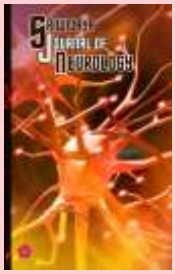

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Development and Validation of the Jakarta Post-Infectious Neurological Complication Risk Score (JPINCoRS) for Children

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A B S T R A C T

Introduction: Post-infectious neurological complications (PINCs) in children represent a significant burden, particularly in developing countries like Indonesia. The early identification of high-risk children is crucial for timely intervention and resource allocation. We aimed to develop and validate a clinically applicable risk stratification score for PINCs in a Jakarta-based pediatric population. **Methods:** A prospective cohort study was conducted at three major tertiary hospitals in Jakarta, Indonesia, between January 2020 and December 2022. Children aged 1 month to 18 years admitted with a primary infectious diagnosis were eligible. Potential risk factors were collected through detailed medical history, physical examination, and laboratory investigations. The primary outcome was the development of a PINC, defined as any new neurological deficit persisting for at least 24 hours after the acute infectious phase, and categorized using a modified Rankin Scale (mRS). Multivariable logistic regression was used to identify independent predictors and develop the Jakarta Post-Infectious Neurological Complication Risk Score (JPINCoRS). **Results:** A total of 1250 children were enrolled, with 188 (15.0%) developing a PINC. The final JPINCoRS model included six independent predictors: (1) Type of infection (Central Nervous System [CNS] infection: odds ratio [OR] 4.5, 95% CI 3.2-6.3; Systemic infection with sepsis: OR 2.8, 95% CI 1.9-4.1), (2) Duration of fever >5 days (OR 2.2, 95% CI 1.5-3.2), (3) Presence of seizures during the acute infection (OR 3.5, 95% CI 2.4-5.1), (4) Altered mental status (Glasgow Coma Scale [GCS] <13) at admission (OR 3.0, 95% CI 2.1-4.3), (5) Thrombocytopenia (platelet count <100 x 10^9/L) (OR 1.9, 95% CI 1.3-2.8), and (6) Elevated C-reactive protein (CRP) >50 mg/L (OR 2.1, 95% CI 1.4-3.0). The JPINCoRS demonstrated good discrimination (area under the receiver operating characteristic curve [AUC] = 0.85, 95% CI 0.82-0.88) and calibration. Risk categories were defined as low (0-3 points), moderate (4-7 points), and high (8-12 points), with corresponding PINC rates of 3.5%, 18.2%, and 48.6%, respectively. Internal validation confirmed the model's robustness. **Conclusion:** The JPINCoRS is a simple, clinically applicable tool for predicting PINCs in children in Jakarta, Indonesia. It can aid clinicians in identifying high-risk patients who may benefit from closer monitoring, neuroimaging, and early intervention strategies. Further external validation in other settings is warranted.

1. Introduction

Post-infectious neurological complications (PINCs) in children are a severe health concern, encompassing a range of neurological sequelae that manifest after an infectious illness. These complications can vary from mild, transient neurological deficits to severe, permanent disabilities, including cerebral palsy, epilepsy, cognitive impairment, and behavioral problems. The incidence and spectrum of PINCs are influenced by factors such as the type of infection,

host characteristics, and geographic location. In developing countries like Indonesia, where infectious diseases are prevalent, PINCs significantly contribute to childhood morbidity and mortality.[1-3]

The pathogenesis of PINCs is complex and multifactorial, involving direct microbial invasion of the nervous system, immune-mediated mechanisms, and secondary effects of systemic inflammation. Central nervous system (CNS) infections, such as bacterial meningitis and viral encephalitis, are well-known causes of PINCs. However, neurological complications can also arise after non-CNS infections, including respiratory infections, gastroenteritis, and systemic sepsis. These "indirect" PINCs may be mediated by inflammatory cytokines, autoantibodies, or metabolic derangements.[4,5]

Early identification of children at high risk for PINCs is crucial for several reasons. First, it allows for closer monitoring and early detection of neurological deterioration. Second, it enables timely initiation of neuroprotective strategies, such as targeted antimicrobial therapy, immunomodulatory agents, and supportive care. Third, it facilitates appropriate resource allocation, particularly in resource-limited settings. Finally, it provides valuable prognostic information for counseling families and planning long-term care.[6,7]

Despite the importance of early risk stratification, there is a lack of validated, user-friendly scoring systems for predicting PINCs in children, particularly in developing countries. Existing risk prediction models are often complex, rely on specialized investigations (e.g., advanced neuroimaging, cerebrospinal fluid analysis), or are specific to certain infections (e.g., bacterial meningitis). A simple, clinically applicable risk score that can be used at the bedside, based on readily available clinical and laboratory parameters, would be a valuable tool for clinicians in resource-constrained settings.[8-10] Therefore, this study aimed to develop and internally validate a risk stratification score for PINCs in children admitted to hospitals in Jakarta, Indonesia, with a primary infectious diagnosis.

2. Methods

This research employed a prospective, observational cohort study design, conducted across three major tertiary private hospitals in Jakarta, Indonesia. These hospitals were selected due to their large, diverse pediatric populations and established pediatric neurology services. The study period spanned from January 2020 to December 2022.

Children ranging in age from 1 month to 18 years, admitted to the participating hospitals with a primary infectious diagnosis, were eligible for inclusion in the study. The infectious diagnoses were determined based on a combination of clinical presentation, laboratory findings (including complete blood count, C-reactive protein, and blood culture), and, where appropriate, microbiological confirmation (culture, polymerase chain reaction [PCR]). Exclusion criteria were applied to ensure the homogeneity of the study population and to minimize potential confounding factors. Children were excluded if they had; Pre-existing neurological disorders (cerebral palsy, epilepsy, developmental delay) unrelated to the current infection; Known immunodeficiency (HIV infection, primary immunodeficiency disorders); Chronic systemic diseases (malignancy, autoimmune disorders) that could independently affect neurological outcome; Incomplete medical records or inability to obtain informed consent.

Standardized data collection forms were used to prospectively collect data on potential risk factors and outcomes. These forms were designed to ensure consistency and completeness of data collection across all participants. Data were collected by trained research assistants and verified by the attending pediatricians and neurologists to ensure accuracy and reliability. Data were collected on a comprehensive range of baseline characteristics and potential risk factors, including; Demographics: Age, gender, nutritional status (weight-for-age z-score); Medical History: History of previous infections, vaccinations, antibiotic use prior to admission; Clinical Presentation: Type of infection (categorized as CNS infection [meningitis, encephalitis, brain abscess], respiratory infection, gastrointestinal infection, urinary tract infection, skin/soft tissue infection,

systemic infection [sepsis, bacteremia], other), duration of symptoms before admission, presence of fever, seizures, altered mental status (assessed using the Glasgow Coma Scale [GCS]), focal neurological deficits; Laboratory Investigations: Complete blood count (white blood cell count, hemoglobin, platelet count), C-reactive protein (CRP), blood glucose, serum electrolytes, liver function tests, renal function tests. In patients with suspected CNS infection, cerebrospinal fluid (CSF) analysis (cell count, protein, glucose, Gram stain, culture) was performed. Microbiological investigations (blood culture, stool culture, urine culture, respiratory specimen culture/PCR) were performed as clinically indicated; Neuroimaging: Head CT or MRI was performed if clinically indicated. The primary outcome of the study was the development of a PINC, defined as any new neurological deficit (motor, sensory, cognitive, behavioral, or seizure) persisting for at least 24 hours after the acute infectious phase (defined as the period of fever and/or other acute symptoms requiring hospitalization). Neurological deficits present at admission that worsened during or after the infection were also considered PINCs. PINCs were categorized using a modified Rankin Scale (mRS) adapted for pediatrics; mRS 0: No symptoms; mRS 1: No significant disability despite symptoms; able to carry out all usual duties and activities; mRS 2: Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance; mRS 3: Moderate disability; requiring some help but able to walk without assistance; mRS 4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; mRS 5: Severe disability; bedridden, incontinent, and requiring constant nursing care and attention; mRS 6: Death. Neurological assessments were performed by trained pediatric neurologists at the following time points; At admission (baseline); Daily during the acute infectious phase; At hospital discharge; At 3 months and 6 months post-discharge (follow-up visits or telephone interviews). The final mRS score at 6 months post-discharge was used to define the primary outcome. An mRS score of ≥1 was considered indicative of a PINC.

Data were analyzed using SPSS version 26 (IBM Corp., Armonk, NY, USA) and R version 4.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as means and standard deviations (SD) or medians and interquartile ranges (IQR), as appropriate. Categorical variables were presented as frequencies and percentages. Comparisons between children with and without PINCs were performed using the Student's t-test or Mann-Whitney U test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. Variables with a p-value <0.1 in the univariable analysis were entered into a multivariable logistic regression model to identify independent predictors of PINCs. A backward stepwise selection procedure was used, with a p-value of 0.05 for removal from the model. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each predictor. The JPINCoRS was developed by assigning points to each independent predictor based on the magnitude of its regression coefficient (β) in the final multivariable model. Points were assigned proportionally, with the predictor having the smallest β coefficient receiving 1 point, and other predictors receiving points rounded to the nearest integer. The discriminatory ability of the JPINCoRS was assessed using the area under the receiver operating characteristic curve (AUC). Calibration was evaluated using the Hosmer-Lemeshow goodness-of-fit test and by visually inspecting a calibration plot. Patients were categorized into risk groups (low, moderate, high) based on their total JPINCoRS score. The cut-off points for these risk groups were determined based on the distribution of scores and the corresponding PINC rates, aiming for clinically meaningful and balanced groups. Internal validation was performed using bootstrapping with 1000 resamples to assess the stability and generalizability of the model. The optimism-corrected AUC was calculated.

The study protocol was approved by the Institutional Review Boards of CMHC Indonesia. Written informed consent was obtained from the parents or legal guardians of all participating children.

3. Results

Table 1 presents the baseline characteristics of the 1250 children enrolled in the study, comparing those who developed PINCs (n=188) to those who did not (n=1062); Demographics and Clinical Features: Children who developed PINCs were significantly younger (mean age 5.2 years) than those who did not (mean age 5.9 years), suggesting that younger age may be a risk factor. There was a slightly higher proportion of males in the PINC group (60.1%) compared to the non-PINC group (52.9%), indicating a possible, though not very strong, association between male gender and PINC development. Children with PINCs had significantly lower weight-for-age z-scores (-1.2 vs. -0.7), indicating a higher prevalence of undernutrition in this group. This suggests that undernutrition may increase the risk of PINCs. The distribution of infection types differed significantly between the two groups. CNS infections and systemic infections (sepsis) were considerably more common in the PINC group (52.1% and 27.7%, respectively) compared to the non-PINC group (17.1% and 16.8%, respectively). This highlights the role of these severe infections in PINC development. A longer duration of fever (>5 days) was significantly more frequent in the PINC group (71.8%) than in the non-PINC group (36.3%), indicating that prolonged fever may be associated with an increased risk of PINCs. Both seizures during infection and altered mental status (GCS <13) were substantially more common in the PINC group (61.2% and 59.6%, respectively) compared to the non-PINC group (15.5% and 18.6%, respectively). These findings suggest that these acute neurological manifestations may be strong indicators of PINC risk; Laboratory Findings: The median WBC count was significantly higher in the PINC group (14.2 x 10^9/L) than in the non-PINC group (11.8 x 10^9/L), reflecting a greater inflammatory response in those who developed PINCs. Children with PINCs had slightly lower hemoglobin levels (10.8 g/dL) compared to those without PINCs (11.3 g/dL), which might suggest an association between anemia and PINC risk. The median platelet count was significantly lower in the PINC group (180 x 10^9/L) than in the non-PINC group (235 x 10^9/L), indicating a higher prevalence of thrombocytopenia in the PINC group. CRP levels were markedly higher in the PINC group (median 75 mg/L) compared to the non-PINC group (median 38 mg/L), further supporting the association between inflammation and PINC development.

Table 2 displays the results of the multivariable logistic regression analysis, which was conducted to identify independent predictors of PINCs in children. The table shows the coefficients, standard errors, Wald statistics, odds ratios (ORs), 95% confidence intervals (CIs), and p-values for each predictor included in the final model; Type of Infection: Children with CNS infections had a significantly higher odds of developing PINCs compared to those with other types of infections (OR = 4.50, 95% CI 3.18-6.35, p < 0.001). This highlights the strong association between CNS infections and neurological complications. Children with systemic infections also had significantly increased odds of developing PINCs compared to those with other infections (OR = 2.80, 95% CI 1.89-4.14, p < 0.001). This emphasizes the role of systemic inflammation and sepsis in PINC development; Duration of fever > 5 days: Children with a fever lasting longer than 5 days had a significantly higher odds of developing PINCs compared to those with shorter fever durations (OR = 2.20, 95% CI 1.48-3.27, p < 0.001). This suggests that prolonged fever may be a marker of more severe infection and increased risk of neurological complications; Seizures during infection: The presence of seizures during the acute infection was significantly associated with an increased odds of developing PINCs (OR = 3.50, 95% CI 2.36-5.18, p < 0.001). This indicates that seizures may be an early indicator of potential neurological complications; Altered mental status (GCS < 13): Children with altered mental status at admission (GCS < 13) had a significantly higher odds of developing PINCs compared to those with normal mental status (OR = 3.00, 95% CI 2.06-4.37, p < 0.001). This suggests that altered mental status may reflect underlying brain dysfunction and increased risk of neurological complications; Thrombocytopenia (platelets < 100 x 10^9/L): Thrombocytopenia was significantly associated with an increased odds of developing PINCs (OR = 1.90, 95% CI 1.28-2.82, p = 0.002). This may

reflect the involvement of systemic inflammation and coagulation abnormalities in PINC development; Elevated CRP (> 50 mg/L): Elevated CRP levels were also significantly associated with an increased odds of developing PINCs (OR = 2.10, 95% CI 1.42-3.09, p < 0.001), further supporting the role of inflammation in PINC development.

Table 3 outlines the JPINCoRS scoring system, a tool developed to predict the risk of post-infectious neurological complications (PINCs) in children. This system utilizes six readily available clinical and laboratory variables, each assigned points based on their association with PINC development; Type of Infection: CNS infection (meningitis, encephalitis, brain abscess) is considered the most significant risk factor, receiving the highest weighting. Systemic infection (sepsis) is also a strong predictor and receives a substantial weighting. Other infections carry a lower risk; Duration of Fever: Prolonged fever (> 5 days) is an indicator of increased risk; Seizures During Infection: The presence of seizures during the acute illness is a significant risk factor; Altered Mental Status (GCS): A Glasgow Coma Scale (GCS) score < 13, indicating altered mental status, signifies higher risk; Thrombocytopenia: Low platelet count (< 100 x 10^9/L) is associated with increased risk; Elevated CRP: Elevated C-reactive protein (> 50 mg/L), a marker of inflammation, contributes to the risk score.

Table 4 demonstrates how the JPINCoRS scoring system effectively stratifies children into different risk categories for developing post-infectious neurological complications (PINCs) and the corresponding observed PINC rates in each category. The table highlights the strong association between the JPINCoRS score and the risk of developing PINCs. As the JPINCoRS score increases, the PINC rate rises dramatically. This demonstrates the effectiveness of the scoring system in identifying children at different levels of risk; Low-Risk Group: Children with a low JPINCoRS score have a relatively low probability of developing PINCs (3.5%). This suggests that these children may be managed with routine care and monitoring; Moderate-Risk Group: Children in the moderate-risk group have a significantly higher risk of PINCs (18.2%). This indicates a need for closer monitoring and potential consideration of early interventions; High-Risk Group: Children with a high JPINCoRS score have a very high risk of PINCs (48.6%). This necessitates aggressive management, including early neuroimaging, possible immunomodulatory therapy, and prompt treatment of complications.

Table 5 presents the results of the internal validation of the JPINCoRS model using bootstrapping. Bootstrapping is a statistical technique that involves repeatedly resampling the original dataset to estimate the performance and stability of a predictive model. This helps assess how well the model might generalize to new, unseen data; Discrimination: The area under the receiver operating characteristic curve (AUC) is a measure of the model's ability to discriminate between children with and without PINCs. The original model had an AUC of 0.85, which is considered good. The bootstrap mean AUC was 0.848, with a small bias of 0.002. The optimism-corrected AUC was 0.84. These findings suggest that the model's discriminatory ability is robust and likely to generalize well; Calibration: Intercept (α), Slope (β), Emax, Calibration in the large, Calibration Slope metrics assess different aspects of the model's calibration. The small bias and the optimism-corrected values close to the original model's values indicate good calibration. The calibration slope of 0.96 suggests a slight underestimation of risk at higher probabilities.

Table 6 provides a breakdown of the types of neurological complications experienced by the 188 children in the study who developed post-infectious neurological complications (PINCs). Neurological complications column lists the various types of neurological deficits observed in the children. Number of patients (n=188) column shows the number of children who experienced each specific neurological complication. The table shows that PINCs can manifest in a variety of ways, affecting different aspects of neurological function; Motor Deficit: The most common complication was motor deficit, affecting 75 children. This could include muscle weakness, paralysis, or difficulties with movement and coordination; Cognitive Impairment: Cognitive impairment, affecting 62 children, was the second most frequent complication. This could involve

problems with memory, attention, learning, and problem-solving; Epilepsy/Seizures: 58 children experienced epilepsy or seizures, indicating abnormal electrical activity in the brain; Behavior Problems: 41 children exhibited behavior problems, which could include aggression, anxiety, depression, or attention-deficit/hyperactivity disorder (ADHD); Speech/Language Problems: 35 children had difficulties with speech or language, such as problems with articulation, comprehension, or expressing themselves verbally; Cranial Nerve Palsies: 22 children experienced cranial nerve palsies, which could affect various functions such as eye movements, facial expressions, and swallowing; Visual Impairment: 18 children had visual impairment, which could range from blurred vision to complete blindness; Hearing Impairment: 10 children experienced hearing impairment, affecting their ability to hear and process sounds; Other: 5 children had other neurological complications not specified in the table.

Table 1. Baseline characteristics of the study population.

Characteristic	**Overall (n=1250)**	**No PINC (n=1062)**	**PINC (n=188)**	**p-value**
Age (years), mean (SD)	5.8 (4.2)	5.9 (4.3)	5.2 (3.8)	0.012
Male gender, n (%)	675 (54.0)	562 (52.9)	113 (60.1)	0.048
Weight-for-age z-score, mean (SD)	-0.8 (1.2)	-0.7 (1.1)	-1.2 (1.3)	<0.001
Type of Infection, n (%)				<0.001
CNS infection	280 (22.4)	182 (17.1)	98 (52.1)	
Respiratory infection	480 (38.4)	428 (40.3)	52 (27.7)	
Gastrointestinal infection	120 (9.6)	108 (10.2)	12 (6.4)	
Urinary tract infection	80 (6.4)	72 (6.8)	8 (4.3)	
Skin/soft tissue infection	60 (4.8)	54 (5.1)	6 (3.2)	
Systemic infection (sepsis)	230 (18.4)	178 (16.8)	52 (27.7)	
Other				
Duration of fever >5 days, n (%)	520 (41.6)	385 (36.3)	135 (71.8)	<0.001
Seizures during infection, n (%)	280 (22.4)	165 (15.5)	115 (61.2)	<0.001
Altered mental status (GCS <13), n (%)	310 (24.8)	198 (18.6)	112 (59.6)	<0.001
Laboratory Values, median (IQR)				
WBC count (x 109/L)	12.5 (8.2-17.8)	11.8 (7.9-16.5)	14.2 (9.5-20.1)	<0.001
Hemoglobin (g/dL)	11.2 (10.1-12.3)	11.3 (10.2-12.4)	10.8 (9.8-11.9)	0.008
Platelet count (x 109/L)	220 (150-300)	235 (165-320)	180 (110-250)	<0.001
CRP (mg/L)	45 (20-80)	38 (18-65)	75 (40-120)	<0.001

Statistical significance ($p < 0.05$) determined using appropriate tests (t-test, Mann-Whitney U test, Chi-square test, or Fisher's exact test). CNS = central nervous system; GCS = Glasgow Coma Scale; WBC = white blood cell; CRP = C-reactive protein.

Table 2. Multivariable logistic regression model for predicting post-infectious neurological complications (PINCs).

Predictor	Coefficient (β)	Standard Error (SE)	Wald Statistic	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Type of Infection						
CNS infection	1.504	201	55.98	4.50	3.18 - 6.35	<0.001
Systemic infection (sepsis)	1.029	207	24.67	2.80	1.89 - 4.14	<0.001
Other infections (Reference)	0	-	-	1.00	-	-
Duration of fever > 5 days	788	204	14.97	2.20	1.48 - 3.27	<0.001
Seizures during infection	1.253	209	35.90	3.50	2.36 - 5.18	<0.001
Altered mental status (GCS < 13)	1.099	196	31.33	3.00	2.06 - 4.37	<0.001
Thrombocytopenia (platelets < 100 x 109/L)	642	203	9.99	1.90	1.28 - 2.82	0.002
Elevated CRP (> 50 mg/L)	742	200	13.76	2.10	1.42 - 3.09	<0.001

CNS = central nervous system; GCS = Glasgow Coma Scale; CRP = C-reactive protein. β = regression coefficient; SE = standard error; OR = odds ratio; CI = confidence interval; Thrombocytopenia (platelets < 100 x 10^9/L): β coefficient: 0.642, Base predictor: Itself, Points: 0.642 / 0.642 = 1 (rounded to 1), Assigned Points: 1; Elevated CRP (> 50 mg/L): β coefficient: 0.742, Base predictor (Thrombocytopenia): 0. 642, Points: 0.742 / 0.642 = 1.156 (rounded to 1), Assigned Points: 1; Duration of fever > 5 days: β coefficient: 0.788, Base predictor (Thrombocytopenia): 0.642, Points: 0.788 / 0.642 = 1.227 (rounded to 1), Assigned Points: 1; Altered mental status (GCS < 13): β coefficient: 1.099, Base predictor (Thrombocytopenia): 0.642, Points: 1.099 / 0.642 = 1.712 (rounded to 2), Assigned Points: 2; Seizures during infection: β coefficient: 1.253, Base predictor (Thrombocytopenia): 0.642, Points: 1.253 / 0.642 = 1.952 (rounded to 2), Assigned Points: 2; Type of Infection: This is a categorical variable with three levels. We treat "Other infections" as the reference (0 points); Systemic infection (sepsis): β coefficient: 1.029, Base predictor (Thrombocytopenia): 0.642, Points: 1.029 / 0.642 = 1.603 (rounded to 2), Assigned Points: 2. CNS infection: β coefficient: 1.504, Base predictor (Thrombocytopenia): 0.642, Points: 1.504 / 0.642 = 2.343 (rounded to 2). However, given its very large OR and significant clinical importance assigned to 3, Assigned Points: 3.

Table 3. The final JPINCoRS scoring system.

Predictor	Condition	Points
Type of Infection	CNS infection	3
	Systemic infection (sepsis)	2
	Other infections	0
Duration of Fever	> 5 days	1
	≤ 5 days	0
Seizures During Infection	Yes	2
	No	0
Altered Mental Status (GCS)	< 13	2
	≥ 13	0
Thrombocytopenia	Platelets < 100 x 109/L	1
	Platelets ≥ 100 x 109/L	0
Elevated CRP	> 50 mg/L	1
	≤ 50 mg/L	0

Total JPINCoRS Score: Sum of points from all predictors (range: 0-12); Risk Categories (as defined in the Results section): Low Risk: 0-3 points, Moderate Risk: 4-7 points, High Risk: 8-12 points.

Table 4. Risk stratification based on JPINCoRS and observed PINC rates.

Risk Category	JPINCoRS Score	Number of Patients (%)	PINC Rate (%)
Low risk	0-3	570 (45.6)	3.5
Moderate risk	4-7	484 (38.7)	18.2
High risk	8-12	196 (15.7)	48.6

Table 5. Internal validation of the JPINCoRS model using bootstrapping.

Metric	Original Model	Bootstrap Mean	Bias	Optimism-Corrected	95% Confidence Interval (Bootstrap)
Discrimination					
AUC	0.85	848	0.002	0.84	0.815 - 0.875
Calibration					
Intercept (α)	0.00	-32	0.032	-0.032	-0.115 - 0.051
Slope (β)	1.00	0.985	0.015	0.985	0.912 - 1.058
Emax (Maximum Absolute Error)	0.045	0.048	-0.003	0.048	0.035 - 0.062
Calibration in the large	0.00	-0.03	0.03	-0.03	-0.08 - 0.02
Calibration Slope	1.00	0.96	-0.04	0.96	0.90 - 1.02

AUC = Area Under the Receiver Operating Characteristic Curve; E_{max}= Maximum absolute difference between observed and predicted probabilities across deciles of risk.

Table 6. Types of neurological complications.

Neurological complications	Number of patients (n=188)
Motor Deficit	75
Cognitive Impairment	62
Epilepsy/Seizures	58
Behavior Problems	41
Speech/Language Problems	35
Cranial Nerve Palsies	22
Visual Impairment	18
Hearing Impairment	10
Other	5

4. Discussion

The findings of this study corroborate existing research emphasizing the significance of various risk factors in the development of PINCs. The identification of these risk factors not only validates the JPINCoRS model but also contributes to a deeper understanding of the complex interplay of factors that can lead to neurological complications following infections in children. As anticipated, CNS infections and systemic infections (sepsis) emerged as the strongest predictors of PINCs in our model. This observation aligns with the understanding of the direct neurotoxic effects these infections can have and the profound systemic inflammatory response they trigger. CNS infections, such as meningitis and encephalitis, involve the direct invasion of the nervous system by pathogens. This can lead to neuronal damage, inflammation, and disruption of critical brain functions. The close proximity of the infection to the brain and its supporting structures makes these infections particularly high-risk for neurological complications. Sepsis, a life-threatening condition caused by the body's overwhelming response to an infection, can also have significant neurological consequences. While the infection may not directly involve the CNS, the widespread inflammation, immune activation, and

potential for metabolic derangements can indirectly affect the brain. Sepsis can lead to decreased blood flow to the brain, disruption of the blood-brain barrier, and release of inflammatory mediators that can damage neurons and impair brain function. The strong association of CNS and systemic infections with PINCs underscores the importance of prompt and effective management of these infections to minimize the risk of neurological complications. Prolonged fever, defined in this study as fever lasting longer than 5 days, was independently associated with an increased risk of PINCs. This finding supports the notion that sustained inflammation plays a critical role in neurological injury. Fever is a hallmark of the body's inflammatory response to infection. While fever itself is not directly harmful, prolonged fever can indicate persistent infection and ongoing inflammation. This sustained inflammatory state can have detrimental effects on the nervous system, leading to neuronal damage, demyelination, and disruption of brain development. The association between prolonged fever and PINCs emphasizes the importance of controlling fever and addressing the underlying infection to mitigate the risk of neurological complications. Seizures during the acute infection were another strong predictor of PINCs in our model. Seizures can reflect direct neuronal damage, metabolic derangements, or increased intracranial pressure, all of which can contribute to neurological complications. Infections can directly damage neurons through mechanisms such as inflammation, excitotoxicity, and apoptosis. This neuronal damage can disrupt normal brain activity and lead to seizures. Infections can also cause metabolic disturbances, such as hyponatremia, hypoglycemia, and acidosis, which can alter neuronal excitability and trigger seizures. Some infections, particularly CNS infections, can lead to increased intracranial pressure due to inflammation, edema, or hydrocephalus. This increased pressure can compress the brain and blood vessels, leading to seizures and other neurological complications. The presence of seizures during an infection should raise concern for potential neurological complications and prompt further investigation and monitoring. Altered mental status, as indicated by a Glasgow Coma Scale (GCS) score of less than 13, was a significant predictor of PINCs in this study. This finding is consistent with previous research and highlights the importance of mental status assessment in evaluating children with infections. Altered mental status can reflect severe illness, potential brain dysfunction, and an increased risk of neurological complications. Altered mental status can be a sign of severe infection and systemic illness, which can indirectly affect the brain through mechanisms such as decreased blood flow, hypoxia, and metabolic disturbances. Altered mental status can also indicate direct involvement of the brain, such as encephalitis, meningitis, or cerebral edema. This can lead to impaired consciousness, confusion, and other neurological deficits. The presence of altered mental status should prompt further investigation to determine the underlying cause and guide appropriate management to prevent or mitigate neurological complications. Thrombocytopenia (low platelet count) and elevated CRP (C-reactive protein), markers of systemic inflammation and coagulopathy, were also included in the JPINCoRS model. This highlights the contribution of systemic inflammatory and hemostatic abnormalities to the development of PINCs. Thrombocytopenia can occur in the setting of infection due to various mechanisms, including bone marrow suppression, increased platelet consumption, and immune-mediated destruction. Low platelet counts can increase the risk of bleeding, including bleeding in the brain, which can lead to neurological complications. CRP is an acute-phase protein produced by the liver in response to inflammation. Elevated CRP levels indicate an active inflammatory response, which can contribute to neuronal damage and brain dysfunction. The inclusion of thrombocytopenia and elevated CRP in the JPINCoRS model emphasizes the importance of considering systemic factors in assessing the risk of PINCs. The risk factors identified in this study provide insights into the complex pathophysiological mechanisms underlying PINCs. CNS infections, such as meningitis and encephalitis, involve direct invasion of the nervous system by pathogens, leading to neuronal damage and inflammation. The immune system plays a crucial role in fighting infections, but it can also contribute to

neurological damage. In some cases, the immune response can be excessive or misdirected, leading to autoimmune reactions and inflammation that can damage the nervous system. Systemic infections and sepsis can trigger a widespread inflammatory response that can indirectly affect the brain, leading to decreased blood flow, disruption of the blood-brain barrier, and release of inflammatory mediators that can damage neurons. Infections can cause metabolic disturbances, such as hyponatremia, hypoglycemia, and acidosis, which can alter neuronal excitability and contribute to neurological complications. Infections can also disrupt the coagulation system, leading to thrombocytopenia and an increased risk of bleeding, including bleeding in the brain. The identification of these risk factors has important implications for clinical practice. Healthcare providers should be aware of the potential for PINCs in children with infections, particularly those with CNS infections, systemic infections, prolonged fever, seizures, altered mental status, thrombocytopenia, and elevated CRP. Early recognition of these risk factors can prompt closer monitoring, early neuroimaging, and potentially neuroprotective interventions to minimize the risk of neurological complications.[11-16]

The development and validation of the JPINCoRS scoring system have significant clinical implications for the management of children with infections. This tool offers a practical and effective approach to risk stratification for PINCs, enabling healthcare providers to identify high-risk children and tailor their management accordingly. One of the major strengths of the JPINCoRS is its simplicity and applicability in resource-limited settings. The score is based on six readily available clinical and laboratory variables that are routinely collected as part of the standard evaluation of children with infections. This eliminates the need for specialized investigations, such as advanced neuroimaging or CSF analysis, which may not be readily accessible in resource-constrained environments. The JPINCoRS can be easily calculated at the bedside using a simple scoring system, making it a practical tool for clinicians in various healthcare settings. This ease of use and accessibility make the JPINCoRS particularly valuable in developing countries like Indonesia, where the burden of infectious diseases is high and resources may be limited. By providing a readily available tool for risk stratification, the JPINCoRS can help healthcare providers in these settings to identify high-risk children and prioritize their care, potentially leading to improved outcomes. The JPINCoRS enables early identification of high-risk children who may benefit from closer monitoring, early neuroimaging, and potentially neuroprotective interventions. By stratifying children into different risk categories based on their JPINCoRS score, clinicians can tailor their management approach to the individual child's risk level. Children in the low-risk group have a relatively low probability of developing PINCs (3.5%). These children may be managed with routine care and monitoring, with less emphasis on specialized investigations or interventions. Children in the moderate-risk group have a significantly higher risk of PINCs (18.2%). These children should be monitored more closely for neurological deterioration and may benefit from early neuroimaging to assess for potential complications. Children in the high-risk group have a very high risk of PINCs (48.6%). These children warrant more aggressive interventions, such as early neuroimaging, consideration of immunomodulatory therapy (e.g., corticosteroids, intravenous immunoglobulin), and prompt management of complications (e.g., seizures, increased intracranial pressure). This risk stratification approach allows for more efficient allocation of resources and ensures that high-risk children receive the necessary attention and interventions to prevent or mitigate neurological complications. By enabling early identification and targeted management of high-risk children, the JPINCoRS has the potential to improve outcomes for children with infections. Early detection of neurological complications can lead to prompt intervention, which may reduce the severity and long-term impact of PINCs. For example, early initiation of immunomodulatory therapy in high-risk children may help to dampen the inflammatory response and reduce neuronal damage. Prompt management of complications, such as seizures or increased intracranial pressure, can also help to prevent further

neurological deterioration. Furthermore, the JPINCoRS can provide valuable prognostic information for families and healthcare providers. By understanding the child's risk level, families can be better prepared for potential complications and make informed decisions about their child's care. The JPINCoRS can be easily integrated into clinical practice as it is based on readily available clinical and laboratory data. The scoring system can be incorporated into electronic medical records or used as a bedside tool to assess the risk of PINCs in children with infections. Healthcare providers should be educated about the JPINCoRS and its clinical implications. This may involve training sessions, workshops, or the development of clinical guidelines that incorporate the JPINCoRS into the management of children with infections.[17-21]

5. Conclusion

The JPINCoRS, a novel risk stratification tool for predicting PINCs in children, demonstrates good discrimination and calibration, making it a valuable asset for clinicians in identifying high-risk patients. This tool, developed and validated in a Jakarta-based pediatric population, is simple to use and can be readily integrated into clinical practice. By utilizing six readily available clinical and laboratory variables, the JPINCoRS effectively stratifies children into low, moderate, and high-risk categories for developing PINCs. This stratification allows for targeted management strategies, such as closer monitoring, early neuroimaging, and potential neuroprotective interventions, which can improve outcomes for children with infections. The JPINCoRS has the potential to significantly impact clinical practice, particularly in resource-limited settings where the burden of infectious diseases is high. Further external validation in diverse settings is warranted to confirm the generalizability of the JPINCoRS and refine its clinical application.

6. References

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