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FEBRILE RESPIRATORY INFECTIONS IN CHILDREN: ASSESSMENT OF CLINICAL SEVERITY AND CEREBRAL VULNERABILITY USING THE NGCS-RS SCALE

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Ключові слова: *нейрогліокапілярна система, церебральна стабільність, педіатричні респіраторні інфекції, системне запалення, нейроваскулярна одиниця, метаболізм астроцитів, церебральна вразливість*

Abstract. Febrile respiratory infections in children: assessment of clinical severity and cerebral vulnerability using the NGCS-RS scale. Bondarenko Ya.D., Kauk O.I., Riznychenko O.K., Cherkashyna L.V., Hovbakh I.O. *Acute respiratory infections in children are accompanied by systemic inflammatory, metabolic, and microcirculatory disturbances that may affect the developing brain even without focal neurological symptoms. During critical neurodevelopmental stages, brain function depends on stable oxygenation, perfusion, and energy metabolism, increasing the vulnerability of the neuro-glio-capillary system to combined inflammatory and hypoxic stress. The aim of this study was to substantiate a systemic model of cerebral stability, identify threshold markers of its alteration, and develop the Neuro-Glio-Capillary System Risk Score (NGCS-RS) for early detection of cerebral vulnerability. A retrospective-prospective study included 1,243 children aged 1 month to 18 years. Clinical and laboratory parameters were analyzed throughout the infection course. Inclusion criteria were confirmed viral or bacterial respiratory infections; children with chronic neurological, endocrine, or metabolic disorders were excluded. Participants were divided into viral infection, bacterial infection, and healthy control groups. Statistical validation involved correlation analysis and prognostic modeling. A critical threshold of alteration was identified: C-reactive protein ≥8 mg/L, body temperature ≥39°C, and oxygen saturation ≤90%. Risk scores differed significantly between groups, with the highest values in bacterial infections. Receiver operating characteristic analysis showed excellent accuracy (AUC 0.87). A cutoff of 10 points yielded 85.3% sensitivity and 83.7% specificity. Respiratory infections may be associated with threshold-dependent potential cerebral instability via neuro-glio-capillary dysregulation. The reference standard for validation comprised independent clinical outcomes not included in NGCS-RS scoring: ICU admission, hospital stay >7 days, and/or objective neurological complications. The revised AUC was 0.87 (95% CI: 0.82-0.92), with sensitivity 85.3% and specificity 83.7%, reflecting robust but clinically realistic discriminative performance. The proposed scale may be used for preliminary risk stratification of children at elevated risk of severe course and potential cerebral vulnerability, requiring intensive monitoring.*

Реферат. Фебрильні респіраторні інфекції в дітей: оцінка клінічної тяжкості та церебральної вразливості за допомогою шкали NGCS-RS. Бондаренко Я.Д., Каук О.І., Різниченко О.К., Черкашина Л.В., Говбах І.О. *Гострі респіраторні інфекції в дітей супроводжуються системними запальними, метаболічними та мікроциркуляторними порушеннями, що можуть впливати на мозок, який розвивається, навіть за відсутності вогнищевих неврологічних симптомів. Під час критичних етапів нейророзвитку функція мозку залежить від стабільної оксигенації, перфузії та енергетичного метаболізму, що підвищує вразливість нейрогліокапілярної системи до поєднаного запального та гіпоксичного стресу. Метою цього дослідження було обґрунтувати системну модель церебральної стабільності, визначити порогові маркери її зміни та розробити шкалу оцінки ризику нейрогліокапілярної системи (NGCS-RS) для оцінювання клінічної тяжкості та церебральної вразливості в дітей з фебрильними респіраторними інфекціями. Ретроспективно-проспективне дослідження включало 1243 дитини віком від 1 місяця до 18 років. Клінічні та лабораторні параметри аналізувалися протягом усього перебігу інфекції. Критеріями включення були підтверджені вірусні або бактеріальні респіраторні інфекції;*

діти з хронічними неврологічними, ендокринними або метаболічними порушеннями були виключені. Учасників було розподілено на групи вірусної інфекції, бактеріальної інфекції та здорового контролю. Статистична валідація включала кореляційний аналіз і прогностичне моделювання. Було визначено критичний поріг для зміни функції: С-реактивний білок ≥8 мг/л, температура тіла ≥39°С та сатурація кисню ≤90%. Значення ризикового бала достовірно відрізнялися між групами, з найвищими показниками при бактеріальних інфекціях. Аналіз ROC-кривих продемонстрував відмінну точність (AUC 0,87). Порогове значення 10 балів забезпечувало чутливість 85,3% та специфічність 83,7%. Респіраторні інфекції можуть індукувати порогозалежну церебральну нестабільність через нейрогліокапілярну дизрегуляцію. Еталонний стандарт для валідації включав незалежні клінічні результати: госпіталізацію до ВРІТ, перебування в стаціонарі >7 днів та/або об'єктивні неврологічні ускладнення. Переглянутий AUC становив 0,87 (95% ДІ: 0,82-0,92), чутливість 85,3% та специфічність 83,7%. Запропонована шкала може бути використана для попередньої стратифікації дітей з підвищеним ризиком тяжкого перебігу та потенційної церебральної вразливості, що потребують інтенсивного моніторингу.

Respiratory febrile infections in children trigger a systemic inflammatory response involving immune, metabolic, and microvascular mechanisms of the CNS [1-6]. The developing brain is highly dependent on aerobic oxidative phosphorylation, has limited macroergic substrate reserves, and is sensitive to changes in cerebral perfusion and oxygenation [2, 3], making even moderate systemic disturbances functionally significant [3, 4, 6]. Respiratory inflammation generates a cytokine profile dominated by IL-1β, IL-6, and TNF-α, modulating cellular metabolism, vascular tone, and neuroglial reactivity via NF-κB and JAK/STAT pathways [5]. Concurrently, infection-associated hyperthermia, ventilation disturbances, and dehydration reduce tissue oxygen delivery and activate HIF-1α-mediated hypoxic signaling [6, 7, 8], shifting energy metabolism toward a glycolytic profile [9].

Lactate accumulation during systemic inflammation and relative hypoxia reflects a targeted metabolic shift at the pyruvate node of the Embden–Meyerhof-Parnas pathway, initiated by HIF-1α activation and proinflammatory cascades (IL-6–STAT3, TNF-α–NF-κB), upregulating hexokinase-2, phosphofructokinase-1, and LDH-A [10, 11]. Concurrent PDH kinase–mediated phosphorylation of the pyruvate dehydrogenase E1 subunit limits acetyl-CoA entry into the TCA cycle, shifting metabolism to a glycolytic mode [11]. The elevated lactate–pyruvate ratio signals energy compensation with limited stability reserve, with lactate modulating intracellular pH, neuronal excitability, and microvascular tone [11, 12]. Systemic cytokinemia remodels tight junction proteins (claudin-5, occludin), upregulates aquaporin-4 in perivascular astrocytes, and may destabilize the glycocalyx [7], while TLR4-dependent microglial activation and oxidative stress may further lower the blood-brain barrier permeability threshold [5, 7, 8], consistent with the pivotal role of microglia in neurovascular integrity [5-12].

Together, systemic inflammation, hypoxia-induced metabolic reprogramming, and blood-brain barrier dysfunction may collectively threaten cerebral homeostasis in pediatric respiratory infections. Darweesh et al. [8] demonstrated that viral infections systematically reprogram host cell metabolism, including in neurovascular unit cells, suggesting a biologically plausible mechanism of potential transient cerebral alteration. Threshold-dependent cerebral stability – where subthreshold stressors synergistically cause functional decompensation – remains poorly characterized in children. The proposed neuro-glio-capillary model and Neuro-glio-capillary system risk score (NGCS-RS) scale shift assessment from descriptive to systems-level risk stratification, translating BBB dynamics, astrocytic metabolism, and microvascular dysfunction into a clinically applicable tool using routine parameters. The study covers: (1) pathophysiological characterization of neuro-glio-capillary integration under inflammatory stress; (2) identification of critical thresholds (C-reactive protein (CRP), temperature, SpO_2, hydration) marking the compensation–subcompensation transition; and (3) development and validation of a multi-domain cerebral risk screening tool.

The aim of the study was to identify the critical thresholds of systemic load that trigger neuro-glio-capillary alteration and asthenovegetative symptoms in children with febrile respiratory infections, and to develop the NGCS-RS scale for early risk stratification and preventive monitoring.

MATERIALS AND METHODS OF RESEARCH

The presented retrospective-prospective study was conducted between 2023 and 2026 at the Municipal Non-Profit Enterprise "City Children's Polyclinic No. 15" of the Kharkiv City Council. Data collected retrospectively from anonymized medical records for 2023-2025 did not require prior ethics approval under institutional policy for de-identified data. The prospective data collection phase (2026) was approved by the Institutional Bioethics Committee (Protocol No. 2, dated February 04, 2026). The study was conducted in accordance with the Declaration of Helsinki. The study design and reporting conform to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Written informed consent was mandatory

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and obtained from parents or legal guardians of all children enrolled prospectively prior to any clinical or laboratory data collection, whereas retrospective data from the 2023-2025 period were analyzed in a strictly anonymized form in accordance with applicable institutional regulations. The cohort included 1,243 children aged 1 month to 18 years (mean 7.1±2.8 years; 52% boys). Inclusion criteria: age under 18, confirmed febrile ARI (viral or bacterial) [13, 14], and written consent. Exclusion criteria: chronic neurological, metabolic, or endocrine disorders, structural cerebral anomalies, acute neuroinfections, or antibacterial/corticosteroid use within 24 hours prior to examination. Group allocation was based solely on etiological diagnosis, established independently of NGCS-RS scoring. Group A (bacterial, n=526) was confirmed by positive bacterial cultures, radiological pneumonia evidence, and/or procalcitonin >0.5 ng/mL [15, 16]. Group B (viral, n=579) – by positive multiplex PCR for respiratory pathogens and/or procalcitonin <0.25 ng/mL with negative cultures. Severity parameters (CRP, temperature, SpO_2) were measured after group assignment and were not used as grouping criteria [6, 16, 17, 18]. Group C (control, n=138) comprised healthy children with normative laboratory values. Age distribution: infants (6.0%, n=75), early childhood (6.8%, n=85), preschool (14.7%, n=183), younger school age (34.2%, n=425), middle school age (28.4%, n=353), and adolescents (9.9%, n=122). Bacterial infection was confirmed by positive bacterial culture (blood, nasopharynx, or sputum), radiological consolidation consistent with pneumonia, and/or procalcitonin ≥0.5 ng/mL. Viral infection was confirmed by positive multiplex RT-PCR [19] for respiratory viruses, procalcitonin <0.25 ng/mL, and absence of bacterial growth. Cases not meeting clear criteria for either category were excluded.

Score weights (0-3 points) were derived from beta-coefficients and ORs of predictors significant at $p<0.10$ in univariable analysis and entered into a multivariable logistic regression model, model fit was confirmed by the Hosmer-Lemeshow test ($p=0.831$) [20]. Normality was assessed by the Shapiro-Wilk test [21]; data are presented as Me (Q1; Q3) or M±SD. Group comparisons used the Kruskal-Wallis test [22] with Dunn's post-hoc correction [23]; categorical variables were analyzed by Pearson's χ^2. Scale reliability was evaluated using Cronbach's alpha and ICC. Logistic regression modelling followed standard procedures [24]; the Hosmer-Lemeshow test [20] assessed calibration. ROC analysis [25] determined the optimal cut-off, AUC, sensitivity, and specificity. Bootstrap resampling (1,000 iterations) was used for internal validation [26]. K-fold cross-validation (k=10) was applied to assess model generalizability [27], achieving 10-fold CV AUC=0.86±0.03. Statistical significance was set at $p<0.05$. Statistical analyses were performed using JASP (version 0.18.3, University of Amsterdam), distributed under the GNU General Public License (GPLv3). Univariable and multivariable logistic regression analyses were performed for each predictor (CRP, body temperature, SpO_2, mucous membranes/skin turgor, hematocrit, and astheno-vegetative symptoms). Score weights spanning from 0 to 3 points were derived from the multivariable logistic regression model. It is important to note that the logistic regression analysis presented in Table 5 represents an auxiliary exploratory analysis demonstrating the general statistical significance of systemic predictors; it does NOT constitute a direct mathematical derivation of the final practical clinical scale (Table 2). To avoid methodological circularity, objective neurological complications – seizures and impaired consciousness (GCS ≤14) – are exclusively defined as primary outcome endpoints and are NOT incorporated as predictors in the logistic regression model or as scoring items in the clinical scale. The practical clinical scale (Table 2) incorporates only early non-specific asthenovegetative symptoms (somnolence, hyporeactivity, irritability, apathy) as the neurovegetative domain. Both sub-components of the Hydration-Hemorheology domain – mucous membrane status/skin turgor and hematocrit – are entered as independent predictors in the regression model (Table 5), mirroring their separate representation in the clinical scale (Table 2), thereby enabling individual β-coefficients to inform the contribution of each subcomponent. The mathematical transformation algorithm involved dividing the multivariable β-coefficients of each statistically significant predictor ($p<0.05$) by the smallest significant β-coefficient value obtained in the model (β-min =0.36), which served as the baseline unit. The resulting raw quotients were subsequently rounded to the nearest whole integer (0, 1, 2, or 3) to establish intuitive, clinically practical integer weights. Collinearity among predictors was assessed using the Variance Inflation Factor (VIF) [28]; VIF values were: CRP =1.43, body temperature =1.38, SpO_2 =1.51, mucous membranes/skin turgor =1.24, hematocrit =1.31, astheno-vegetative symptoms =1.34 (all VIF <2.0, indicating acceptable collinearity). Patients with missing data on any predictor were excluded by listwise deletion; the final analytic sample in the logistic regression model comprised n=1,187 (95.5% of the original cohort; n=56 excluded due to incomplete SpO_2 or hematocrit measurements).

RESULTS AND DISCUSSION

Threshold model of cerebral stability. Integrative analysis of clinical and biochemical parameters identified a critical factor combination associated with the

transition from compensated neuro-glio-capillary regulation to cerebral subcompensation: simultaneous hyperthermia >39.0°C, CRP ≥8 mg/L, and SpO_2 <90% [29, 30] Based on these findings, three levels of neuro-glio-capillary functional resilience were defined, reflecting sequential phases of adaptation, subcompensation, and decompensation of cerebral homeostasis (Table 1).

Table 1

Cerebral Stability levels

Stability Level	Criteria	Physiological Status	Probability of a clinical profile linked to possible cerebral vulnerability
I. Normostable	**CRP<3 mg/L, SpO_2 >95%, T<38.5°C**	**Intact BBB, normal neuroglial metabolism**	**<10%**
II. Subcompensated	**CRP 3–8 mg/L, SpO_2 91–94%, T 38.5–39.0 °C**	**Reversible gliocapillary alteration, asthenovegetative symptoms**	**40-60%**
III. Decompensated	**CRP≥8 mg/L, SpO_2 ≤90%, T≥39.0°C**	**Potential BBB compromise, clinically inferred microcirculatory instability, transient neurodysfunction [31]**	**80-95%**

Overproduction of proinflammatory cytokines (IL-6, TNF-α) induces microglial activation, increased blood–brain barrier permeability, and local microcirculatory disorders [6, 7, 32]. This dysfunction of the neurovascular unit leads to transient general cerebral symptoms without focal neurological deficits.

NGCS-RS (Basic Clinical Screening Version). Based on these pathophysiological patterns, the NGCS-RS Basic scale (Neuro-Glio-Capillary System Risk Score) was developed for the assessment of clinical severity and preliminary risk stratification of cerebral vulnerability in children with febrile respiratory infections. Intended for primary care and outpatient settings, it provides quantitative cerebral risk assessment without specialized diagnostics, integrating six key predictors – systemic inflammatory load, thermo-metabolic stress, oxygenation status, hydration–hemorheological balance (mucous membranes/skin turgor and hematocrit), and neurovegetative functional status (astheno-vegetative symptoms) – into a multiparametric scoring model for patient stratification and timely clinical decision-making.

Pathophysiological essence of the criteria. C-reactive protein serves as a molecular indicator of blood-brain barrier permeability. Its elevation activates the IL-6-TNF-α axis, remodeling tight interendothelial junctions (claudin-5, occludin) and upregulating aquaporin-4 in astrocytes, forming a permeability "window" for peripheral cytokines – triggering microglial activation, microedema, and reduced cognitive energy efficiency [6, 7, 32, 33].

Body temperature elevation. The cytokine-induced pyrogenic cascade drives metabolic reprogramming of glial cells, shifting from oxidative phosphorylation to glycolysis. This metabolic protection state limits neuronal activity, manifesting clinically as asthenia, somnolence, and psychomotor slowing [6, 7].

Impaired oxygenation. Decreased saturation triggers hypoxic-ischemic decompensation via HIF-1α activation and VEGF induction, increasing microvascular permeability. A vicious cycle ensues: reduced oxygenation enhances microglial activation and cytokine production, which deepens hypoxia – a critical risk point for loss of cerebral homeostasis [6, 7, 32, 33].

Dehydration. Cytokine-dependent vascular hydrodynamic restructuring causes fluid redistribution and hematocrit changes, impairing capillary transport of oxygen and glucose and reducing perivascular exchange efficiency. Astrocytes lose adequate buffering capacity for K^+, NH_4^+, and glutamate, producing ionic instability and subclinical excitotoxicity – clinically expressed as irritability, impaired attention, and cognitive dysfunction. Combined with hematocrit-dependent restructuring, dehydration represents a key mechanism of transition into neuro-glio-capillary instability [6, 7]. The obtained data are presented in Table 2.

NGCS-RS-Basic score interpretation follows the risk levels in Table 3, reflecting sequential transition from preserved compensation to subcompensation and critical decompensation of cerebral regulation. Each level corresponds to a defined clinical profile and recommended management strategy – from observation to urgent intervention.

Group A (n=526): Bacterial infections. Characterized by intense systemic inflammatory response with fever, desaturation, dehydration, and systemic intoxication. The mean NGCS-RS score was 11.8±2.6 (95% CI: 11.6-12.0; median 12.0; IQR 10.0-14.0),

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corresponding to the high cerebral risk zone. No patient fell within the low-risk zone; 14.4% (n=83) reached the critical level (≥14 points), with a mean age of 3.8±2.1 years, of whom 87.2% required hospitalization with intensive monitoring. These findings suggest that bacterial respiratory infections may be a powerful trigger of neuro-glio-capillary alteration.

Table 2

Components and Scoring of the NGCS-RS-Basic Scale

Domain	Parameter	0 points	1 point	2 points	3 points
Systemic Inflammatory Load	CRP (mg/L)	<5	5-7	8-12	>12
Thermo-Metabolic Stress	T (°C)	<38.0	38.0-38.5	38.6-39.0	>39.0
Oxygenation	SpO_2 (%)	≥96	94-95	91-93	≤90
Hydration–Hemorheology	Mucous membranes and skin turgor	Moist mucosa, normal skin turgor	Mildly dry mucosa	Dry mucosa, reduced skin turgor	Severely dry mucosa, marked skin turgor reduction, decreased urine output
	Hematocrit (Hct, %)	36-42	33-35 or 43-45	30-32 or 46-50	<30 or >50
Neurovegetative Functional Status	Astheno-vegetative symptoms	Normal activity, no symptoms	Reduced activity, easy fatigability	Somnolence, hypo-reactivity, irritability	Marked lethargy, apathy, or pronounced psychomotor instability

Group B (n=579): Uncomplicated viral infections. Characterized by a mild systemic inflammatory response, stable oxygenation, and preserved or minimally altered hydration status. The mean NGCS-RS score for this cohort was 3.2±1.6 points (95% CI: 3.1-3.3; median 3.0; IQR 2.0-4.0), which strictly corresponds to the low cerebral risk zone (0-5 points). The clinical-laboratory distribution demonstrated that 91.2% (n=528) of patients fell within the low-risk stratum, 6.7% (n=39) were classified into the moderate-risk zone, and only 2.1% (n=12) exhibited a high-risk profile. No patient with uncomplicated viral infection reached the critical risk threshold (≥14 points). Hospitalization with intensive monitoring or day-care observation was required for only 2.3% (n=13) of children in this group, primarily due to non-neurological, age-related feeding difficulties or transient hyperthermia. These precise statistical indicators confirm that uncomplicated viral respiratory pathogens predominantly preserve native neuro-glio-capillary compensation mechanisms and possess a significantly lower potential for inducing systemic-cerebral instability compared to bacterial infections.

Table 3

Stratification of Risk Levels and Clinical Management Guidelines

Score	Risk Level	Clinical Interpretation	Recommendations
0-5	Low	Preserved cerebral stability; no systemic maladaptation	Outpatient care; reassessment in 24–48 h
6-9	Moderate	Early neuro-glio-capillary changes; emerging metabolic and microcirculatory stress	Clinical and neurological screening; monitor SpO_2, temperature, hydration
10-13	High	Potential cerebral instability; neurovegetative dysfunction and clinically inferred microcirculatory instability	Hospital/day-care observation; monitor SpO_2, CRP, hematocrit, consciousness; correct hydration
≥14	Critical	High risk of neuro-glio-capillary failure; impaired microcirculation, evolving cerebral vulnerability risk	Emergency care; oxygen therapy, fluid resuscitation, continuous monitoring, urgent neurological consult

Group C (n=138). Clinically healthy children with normal laboratory parameters, body temperature, saturation, and hydration. The mean NGCS-RS score was 0.4±0.6 (median 0.0; IQR 0.0-1.0), corresponding to the low-risk zone (0-5 points), confirming preserved cerebral stability in the absence of systemic inflammatory load. Near-zero scores across all domains with minimal physiological fluctuations confirm high NGCS-RS specificity in differentiating normality from cerebral risk. Domain-specific data are presented in Table 4.

Table 4

NGCS-RS-Basic Structure Across Groups

Parameter	Group A	Score	Group B	Score	Group C	Score
CRP (mg/L)	42.7±28.3 8-12: 24.6%; >12: 75.4%	2.4±0.7	4.1±1.8 <5: 68.4%; 5–7: 31.6%	0.6±0.5	0.3±0.2 <5: 100%	0.0±0.0
T (°C)	39.3±0.6 38.6-39.0: 18.1%; >39.0: 81.9%	2.6±0.6	38.2±0.4 <38.0: 24.3%; 38.0-38.5: 58.2%; 38.6-39.0: 17.5%	0.8±0.6	36.6±0.3 <38.0: 100%	0.0±0.0
SpO_2 (%)	91.2±2.8 91-93: 52.4%; ≤90: 47.6%	2.1±0.9	96.8±1.2 ≥96: 82.1%; 94-95: 17.9%	0.3±0.5	98.4±0.8 ≥96: 100%	0.0±0.0
Hydration status	Mild: 31.2%; moderate: 48.5%; severe: 20.3%	1.8±0.9	Normal: 73.8%; mild dryness: 26.2%	0.4±0.6	Normal: 100%	0.0±0.0
Hct (%)	41.8±5.4 36-42: 42.3%; 43-45 or 33-35: 38.6%; >45 or <33: 19.1%	1.2±1.1	38.4±2.1 36-42: 91.3%; 33-35 or 43-45: 8.7%	0.2±0.4	38.9±1.8 36-42: 94.4%; 33-35 or 43-45: 5.6%	0.0±0.2
Asthenovegetative symptoms	Reduced activity: 14.7%; somnolence: 70.9%; lethargy: 14.4%	2.3±0.7	Normal: 47.2%; mild fatigue: 44.6%; somnolence: 8.2%	0.9±0.8	Normal: 68.9%; mild fatigue: 31.1%	0.4±0.6

Validation of the NGCS-RS scale. The reference standard comprised independent clinical outcomes not included in NGCS-RS scoring: ICU admission, hospital stay >7 days, and/or objective neurological complications (seizures, impaired consciousness GCS ≤14). High risk was identified in 443 patients (35.6%): Group A – 431 (81.9%), Group B – 12 (2.1%), Group C – 0. Among patients categorized under the high-risk and critical strata (total n=443) who experienced adverse clinical outcomes, objective acute neurological complications were explicitly documented in 21.0% (n=93) of cases. Specifically, manifest febrile seizures (including complex and prolonged episodes) occurred in 13.1% (n=58) of these high-risk patients, while a transient or sustained alteration of consciousness with a Glasgow Coma Scale score of GCS ≤14 was verified in 7.9% (n=35) of individuals. This granular event distribution confirms the scale's sensitivity toward acute cerebral vulnerability rather than generic systemic single-organ failure. ROC analysis yielded AUC =0.87 (95% CI: 0.82-0.92); at the optimal threshold ≥10 points: sensitivity 85.3%, specificity 83.7%, PPV 84.1%, NPV 85.0%, accuracy 84.5%. Hosmer-Lemeshow calibration confirmed predicted-observed agreement (χ^2 =4.27, p=0.831; slope 0.98 [0.92-1.04]; Brier score 0.043). AUC remained stable across age subgroups (p=0.724) and sexes (p=0.412). Internal consistency: Cronbach's α =0.710 (0.682-0.736); inter-rater reliability: ICC =0.986 (0.973-0.993), κ=0.916 (0.845-0.987). Construct validity: F=3353, p<0.001, Cohen's d=4.13 (A vs B); correlations with fever duration (r=0.742), hospitalization (r=0.816), leukocytes (r=0.581), procalcitonin (r=0.693), pSOFA (r=0.724; all p<0.001). Hospitalization rates by risk stratum: low 1.3%, moderate 27.7%, high 80.2%, critical 97.6%; OR per point 2.08 (p<0.001), hospitalization outcome sub-analysis: AUC=0.967; R^2 =0.648 for length of stay. Score dynamics declined from 12.4±2.1 at admission to 3.2±1.8 at discharge (F=342.7, p<0.001, η^2 =0.648; SRM = -2.71, MCID =2.4). For the primary outcome (composite adverse events: ICU admission, hospital stay >7 days, and/or neurological complications), bootstrap AUC=0.88 (0.83-0.93). The predictive model for the primary composite outcome demonstrated a highly realistic and stable discriminative capability with an overall AUC of 0.87 (95% CI: 0.82-0.92), which remained consistent during internal validation protocols, while an R^2 =0.648 was

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observed for the length of hospital stay. NGCS-RS outperformed pSOFA: ΔAUC = +0.053, NRI=34.6%, IDI=0.128 (all p<0.001), with equivalent performance across infection localizations (p=0.538).

Among all enrolled children (N=1,243), neurological events were recorded in 7.5% of cases (n=93). Specifically, seizures occurred in 58 children (4.7%), and impaired consciousness (GCS ≤14) was documented in 35 children (2.8%). A sub-group ROC analysis for the composite neurological outcome (seizures and/or GCS ≤14) yielded AUC=0.84 (95% CI: 0.79-0.89), confirming the discriminative capacity of the NGCS-RS scale for cerebral vulnerability specifically.

Table 5

Multivariable Logistic Regression Analysis and Derivation of NGCS-RS Score Weights

Predictor	Univariate OR (95% CI)	p	Multivariate β	Multivariate OR (95% CI)	p	Score (0-3)
CRP (mg/L)	**3.2 (2.1-4.8)**	**<0.001**	**1.12**	**3.1 (2.1-4.5)**	**<0.001**	**3**
Body temperature (°C)	**2.1 (1.5-3.0)**	**<0.001**	**0.74**	**2.1 (1.5-3.0)**	**<0.001**	**2**
SpO_2 (%)	**1.9 (1.4-2.7)**	**<0.001**	**0.71**	**2.0 (1.4-2.9)**	**<0.001**	**2**
Mucous membranes/Skin turgor	**1.7 (1.2-2.4)**	**0.002**	**0.39**	**1.5 (1.1-2.1)**	**0.021**	**1**
Hematocrit (Hct, %)	**1.5 (1.1-2.0)**	**0.012**	**0.36**	**1.4 (1.0-2.0)**	**0.036**	**1**
Astheno-vegetative symptoms	**2.3 (1.6-3.3)**	**<0.001**	**0.68**	**2.0 (1.4-2.8)**	**<0.001**	**2**

Notes: score weights derived by dividing each multivariate β-coefficient by the minimum significant β (0.36) and rounding to the nearest integer (0-3). Mucous membranes/skin turgor (β = 0.39) and hematocrit (β = 0.36) each carry weight 1 individually; their combined additive contribution within the Hydration-Hemorheology domain mirrors their dual representation in the clinical scale (Table 2). Model calibration: Hosmer-Lemeshow test χ^2 =4.27, p=0.831; AUC=0.87 (95% CI: 0.82-0.92); Brier score = 0.043; Nagelkerke R^2 = 0.612; sensitivity 85.3%, specificity 83.7% at threshold ≥10 points.

Limitations include absent external validation, composite surrogate criterion, domain subjectivity, single-center design, and exclusion of critically ill patients. Multicenter prospective studies with independent validation, objective biomarkers, and long-term neurodevelopmental follow-up are required before widespread clinical implementation.

The results should be interpreted within a systemic view of the brain as an open metabolic–microvascular system with limited adaptive reserve. In childhood, active ontogenetic maturation with high dependence on perfusion, oxygenation, and energy substrate stability renders this system vulnerable to disproportionate functional shifts under even moderate systemic inflammation. Bondarenko et al. (2025) [6] confirmed a clear correlation between inflammatory intensity and neurological manifestations: at CRP 1-7 mg/L, mild symptoms predominated (lethargy 73%, tachycardia 40%) with preserved consciousness and SpO_2 >95%, whereas at CRP ≥8 mg/L, disturbances of consciousness (33%), desaturation to 88-90% (27%), motor disturbances (20%), and tachycardia (80%) were observed, with a critical temperature threshold of ~39.0°C combined with dehydration (33%) [6]. Takahashi et al. (2022) demonstrated that astrocytes induce vasodilation or vasoconstriction depending on oxygenation status: under hypoxia, increased lactate production leads to prostaglandin E2–mediated vasodilation, whereas under sufficient oxygenation 20-HETE induces vasoconstriction; loss of astrocytic support causes neurovascular unit dysfunction underlying numerous neurological disorders [34].

The combination of hyperthermia, elevated CRP, and reduced SpO_2 forms a unified threshold state within which cerebral metabolism and microcirculation are reorganized. Song et al. (2016) demonstrated a similar threshold effect: systemic inflammation or short-term hypoxia alone did not induce cerebral edema, whereas their combination did so through synergistic astrocyte and microglial activation, blood-brain barrier disruption, and reduced Na^+/K^+-ATPase activity, confirming the concept of a critical threshold formed by multiple interacting stressors [35]. This state is characterized by glial transition to a glycolytic compensatory mode, reduced astrocytic metabolic support of neurons, and increased capillary sensitivity to cytokine-mediated influences. Pamies et al. (2021) demonstrated that neuroinflammatory response to TNFα and IL1β is accompanied by increased glycolysis and lactate release, with upregulation of GLUT1, MCT4, and PKM2, increased basal glycolytic rate, and simul-

taneous decrease in respiration and ATP production – consistent with metabolic reprogramming of astrocytes during inflammation. [36] Thus, systemic inflammation acts as both a trigger and modulator of cerebral resilience, shifting the neuro-glio-capillary unit toward metabolic vulnerability.

The proposed threshold model differs from linear "infection severity – neurological severity" concepts: clinically minor infections may cause latent decreases in cerebral resilience without focal symptoms, supporting the view of the brain as a target organ of systemic inflammation. The NGCS-RS scale formalizes these interactions into an integral risk indicator whose value lies in the systemic combination of parameters, enabling identification of the subcompensation phase critical for preventive intervention.

Pathophysiological mechanisms discussed above, including potential BBB compromise, astrocytic metabolic reprogramming, and microglial activation, are presented as hypothetical frameworks consistent with our previous research [5, 7, 20]. These mechanisms have not been directly measured in the current cohort and should be interpreted as biologically plausible explanations for the observed clinical findings, requiring confirmation by future studies incorporating direct neurological outcome measures, neuroimaging, and cerebrospinal fluid analysis.

CONCLUSION

1. Febrile respiratory infections in children can alter the threshold function of the neuro-glio-capillary complex under the combined influence of inflammatory, thermo-metabolic, and hypoxic loads.
2. Asthenovegetative symptoms during infection may be pathophysiologically associated with potential metabolic reprogramming of glial cells and reduced cerebral energy stability, consistent with the proposed neuro-glio-capillary model.
3. Critical threshold biomarkers were identified: C-reactive protein ≥8 mg/L, body temperature ≥39°C, and SpO_2 ≤90%, the simultaneous exceeding of which indicates functional overload of cerebral regulatory systems.
4. Bacterial respiratory infections are associated with a significantly higher clinical load and an increased risk of potential cerebral vulnerability compared to uncomplicated viral infections, whose clinical profiles demonstrate the predominant preservation of compensatory physiological mechanisms.
5. The neuro-glio-capillary system risk score scale may be used for preliminary stratification of children with an elevated risk of severe course and potential cerebral vulnerability, supporting differentiated monitoring and pathogenesis-oriented decision-making in outpatient practice.

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