would better represent the pathophysiology, but would require a much larger sample and prospective timestamped collection (sepsis markers, quantified oedema, intracranial pressure); with 16 deaths, it would be

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over-parameterised and very unstable. **(v) No external validation of the DAG.** The graph is a conceptual representation of the assumed relationships, based on the literature and on clinical and causal reasoning formulated before model estimation; it makes adjustment choices explicit without proving causality. **(vi) The 19-day threshold.** It is the median. The mediation treats the delay as continuous; the analysis of determinants (Table 2) and part of the sensitivity analyses use this threshold, and the 14- and 21-day thresholds confirm the direction of the estimates, which limits the risk of an arbitrary dichotomisation.

5. Conclusion

In this Ivorian ISI cohort, the delay was mainly prehospital and went together with rurality, referred status and a lower GCS on arrival. These are the most consistent links of the study. The effect of the delay on mortality remained imprecise, and the share that would pass through the GCS (~19%) is very uncertain. The prehospital delay is therefore a potential target for organisational interventions, to be evaluated by prospective multicentre studies that measure each component of the delay. Improving prehospital pathways is a lead to be evaluated for reducing ISI mortality in resource-limited settings; these data do not rank it against other levers, notably in-hospital ones. Only prospective and interventional studies (implementation science) will tell whether shortening the prehospital delay improves survival and neurological outcome.

Key messages

- Time is lost mostly before admission: 19 days in median, versus 2 days to surgery.
- The delay goes together with rurality, referral and a lower GCS on admission.
- The effect of the delay on mortality remains imprecise; an exploratory share (~19%, very wide CI) is compatible with mediation by the GCS.
- Reducing the prehospital delay is a potential target, to be evaluated prospectively; it is not a demonstrated intervention.

Declarations

Ethical approval: The study received the approval of the Institutional Ethics Committee of Bouaké University Hospital (no. CEI/CHU-BKE/132/2026); data anonymised.
Consent: obtained for prospective inclusions (2025–2026); waiver granted for the retrospective phase, the data being anonymised.

Data availability: the anonymised individual database is no longer available from the authors; the results reported are those of the analyses carried out by the authors, whose aggregated values appear in the text, tables and supplementary material.

Conflicts of interest: none declared.
Funding: no specific funding.
Author contributions: provided in the title page file (double-blind review).

Transparency: the authors affirm that this manuscript is an honest, accurate and transparent account of the study, with no important omission.

Related publications: other manuscripts come from the same cohort (150 admissions, 148 patients): clinical and prognostic profile, admission triage score, potentially avoidable mortality (target trial emulation on the delay, without the GCS as mediator), explainable machine learning, diagnostic and antibiotic stewardship, paediatric sub-study, unsupervised phenotypes. The present component shares with the one on avoidable mortality the exposure (delay) and the outcome (death), but differs in the estimand (mediation by the GCS). The editorial status of each is specified in the cover letter.

Supplementary material (separate file, S1–S12): variable dictionary (S1); missing data (S2); model equations and coefficients (S3); percentile and BCa bootstrap (S4); Firth regression (S5); diagnostics (S6); splines (S7); E-value (S8); full sensitivity analyses (S9); high-resolution DAG, PDF and SVG (S10); annotated STROBE (S11) and AGReMA (S12) checklists. Figures 1 to 7 exist as SVG, vector PDF, PNG and 600-dpi TIFF.

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