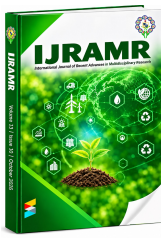
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REVIEW ARTICLE

PREHOSPITAL DELAY AND THE CARE CASCADE IN INTRACRANIAL SUPPURATIVE INFECTIONS: AN EXPLORATORY MEDIATION ANALYSIS OF IN-HOSPITAL PROGNOSIS IN A RESOURCE-LIMITED IVORIAN COHORT

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ABSTRACT

Background: In our cohort of intracranial suppurative infections (ICS), the median interval from symptom onset to admission reached 19 days, a salient feature. **Hypothesis:** We hypothesised that a longer prehospital delay is associated with higher in-hospital mortality, partly through deterioration of consciousness at admission (Glasgow Coma Scale, GCS). **Methods:** Single-centre secondary analysis of 150 stays (148 patients; 16 deaths; mortality 10.7%). The care cascade separated the prehospital phase (onset → admission; n = 150) from the in-hospital phase (admission → surgery; n = 115). Associations between delay, GCS and lesion characteristics used Spearman's coefficient and age- and sex-adjusted models. A counterfactual mediation analysis (natural direct and indirect effects as odds ratios; percentile bootstrap, 2,000 resamples) followed an a priori directed acyclic graph. Firth regression, sensitivity analyses and an E-value assessed robustness. Given 16 deaths, 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 referred status (aOR 1.88; 0.96–3.67). A longer delay was associated with a lower admission GCS ($\rho = -0.25$; $p = 0.002$; −0.67 points per 10 days after adjustment), with no association with lesion size. The total effect on death was imprecise (OR 1.79 per +10 days; 0.85–4.52). The share transiting through GCS was about 19% but very wide (−48 to 105%); the indirect effect (OR 1.11; 0.99–1.39) was non-significant. **Conclusion:** The delay in ICS care was mainly prehospital and associated with structural access factors (rurality, referral) and with neurological deterioration at admission. The delay–rurality and delay–GCS links were most robust; the effect on mortality remained imprecise. Prehospital delay is a candidate target for organisational interventions, whose effectiveness must be assessed prospectively.

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INTRODUCTION

Despite advances in imaging, antibiotic therapy and neurosurgery, intracranial suppurative infections (ICS) remain among the most time-dependent neurosurgical emergencies, their prognosis depending closely on early diagnosis and drainage (1–3). In high-income countries the interval between symptom onset and management is usually measured in days; in our Ivorian cohort it reached a median of 19 days, two to three times the values reported elsewhere (1, 4). Unlike the biology of the infection, this delay is a target potentially modifiable through the organisation of care. It falls within the field of global neurosurgery: the Lancet Commission on Global Surgery and subsequent work have shown that timely, safe surgical care is unavailable to a large share of the population of low- and middle-income countries, particularly in sub-Saharan Africa (5, 6). The prognostic component of this series identified impaired consciousness at admission (GCS < 9) as the main factor independently associated with death, while suggesting that delay was an upstream determinant of it. Our aim was not only to measure this delay, but to explore the mechanism by which it might translate into mortality. We first decompose the care cascade to locate the principal segment of delay, then formally examine, through a causal mediation analysis (7–10), the extent to which the delay–death association is compatible with a pathway through clinical severity at admission.

Hypothesis: We hypothesised that a longer prehospital delay is associated with higher in-hospital mortality, and that this

association passes in part through a deterioration of consciousness at admission (GCS). To our knowledge, this is the first study from sub-Saharan Africa combining care-cascade analysis and causal mediation applied to ICS.

Patients and methods

Population, statistical unit and selection: Secondary analysis of the analytical database described in the previous components, collected at Bouaké Teaching Hospital between 2016 and 2026, in accordance with the STROBE guidelines (11). The statistical unit was the hospital stay: 150 stays corresponding to 148 patients. Two patients each contributed two stays, corresponding to distinct infectious episodes (same identity, separate management) and retained as independent observations. A sensitivity analysis restricted to one stay per patient (n = 148) was planned to confirm the absence of influence of this weak dependence.

Of the 150 stays initially identified, none was excluded from the analytical core (age, sex, prehospital delay, GCS, vital status: 100% completeness). The primary endpoint was in-hospital mortality (16 deaths; 10.7%). Missing data were not imputed; a complete-case analysis was used, the available numbers being detailed in Table 1. The flow diagram is presented in Figure 1.

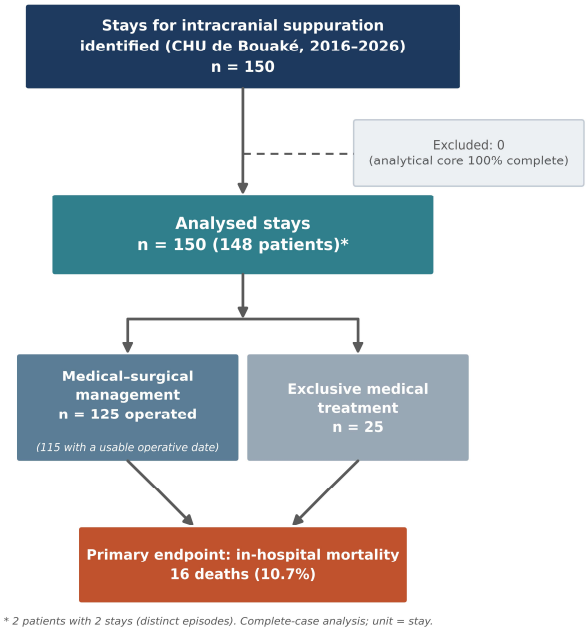


Figure 1. Inclusion flow diagram (STROBE). No stay was excluded from the analytical core; the statistical unit is the stay. Of the 150 stays, 125 were managed surgically (115 with a usable operative date) and 25 by exclusive medical treatment.

Definition of the cascade and of the delays: The exposure variable ("prehospital delay") measured the interval between symptom onset and admission to the teaching hospital. It is not equivalent to the delay to radiological diagnosis, which was not reliably time-stamped in the records. The in-hospital phase was measured by the admission-to-surgery interval, available for 115 of the 125 surgically managed patients (usable operative date). The access pathway was characterised by referral status, area of residence and mode of transport. No time stamp of first medical contact was available; referral status is its only indirect indicator. This partition follows the logic of the "three delays" model (12), the prehospital phase grouping the decision to seek care and access to an appropriate facility.

Causal framework and adjustment variables: The causal structure was defined a priori using a directed acyclic graph (DAG; Figure 2) (13). Age and sex were considered confounders of the relationships between delay, GCS and death, and were therefore included in the models. Rurality and referral status, located upstream of delay on the presumed causal pathway, were analysed as determinants of delay but not adjusted for in the mediation models, to avoid over-adjustment. Adjustment variables were selected on the basis of clinical and causal reasoning, not statistical significance alone.

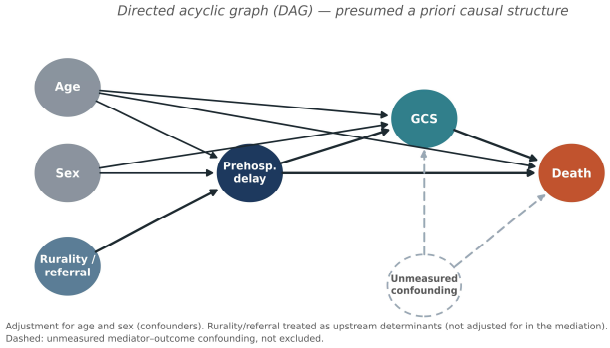


Figure 2. Directed acyclic graph (DAG) defining a priori the presumed causal structure and justifying the adjustment choices (age and sex as confounders; rurality/referral as upstream determinants not adjusted for in the mediation)

Statistical analysis and mediation: Delays are described by their median and IQR. Subgroup comparisons used the Mann–Whitney test; determinants of a prolonged delay (> 19 days, a median threshold reserved for descriptive analyses) used adjusted logistic regression. The delay–GCS association was quantified with Spearman's coefficient and then with age- and sex-adjusted linear regression (residual diagnostics without major departure from assumptions). The mediation analysis followed the counterfactual natural-effects framework (7–10), in accordance with the AGReMA guidelines (8). The exposure was delay (a +10-day contrast), the mediator continuous GCS, the outcome death, with adjustment for age and sex. A linear model linked delay to GCS (path a) and a logistic model linked GCS to death conditional on delay (path b); the model specification is given in Supplementary Table S2. Natural direct (NDE) and indirect (NIE) effects were expressed as ORs under the assumptions of no exposure–mediator interaction and of a rare event; the proportion mediated was computed on the log-OR scale. Confidence intervals were estimated by non-parametric bootstrap (resampling of stays with replacement, 2,000 replications — a number chosen to stabilise the extreme quantiles while remaining computationally realistic — with a fixed seed). Percentile-type intervals were retained as the primary measure; their concordance with bias-corrected and accelerated (BCa) intervals (14) was checked, as was the stability of estimates across resampling subsamples (15). Given the small number of events (16 deaths; about 3 events per variable in the outcome model), the models were deliberately parsimonious (16, 17) and a Firth penalised logistic regression (18, 19) was performed as a sensitivity analysis to reduce small-sample bias and the risk of separation. Robustness to unmeasured confounding was assessed with the E-value method (20). Diagnostics of the linear model (normality and homoscedasticity of residuals, influential

observations by Cook's distance, collinearity by variance inflation factors) and linearity of the exposure (restricted cubic splines) were examined. Missing data, limited and not concerning the analytical core (delay, GCS, death: 100% completeness), were not subjected to multiple imputation: a complete-case analysis was judged appropriate in the absence of evidence for a non-random mechanism. Results should be interpreted as exploratory. Analyses were performed with Python 3.12 (statsmodels 0.14, SciPy 1.17, NumPy 2.4, pandas; a Firth implementation developed for the study).

Mediation assumptions: The causal interpretation of natural effects relies on the absence of unmeasured confounding between exposure and mediator, between mediator and outcome, and between exposure and outcome, on correct temporality, and on measurement without systematic error. These conditions cannot be guaranteed in a retrospective observational study; their consequences are discussed in the limitations.

Sensitivity analyses: The following were planned: delay as a continuous variable and under different thresholds (> 14, > 19, > 21 days); an alternative dichotomous mediator (GCS < 9); a Firth regression of the logistic models; an exploration of the non-linearity of delay using splines; and restriction to one stay per patient.

Ethics: The study was conducted in accordance with the principles of the Declaration of Helsinki and received the approval of the Institutional Ethics Committee of Bouaké Teaching Hospital (CHU de Bouaké) (approval no. CEI/CHU-BKE/105/2026). As the centre had no constituted ethics committee over the study period itself, the study had initially been authorised by the head of the Department of Neurosurgery and by the hospital management. Individual informed consent was waived: the data were collected in the course of routine care and analysed in anonymised form, a dispensation covered by that approval.

RESULTS

A cascade with a predominantly prehospital delay: The prehospital phase concentrated almost all of the time elapsed before intervention: a median of 19 days (IQR 15–25; n = 150), versus 2 days (IQR 1–3) for the admission-to-surgery delay in 115 of the 125 operated patients (usable operative date). The prehospital median was thus about nine to ten times the in-hospital median — a descriptive, unadjusted comparison, based on different sample sizes (Figure 3, Table 1). The principal segment of delay therefore lay upstream of the referral centre.

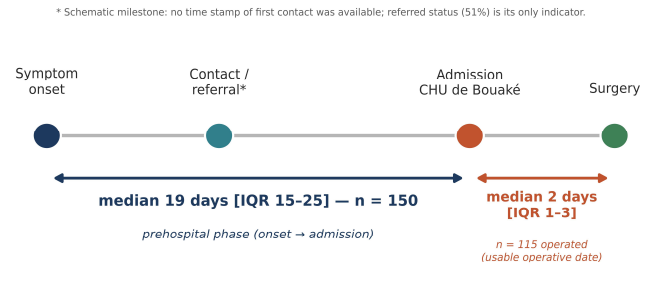


Figure 3. Care cascade. The prehospital phase (onset → admission; n = 150) concentrates most of the delay; the in-hospital phase (admission → surgery) is measured only in 115 of the 125 operated patients (usable operative date). First medical contact was not time-stamped.

A delay associated with structural access factors: Prehospital delay was not randomly distributed. It was longer in patients living in rural areas (n = 78; median 20 vs 16 days in the 72 urban patients; p = 0.0002) and in referred patients (n = 77; 20 vs 17 days in the 73 non-referred patients; p = 0.004), and tended to be longer with ambulance transport (21 vs 18 days), probably reflecting remoteness (Figure 4). Among referred patients, delays were homogeneous across the referring facility (medians 19–21 days).

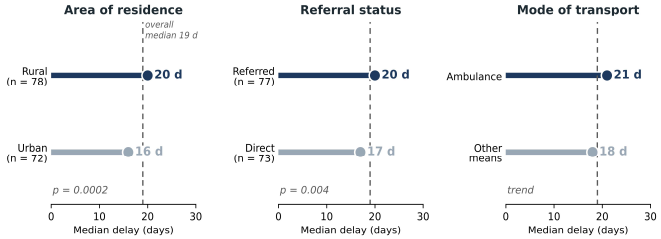


Figure 4. Median prehospital delay by area of residence, referral status and mode of transport. Points show group medians (days); the dashed line indicates the overall median (19 days). p-values: Mann–Whitney test

In multivariable analysis (Table 2), rural residence was associated with an increased probability of a prolonged delay (> 19 days) after adjustment for age and referral status (aOR 2.27; 95% CI 1.16–4.43; p = 0.017); referred status was borderline (aOR 1.88; 95% CI 0.96–3.67; p = 0.065). These associations place delay more within the field of structural inequalities of access than within the natural history of the infection.

Delay and severity at admission: A longer delay was associated with a lower admission GCS: a significant negative correlation (Spearman's ρ = −0.25; p = 0.002; n = 150), persisting after adjustment for age and sex (−0.67 GCS points per 10 days; 95% CI −1.26 to −0.08; p = 0.027) (Figure 5). By tertile of delay (≤ 16 days, n = 55; 17–21 days, n = 45; ≥ 22 days, n = 50), the proportion of GCS < 9 was 5%, 20% and 14% — higher in the two longest tertiles than in the first, without a strictly monotonic gradient — while mortality rose monotonically (5%, 11%, 16%).

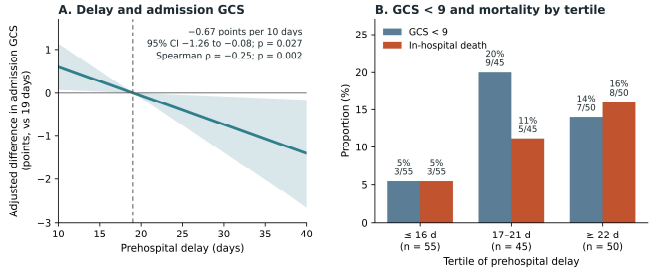


Figure 5. (A) Age- and sex-adjusted difference in admission GCS according to prehospital delay, relative to the median delay of 19 days (slope −0.67 points per 10 days; shaded band: 95% CI of the slope). (B) Proportion of GCS < 9 and in-hospital mortality by tertile of delay (sizes: 55, 45, 50)

No association was found, in contrast, between delay and radiological lesion burden: neither with the maximum collection size (ρ = 0.10; p = 0.23; n = 144) nor with the presence of mass effect (delay median 19 vs 17 days; p = 0.23).

Table 1. Analytical sample sizes, completeness and delays of the cascade segments

Variable / segment	n available	Missing	Median (days)	IQR
Onset → admission delay	150	0%	19	15–25
Admission → surgery delay (operated)	115	—*	2	1–3
GCS at admission	150	0%	13	10–15
Maximum lesion size	144	4%	36	30–44
Mass effect (presence)	150	0%	—	—

** The admission → surgery delay is computable only for 115 of the 125 surgically managed patients (usable operative date); 25 patients received exclusive medical treatment and 10 operated patients are excluded from this delay calculation alone, for lack of a reliable operative date. The "portal of entry → suppuration" delay (an infectious-disease estimate, n = 129, median 17 days) does not belong to the care cascade and is reported in Supplementary Table S1 rather than here. Mortality and mediation analyses concern the 150 stays (16 deaths). IQR: interquartile range.*

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 model of the probability of a delay > 19 days, mutually adjusted (rurality, referral) and for age; the model outcome is the prolonged delay, not death. aOR: adjusted odds ratio. Descriptively, crude mortality was 10/78 in rural vs 6/72 in urban settings, and 9/77 among referred vs 7/73 among direct patients.

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

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

Natural effects under the assumptions of no interaction and of a rare event; percentile bootstrap, 2,000 replications, age/sex adjustment. The low precision of the estimates reflects the limited number of observed deaths and mandates an exploratory reading. The total effect is obtained by composition of the natural effects (NDE × NIE = 1.79) and may differ slightly from the OR of a simple logistic regression of delay on death (1.68; Table 4); the reported E-value relies on this total effect.

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 days)	—	1.68 (0.89–3.18)	0.11	Logistic
Continuous (+10 days)	—	1.67 (0.90–3.10)	—	Firth

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

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

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

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

Table 6. Potential translation of the results into action pathways, by level of the health system (to be assessed prospectively, not recommendations)

Level	Action pathway	Potential priority
Community	Awareness of neurological warning signs	High
Peripheral hospital	Early recognition and referral protocol	Very high
Region	Rapid access to imaging; tele-expertise	High
Teaching hospital	Optimisation of the (already short) operative circuit	Moderate
National system	Neurosurgical networks; delay indicators	Research/policy

Indicative prioritisation based on our observations (the in-hospital segment being already brief, the main lever is prehospital). These pathways must be assessed before any generalisation.

Absence of significance does not demonstrate absence of effect and may reflect a lack of power or imperfect measurement; it nonetheless suggests that time-related deterioration was expressed clinically rather than through these morphological markers.

Exploratory mediation analysis: The total effect of a 10-day increase in delay on death was imprecise and compatible with no effect (OR 1.79; 95% CI 0.85–4.52; n = 150, 16 deaths), the interval including 1. Its decomposition placed the direct effect — outside GCS — at an OR of 1.61 (95% CI 0.81–3.66) and the indirect effect, transiting through GCS, at an OR of 1.11 (95% CI 0.99–1.39) (Figure 6, Table 3). The estimate is compatible with a partially mediating role of GCS, without demonstrating it.

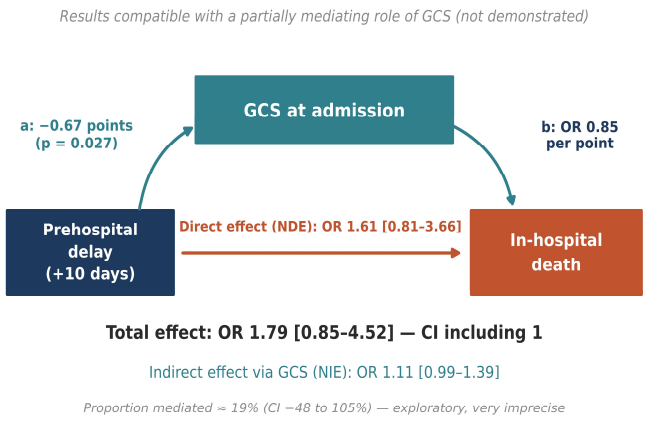


Figure 6. Mediation decomposition. The total effect of delay on death is imprecise (CI including 1). The indirect effect through GCS and the proportion mediated are provided for exploratory purposes, with very wide intervals

3.5. Sensitivity analyses

Sensitivity analyses were consistent in direction with the main analysis, while remaining imprecise (Table 4). Depending on the threshold used, the aOR of death associated with a prolonged delay ranged from 1.49 (> 14 days) to 2.36 (> 21 days), all intervals including 1; continuous delay gave an aOR of 1.68 per +10 days (95% CI 0.89–3.18). An alternative dichotomous mediator (GCS < 9) yielded a higher mediated share (~42%) but unstable, owing to quasi-separation linked to the small sample. None of these variants changed the message: consistent direction, insufficient precision to conclude an effect.

Robustness, penalised regression and diagnostics: Firth regression. Repeated under Firth penalisation (Supplementary Table S3), estimates were superimposable on the standard analysis: total effect of delay OR 1.67 (95% CI 0.90–3.10); in the mediation outcome model, direct effect OR 1.59 and indirect effect OR 1.11 (mediated share ≈ 18%); determinants of prolonged delay, rural OR 2.22 (1.13–4.32) and referral OR 1.85 (0.95–3.60). Penalisation therefore changed neither the direction nor the magnitude of the associations, ruling out a separation bias despite the 16 deaths.

Concordance of bootstrap intervals: Percentile and BCa intervals were concordant (Supplementary Table S4; indirect effect: percentile 0.99–1.39 vs BCa 1.00–1.41; direct effect: 0.81–3.66 vs 0.76–3.49), and bootstrap estimates were stable across subsamples, which justifies the use of the percentile interval.

Model diagnostics: The linear delay→GCS model explained a small share of the variance ($R^2 = 0.047$; adjusted $R^2 = 0.028$), as expected for a single determinant of a multifactorial clinical score. Residuals departed from normality (Shapiro W = 0.92; $p < 0.001$), which is usual for a bounded, discrete score such as GCS; homoscedasticity was respected (Breusch–Pagan p = 0.87), no observation reached a concerning influence threshold (maximum Cook's distance 0.06), and no collinearity was detected (variance inflation factors ≈ 1.0). Inference not resting on the normality assumption alone, Spearman's rank correlation — distribution-free — confirmed the association ($\rho = -0.25$; p = 0.002).

Linearity: Restricted-cubic-spline modelling suggested a modest departure from linearity of the delay→GCS relationship (likelihood-ratio test p = 0.028), without reversing its direction; a log transformation of delay did not change the correlation. The linear coefficient (−0.67 points/10 days) should therefore be read as an average slope. Spline modelling of the death model was not feasible (singular matrix) with 16 events, which supports the choice of a parsimonious parameterisation.

Unmeasured confounding: The E-value of the total effect (after risk-ratio approximation for a non-rare outcome) was 2.01: an unmeasured confounder would need to be associated with both delay and death with a risk ratio of at least 2.0 to fully explain the point estimate. As the confidence interval already includes no effect, the corresponding E-value was 1.0, underlining that no confounding is required to make the result compatible with the absence of effect.

Discrimination: Descriptively — prediction not being the aim of this component — the outcome model (death ~ delay + GCS + age + sex) showed moderate discrimination (apparent AUC 0.71; 95% CI bootstrap 0.60–0.88; optimism-corrected 0.64) and a Brier score of 0.09, a value close to 0 reflecting good overall accuracy of the predicted probabilities. Detailed calibration (intercept, slope, curve) and decision-curve analysis are presented in the prognostic component (component 2). The estimates of all multivariable models are summarised in Table 5.

DISCUSSION

This secondary analysis sheds light on the possible mechanisms linking delay in care to the prognosis of ICS in a resource-limited setting. It is organised around four messages: where the delay lies, how it might act, what this implies, and what remains to be demonstrated.

Where the delay lies: The delay was concentrated overwhelmingly in the prehospital phase. The in-hospital delays observed (median of 2 days to surgery) suggest relatively rapid management after admission, whereas the prehospital phase reached 19 days. The principal segment of delay therefore lies upstream of the referral centre, which directs improvement levers towards care-seeking and access rather than towards the operating theatre (5, 6).

How the delay might act: Delay appears to be associated mainly with structural access factors: its link with rural

residence and referral status, independently of age, places ICS within the field of global neurosurgery, whose deficit is particularly marked in sub-Saharan Africa (5, 6). Mechanistically, a longer delay was associated with a lower admission GCS (a robust path a), and GCS was the main determinant of death in the prognostic component. The results are thus compatible with a partially mediating role of severity at admission, without demonstrating it: the estimated mediated share (~19%) was very imprecise and the total effect itself remained compatible with no effect. The strongest associations of this work are therefore the delay–rurality and delay–GCS links, rather than the effect of delay on mortality. Pathophysiologically, several mechanisms make the link between a longer delay and deterioration of consciousness plausible. Prolonged time favours the evolution of cerebritis into an organised abscess and the expansion of the collection, with increased perilesional vasogenic oedema, raised intracranial pressure, mass effect and risk of herniation; it also exposes to complications — ventriculitis, hydrocephalus, seizures, systemic sepsis — that impair alertness independently of lesion volume (1–3). GCS clinically integrates this cascade, which explains why it is the most measurable intermediate link between time lost and outcome.
The absence of an association between delay and radiological markers (size, mass effect) deserves discussion. Imaging captures only one instant of the infectious process and does not reflect its full dynamics; clinical severity also depends on lesion location, oedema, sepsis or comorbidities; and consciousness may deteriorate without a major increase in collection diameter. A prolonged delay might thus be harmful through pathways not captured by these markers, consistent with the predominance of the direct effect in the decomposition.

Our cohort profile matches that of contemporary African series. The observed mortality (10.7%) is close to that reported in South Africa (12% (21)), Cameroon (17% (22)) and Nigeria (14–17% (23, 24)), despite a lower microbiological yield and prolonged delays — a recurring pattern in these settings, where diagnostic delay is among the identified prognostic factors (23). The most recent West African series confirm this picture: a review of 201 cases in Guinea (25) and a Togolese series (26) report male predominance, ENT portals of entry and CT-dominated management, while an African systematic review highlights the heterogeneity of definitions and the scarcity of structured prognostic analyses (27). This convergence, to be interpreted cautiously, suggests that the performance of the in-hospital phase can partly compensate for structural constraints common to the region. As a benchmark, a European cohort reported a median symptom-to-antibiotic delay of only 7 days (28), nearly three times shorter than ours, underscoring the magnitude of access delay in our setting. Reference diagnostic and therapeutic management is now codified by the European ESCMID guidelines (29), whose adaptation to resource-limited settings remains a challenge.

What this implies: These observations, compared with a mortality (10.7%) close to that of the large international cohorts despite far longer delays (1, 4, 30), suggest that the efficiency of the in-hospital phase does not suffice to compensate for time lost upstream, all the more so as a survival bias — patients who die before transfer are not represented — imposes caution. Because it potentially acts upstream of the main prognostic factor, prehospital delay is a priority target to be assessed. These findings place ICS within the field of global neurosurgery. The Lancet Commission on Global Surgery established that timely, safe surgical access is lacking for a large share of the population of low- and middle-income countries (6, 31, 32), and the neurosurgical deficit there is particularly marked (5, 33).

Health-system strengthening and resilience are now recognised as the preferred route to close this deficit (34, 35). The delay we describe is the local expression of this deficit: concentration of resources in a single centre, poorly structured referral pathways, unequal access to imaging, and financial barriers liable to cause catastrophic expenditure.

Unlike age or comorbidities, this delay represents a potentially modifiable organisational factor and can be read as an organisational indicator of quality of care. Its association with rural residence reflects less equality (theoretical availability of services) than equity of access (real capacity to benefit) (36), a question directly relevant to universal health coverage (37) and to the integration of essential neurosurgical care into national surgical plans (NSOAP) (38).

The finding echoes work applying the “three delays” model to surgery in sub-Saharan Africa, where in-hospital and referral delay weigh on operative mortality (39). These issues — timely access, geographical accessibility, essential neurosurgery and “bellwether” procedures, risk of catastrophic expenditure — extend beyond ICS to all time-dependent neurosurgical emergencies, as with ischaemic stroke (“time is brain” (40)) or severe traumatic brain injury (41), for which loss of chance is also largely built before arrival at the expert centre.

Situated within work on care pathways — abundant for stroke, trauma or cancer but rare for ICS — this study shifts the question from “why does the delay exist?” to “how can it be reduced?”, thereby belonging to implementation research (42–45). It must be stressed, however, that identifying a modifiable factor does not guarantee that an intervention targeting it will yield the expected benefit: this hypothesis must be tested in interventional studies. The analytical framework used here (cascade + DAG + mediation + Firth + bootstrap) is, moreover, transposable to other time-dependent neurosurgical emergencies.

Beyond ICS, these results illustrate how the prehospital phase can serve as a measurable indicator of the performance of a neurosurgical system in a resource-limited setting, bringing this work closer to health-systems science. The following avenues follow from our observations and do not constitute universal recommendations. At the patient and first-line level: awareness of the early recognition of ICS in any infectious syndrome with neurological expression.

At the network level: regional transfer protocols, access to first-line brain imaging, and neurosurgical tele-expertise between peripheral centres and the referral centre. At the governance level: monitoring of simple indicators decomposing the pathway (onset→first contact, first contact→referral, referral→admission, admission→imaging, admission→surgery) to target the most contributory segment. These pathways are summarised by level of the health system in Table 6 and in the synthesis diagram (Figure 7).

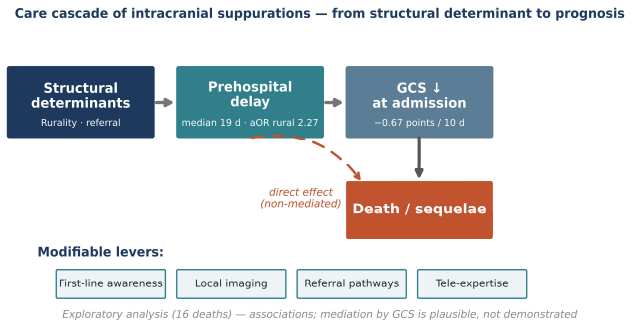


Figure 7. Synthesis. From structural determinants (rurality, referral) to prehospital delay, then to neurological deterioration and prognosis, with the modifiable levers. Exploratory diagram: the links shown are associations; mediation through GCS is plausible but not demonstrated.

These results open a research agenda: multicentre validation in West Africa; prospective, time-stamped measurement of each delay component; multiple-mediator mediation analysis (GCS, sepsis, size and multiloculation of the collection); and, ultimately, evaluation of organisational interventions to shorten the prehospital phase, alone able to establish a causal relationship that the present analysis cannot demonstrate.

Hierarchy of results by level of evidence. It is useful to distinguish what these data establish from what they suggest. Well-supported results: a prolonged prehospital delay, and its association with rurality and with a lower admission GCS. Plausible but imprecise results: a partially mediating role of GCS between delay and death. Results to be confirmed: the quantitative magnitude of the effect of delay on mortality, whose estimate remains compatible with no effect.

Strengths and limitations

Strengths: a homogeneous West African cohort recruited over ten years, explicit definition of the delays, a pre-specified causal framework (DAG), adjusted analyses with bootstrap validation, and the first mediation–cascade decomposition in this setting.

Limitations: the small number of events (16 deaths) limits power — particularly for the mediation analysis, whose indirect effects remain imprecise — exposes to a risk of over-adjustment and imposes parsimonious models and an exploratory interpretation. The study is single-centre and mostly retrospective (selection, information and referral biases), without external validation. Imaging was not standardised (CT most often, MRI variable), microbiology relied on a single sample without repeated follow-up, and a referral bias is possible, the teaching hospital preferentially receiving the most severe forms. The symptom-onset date, self-reported, is subject to recall bias, and the measured delay (onset → admission) is not equivalent to the diagnostic delay. Patients who died before transfer are not included (survival bias). The lack of a first-medical-contact time stamp prevents a fine decomposition of the prehospital phase (decision, travel, orientation). Finally, the mediation analysis relies on assumptions that are not verifiable in observational data (no unmeasured exposure–mediator and mediator–outcome confounding, temporality, no measurement error): residual confounding cannot be excluded, the presumed causal structure has not been externally validated, and mediation analysis does not demonstrate causality. These analyses should therefore be regarded as hypothesis-generating and not confirmatory. Bootstrap intervals reflect only sampling uncertainty and do not correct the biases inherent in retrospective collection.

Anticipating the main methodological criticisms: Several methodological questions may legitimately be raised on reading this study; we address them explicitly. (i) The small number of deaths (16). This reflects the true mortality of the cohort, not a selection; it limits power but also attests to the quality of in-hospital management. The risk of over-adjustment was contained by parsimonious models, a Firth regression and bootstrap validation. (ii) Using mediation despite this power. The aim was not to prove a mechanism but to explore a pre-specified pathophysiological hypothesis, prioritising, in accordance with AGReMA, the direction and consistency of effects over their significance.

GCS as the sole mediator. Other intermediates are plausible (sepsis, intracranial hypertension, hydrocephalus, ventriculitis, expansion of the collection), but GCS was the only mediator available completely, in standardised form and chronologically coherently in all patients, and was already the main independent prognostic factor of component 2.

The absence of a multiple-mediator model: Such a model would better represent the pathophysiology, but would require a far larger sample and prospective time-stamped collection (sepsis markers, quantified oedema, intracranial pressure); with 16 deaths it would be exposed to over-parameterisation and strong instability.

External validation of the DAG: The graph is a conceptual representation of the assumed relationships, based on the literature and a priori clinical reasoning; it makes the adjustment choices explicit but does not constitute proof of causality.

The 19-day threshold: It corresponds to the median and served only for descriptive analyses; the main analyses treat delay as continuous, and the alternative thresholds (14, 21 days) confirm the stability of the direction of the estimates, reducing the risk of interpretation tied to an arbitrary dichotomisation.

CONCLUSION

In this Ivorian cohort of ICS, the delay in care was mainly prehospital and associated with rurality, referral status and a deterioration of consciousness at admission. The most robust associations concerned the delay–rurality and delay–GCS links; the effect of delay on mortality remained imprecise, and the exploratory share transiting through GCS (~19%) was surrounded by strong uncertainty.

These results suggest that prehospital delay is a priority target for organisational interventions, whose effectiveness must be assessed by prospective multicentre studies measuring each delay component separately. Improving prehospital neurosurgical pathways may be one of the most actionable strategies to reduce avoidable ICS mortality in resource-limited settings. Only prospective, multicentre and interventional studies (implementation science) will determine whether a reduction in prehospital delay translates into a measurable improvement in survival and neurological outcome.

Key points

- The delay in ICS care is essentially prehospital (median 19 days) and far exceeds the in-hospital delay to surgery (2 days).
- It is associated with structural access factors (rurality, referral) and with a lower admission GCS.
- The effect of delay on mortality remains imprecise; an exploratory share (~19%, very wide CI) is compatible with mediation through GCS.
- Reducing prehospital delay is a priority target to be assessed prospectively, not a demonstrated intervention.

Declarations

Ethics approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and received the approval of the Institutional Ethics Committee of Bouaké Teaching Hospital (CHU de Bouaké) (approval no. CEI/CHU-BKE/105/2026). As the centre had no constituted ethics committee over the study period itself, the study had initially been authorised by the head of the Department of Neurosurgery and by the hospital management (section 2.5).

Consent: the dispensation from individual informed consent — the data having been collected in the course of routine care and analysed in anonymised form — is covered by that approval.

Data availability: the individual-level data underlying this study are not publicly available. All aggregated results supporting the findings are reported in the article and its supplementary material.

Conflicts of interest: none declared.

Funding: no specific funding.

Overlap with previous work: this analysis uses the same institutional cohort as several works by the same group (epidemiological and prognostic description of the cohort, the TRIAGE-SIC triage score, an explainable machine-learning analysis, diagnostic stewardship and a target-trial emulation of delay). This component addresses a distinct question — decomposition of the care cascade and mediation of prognosis by delay — and in no way constitutes an external validation of those works; the analyses should be regarded as non-independent within a single population.

Author contributions: all authors contributed substantially to the conception of the study, data collection, analysis and interpretation of results, or to drafting and critical revision of the manuscript; all read and approved the submitted version and take collective responsibility for it.

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

Supplementary material: Supplementary Tables S1–S4 (delay outside the care cascade; model specification; Firth penalised estimates; bootstrap concordance, diagnostics and E-value) and the STROBE checklist are provided as separate files.

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

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