Clinical and Laboratory Predictors of Poor Outcomes in Pediatric Cerebral Malaria in Nigeria

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Received: 19 May 2024

Accepted: 3 August 2024

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DOI 10.5001/omj.2024.112

Abstract

Objective: Despite being a common feature of severe malaria in children, cerebral malaria remains poorly understood, with associated poor outcomes. Herein, we described the burden of childhood cerebral malaria and identify factors predictive of poor hospitalization outcomes (death and neurological outcomes) and short-term poor neurological outcomes.

Methods: This study was a retrospective review of children diagnosed with cerebral malaria at a tertiary hospital in northwestern Nigeria from 1st January 2019 to 31st December 2022. We retrieved relevant information, including hospitalization outcomes (discharge, death, and neurological sequelae) and neurological status at follow-up.

Results: There were 284 cases of cerebral malaria out of 8,295 pediatric admissions and 948 cases of severe malaria, with a prevalence of 3.4% and 30.0%, respectively. Most of the clinical and laboratory features were comparable between survivors and non-survivors, except hypoxemia (p=0.016), duration of loss of consciousness (p<0.001), acidosis (p=0.002), white blood cell count (p=0.006), serum sodium (p=0.005), and serum creatinine (p<0.001). Variables that predicted hospitalization deaths were hypoxemia with adjusted odds ratio (AOR) of 6.1 [95% confidence interval (CI) of 1.672 to 22.043), serum creatine > 1.5 mg/dl [AOR of 6.7 (95% CI, 2.160 to 20.905)] and the first 24 hours of hospitalization [AOR of 5.9, 95% CI of 2.423 to 14.535)]. Forty-nine (19.6%) of 250 survivors had neurological complications at discharge. Age less than five increased the odds of neurological complications at discharge (AOR 2.1, 95% CI, 1.094–3.876). At follow-up, of the 49 patients with neurological complications, 24 (49.0%) recovered fully.

Conclusions: This study demonstrates that cerebral malaria is linked to a very high death rate and neurological complications, particularly among under-fives. Hypoxemia and elevated serum creatinine levels were associated with an increased risk of hospitalization death.

Keywords: Cerebral malaria, outcome, children, Sub-Saharan Africa

Introduction

Malaria, a protozoan infection, is endemic to tropical countries and responsible for a significant burden of disease and death especially in sub-Saharan Africa.[1] The 2023 World Malaria Report recorded 249 million cases of malaria and 580,000 deaths.[2] Though an improvement from malaria indices recorded almost two decades ago, the 2023 world malaria report indicated that it continues to pose a significant public health challenge.[2,3] Of the global

burden of malaria, Nigeria along with ten other countries are responsible for about 70% of these cases and deaths; a situation that led to adoption of pragmatic approach called "high burden, high impact" by WHO and the roll back malaria (RBM) in 2018.[4] Despite this approach, Nigeria recorded an estimated 68 million cases of malaria and 194 000 deaths in 2021 and has remained top among other countries with 27% of the global burden of the disease.[5]

Similar to many regions globally, in Nigeria, a significant proportion of malaria-related deaths are concentrated among children, particularly those under the age of five, who constitute as much as 80% of the fatalities.[5] These deaths are often due to severe forms of the disease, with end-organ damages and subsequent poor outcomes.[6] Amongst the frequently affected organ-systems during severe malaria is the central nervous system, which involves a diffuse encephalopathy with neurological manifestations otherwise referred to as 'cerebral malaria'.[7] Cerebral malaria is frequently observed in severe cases of malaria during childhood, constituting a significant proportion ranging from 20% to 75% of the overall burden of severe malaria.[8-10] In addition, about 20 to 30% of survivors of cerebral malaria may have neurological complications at discharge with some of them progressing to permanent neurological impairments.[11,12]

Although a common complication of severe malaria in children, the full pathophysiologic mechanism underlying the brain injuries and subsequent poor outcomes are yet to be fully understood, which calls for more studies (both in the experimental animal models and the patients that bear the grunt of the outcomes).[7,12-14] This is because improving the poor outcomes associated with cerebral malaria will involve understanding the associated factors, especially in resource-constrained settings. Understanding these factors will allow targeted interventions and ultimately improve outcomes. Considering the above, we retrospectively reviewed childhood cerebral cases managed from January 1, 2019, to December 31, 2022, at a tertiary health facility in northwestern Nigeria. In this study, we described the burden of childhood cerebral malaria and identified factors predictive of in-hospital mortality and short-term poor neurological outcomes.

Methods

This study retrospectively analyzed children diagnosed with cerebral malaria who were managed at a tertiary hospital in northwestern Nigeria from January 1, 2019, to December 2022.The hospital has a 24-bed emergency pediatric complex, in which children with acute emergencies are managed. The facility receives referrals from within and outside Katsina State, northwestern Nigeria.

We included children from ages three months to 14 years with confirmed malaria based on a positive rapid diagnostic test or microscopic confirmation of *Plasmodium falciparum* and features of cerebral malaria. According to WHO criteria, cerebral malaria was defined based on the presence of the following: i. Evidence of impaired consciousness (Blantyre coma score less than 3 or Glasgow coma score of less than 11) that lasted for at least 30 min ii. Presence of malaria parasitemia (either a positive rapid diagnostic test or presence of *Plasmodium falciparum* under a blood film examination) iii. Absence of any other plausible cause of the encephalopathy.[15] We excluded those with other forms of malaria without features of cerebral malaria,[15] those with underlying chronic diseases, cancers, and pre-existing underlying neurological abnormalities.

The minimum sample size for this study was estimated using the online sample size calculator Raosoft® (http://www.raosoft.com/samplesize.html). Using prevalence of 5.6% of cerebral malaria obtained among children in a study in southwestern Nigeria, we obtained a minimum sample size 224 at 95% confidence level and 3% margin of errors.[16]

From electronic health records, we retrieved the following information of children with cerebral malaria (age, sex, duration of illness, presenting complaints, physical findings at admission, neurological sequels observed at discharge, dichotomous outcomes of discharge or death, follow-up date, and neurological status at follow-up), and neurological outcomes during follow-up were extracted and recorded as either fully recovered, recovering, or unknown neurologic outcome (for those with loss to follow-up).

Our main outcomes were the variables at admission (clinical and laboratory features at hospitalization) that predicted hospitalization deaths and neurological complications, while secondary outcomes included the description of the profiles of children with cerebral malaria and recovery from neurological sequelae.

The data extracted were analyzed using IBM-SPSS Statistics (Version 25). The age (not normally distributed) was summarized with a median and interquartile range (IQR) and categorical variables were summarized with frequency Tables. Chi-square and Fisher exact tests were used to examine the relationships between the clinical features, laboratory findings (baseline at admission), and outcomes (hospitalization deaths, occurrence of neurological complications, and recovery at post-discharge). From the bivariate analysis, variables that were significant, along with age and sex, were entered into a binary logistic regression with non-survivors (hospitalization outcome) as the dependent variable. We expressed the results of the binary logistic regression as adjusted odds ratios with 95% confidence intervals. Statistical significance was set at $p < 0.05$.

This study was conducted in accordance with the Declaration of Helsinki. The Federal Medical Centre Human Health Ethical Review Committee approved the study (FMCNHREC.REG.N003/0830441). Because this was a retrospective study, the committee waived the requirement for informed consent. Data were extracted anonymously with de-identification of the study children and kept with absolute confidentiality.

Results

Of 8,295 pediatric admissions in a four-year study period, there were 284 cases of cerebral malaria with a prevalence 3.4%. Of the 948 cases of severe pediatric malaria during the study period, 284 (30.0%) had cerebral malaria. The median (interquartile range) age of children with cerebral malaria [3.0 to 8.0)] was higher than the median age (interquartile range) of 4.0 (2.0 to 8.0) of those children without cerebral malaria (U=85,444.50, *p*=0.017). Among the cerebral malaria cases, there were more males (164; 57.7%) and children aged five and above (160; 56.3%). Further details are provided in Table 1.

Table 1: Age and sex distribution of the study participants.

Variable	**Total**		**Male**		**Female**	
Age group (Years)	N = 284	%	N = 164	%	N = 120	%
Less than one	3	1.1	2	1.2	1	0.8
One to less than five	121	42.6	72	43.9	49	40.8
Five to ten	126	44.4	68	41.5	58	48.3
Ten and above	34	11.9	22	13.4	12	10.0

Of the 284 cases of cerebral malaria, 73.9% (210) had only cerebral malaria, 29 (10.2%) had both cerebral malaria and hemoglobinuria, and the least were children with cerebral malaria along with multiple other clinical features (6; 2.1%), as shown in Figure 1.

Figure 1: Spectrum of cerebral malaria along with other clinical features.

Most clinical features were comparable between survivors and non-survivors among children with cerebral malaria, except for the presence of hypoxemia ($p = 0.016$) and duration of loss of consciousness ($p < 0.001$). In addition, the length of hospitalization was shorter among the non-survivors ($p < 0.001$) (Table 2). Among the laboratory findings, variables that were significantly associated with hospitalization outcomes were the presence of acidosis, white blood cell counts, serum sodium, and serum creatinine (Table 3).

Table 2: Clinical and laboratory features (baseline) among children with cerebral malaria.

Variable	**Subgroup**	**Total n = 284**	**Survivors N = 250**	**Non-survivors N = 34**	**Test**	***p*-value**
Age (years)	< 5	124 (43.7)	107	17	0.631	0.464
	≥ 5	160 (56.3)	143	17		
Sex	Male	164 (57.7)	146	18	0.366	0.582
	Female	120 (42.3)	104	16		
Fever	Yes	266 (93.7)	234	32	0.014	1.000

	No	18 (6.3)	16	2		
Vomiting	Yes	51 (18.0)	46	5	0.277	0.812
	No	233 (82.0)	204	29		
Hypoxemia	< 90	19 (6.7)	13	6	7.428	0.016
	≥ 90	265 (93.3)	237	28		
Resp. distress	Yes	69 (24.3)	58	11	1.363	0.286
	No	215 (75.5)	192	23		
Tachycardia	Yes	137 (48.2)	119	18	.342	0.587
	No	147 (51.8)	131	16		
Loss of consciousness	Yes	118 (41.5)	102	16	0.483	0.579
	No	166 (58.5)	148	18		
Duration of LOC (hours)	≤ 24	68 (23.9)	47	21	30.339	<0.001
	> 24	216 (76.1)	203	13		
Convulsions	Yes	193 (68.0)	169	24	0.123	0.846
	No	91 (32.0)	81	10		
LOH (hours)	> 24	231 (81.3)	211	20	12.898	<0.001
	≤ 24	53 (18.7)	39	14		
Acidosis*	< 15	53 (18.7	40	13	9.748	0.002
	≥ 15	231 (81.3)	210	21		
WBC ($X\ 10^9$/L)	> 10	92 (32.4)	74	18	7.445	0.006
	≤ 10	192 (67.6)	176	16		
Neutrophils (%)	≤ 60	162 (57.0)	140	22	0.926	0.362
	> 60	122 (43.0)	110	12		
Lymphocytes (%)	≤ 40	156 (54.9)	138	18	0.062	0.804
	> 40	128 (45.1)	112	16		
PCV (%)	≥ 15	263 (92.6)	231	32	0.129	1.000
	< 15	21 (7.4)	19	2		
Platelets ($X\ 10^9$/L)	< 150	125 (44.0)	113	12	3.130	0.272
	150-450	149 (52.5)	127	22		
	≥ 450	10 (3.5)	10	0		
Sodium (mmol/L)	≥ 125	194 (68.3)	178	16	8.058	0.005
	< 125	90 (31.7)	72	18		
Potassium (mmol/L)	≤ 5.5	10 (3.5)	9	1	0.038	1.000
	> 5.5	274 (96.5)	241	33		
Cr (mg/dL)	≤ 1.5	260 (91.5)	236	24	21.935	<0.001
	> 1.5	24 (8.5)	14	10		

*Resp-respiratory; LOC-loss of consciousness; LOH-length of hospitalization;*Bicarbonate less than 15 mmol/L; WBC-White blood cell counts; PCV-Packed cell volume; Cr-Creatinine.*

Table 3: Predictors (clinical and laboratory features) of hospitalization deaths among children with cerebral malaria.

Variables**	**Sub-categories**	**N = 34**	**Beta coefficient**	**standard error**	**AOR**	**95% CI**	***p*-value**
Age (years)	< 5	17	-0.494	0.421	1		0.241
	≥ 5	17			0.610	0.267, 1.393	
Sex	Female	16	-0.136	0.439	1		0.789
	Male	18			0.873	0.369, 2.061	
Hypoxemia	≥ 90	28	1.804	0.658	1		0.006
	< 90	6			6.071	1.672, 22.043	

LOH (hours)	> 24	13	1.781	0.457	1		<0.001
	≤ 24	21			5.934	2.423, 14.535	
Acidosis*	≥ 15	21	0.900	0.492	1		0.067
	< 15	13			2.459	0.938, 6.444	
WBC (X 109/L)	≤ 10	16	0.667	0.435	1		0.125
	> 10	18			1.948	0.830, 5.232	
Sodium (mmol/L)	≥ 125	16	0.806	0.433	1		0.062
	< 125	18			2.240	0.959, 5.232	
Creatinine (mg/dL)	≤ 1.5	24	1.905	0.579	1		<0.001
	> 1.5	10			6.720	2.160, 20.905	

***Baseline at admission; LOH-Length of hospitalization; WBC-white blood cells count; *bicarbonate less than 15 mmol/L; OR-odds ratio; AOR-adjusted odds ratio; CI-Confidence interval.*

Of the 284 children in this study, 34 deaths were recorded during hospitalization, with a case fatality rate of 11.9%. After adjusting for confounders, variables (baselines at admission) that predicted hospitalization deaths were the presence of hypoxemia with an adjusted odds ratio (AOR) of 6.1 (95% confidence interval (CI) of 1.672–22.043), and baseline serum creatine greater than 1.5 mg/dl with an AOR of 6.7 (95% confidence interval, 2.160–20.905]. Also, the first 24 hours of hospitalization was highly predictive of death with AOR of 5.9 (95% confidence interval of 2.423 to 14.535) as shown in Table 4.

Table 4: Neurological outcomes among children with cerebral malaria.

Types	**N = 49**	**Male N = 25**	**Female n = 24**	**Chi-square**	***p*-value**
		At discharge			
Seizures	13 (26.5)	9 (36.0)	4 (16.7)	3.862	0.443
Motor deficit	11 (22.4)	4 (16.0)	7 (29.2)		
Cortical blindness	10 (20.4)	4 (16.0)	6 (25.0)		
Speech impairment	9 (18.4)	4 (16.0)	5 (20.8)		
Cognitive impairment	6 (12.2)	4 (16.0)	2 (8.3)		
		At follow-up			
Recovered	24 (49.0)	7 (28.0)	17 (70.8)	9.471	0**.008**
Still recovering	18 (36.7)	12 (48.0)	6 (25.0)		
Loss to follow-up	7 (14.3)	6 (24.0)	1 (2.4)		

Of the 250 cerebral malaria survivors, 49 (19.6%) had neurological complications at discharge. Based on the distribution of neurological complications, the most common complications were seizures (13, 26.5%), followed by motor deficits (11; 22.4%) and cognitive impairment (6;12.2%), as shown in Table 4. Among the clinical features, age and the presence of fever were associated with neurological complications at discharge from the hospital (Table 5). For age, children less than five years had higher odds of neurological complications with an adjusted odds ratio (OR) of 2.1, 95% confidence interval (CI) of 1.094 to 3.876 compared with children five years and above. In contrast, children with fever had lower odds of neurological complications at discharge (OR 0.3,

95% CI, 0.099–0.798). In contrast to clinical features, none of the laboratory features were significantly associated with neurological complications at discharge (Table 5).

Table 5: Factors associated with neurological complications at discharge.

Variable**	Subgroup	Total n = 250	Neurological complications		Chi-sq	*p*-value
			Yes (n = 49)	No (n = 241)		
Age (years)	< 5	107 (42.8)	28	79	5.121	**0.025**
	≥ 5	143 (57.2)	21	122		
Sex	Male	146 (58.4)	25	121	1.366	0.261
	Female	104 (41.6)	24	80		
Fever	Yes	234 (93.6)	42	192	6.327	**0.020**
	No	16 (6.4)	7	9		
Vomiting	Yes	46 (18.4)	8	38	0.175	0.692
	No	204 (81.6)	41	163		
Hypoxemia	< 90	13 (5.20	2	11	0.155	1.000
	≥ 90	237 (94.8)	47	190		
Resp. distress	Yes	58 (23.2)	10	48	0.267	0.606
	No	192 (76.80	39	153		
Tachycardia	Yes	131 (52.4)	25	106	0.047	0.874
	No	119 (47.6)	24	95		
Loss of consciousness	Yes	102 (40.8)	20	82	0.000	1.000
	No	148 (59.2)	29	119		
Duration of LOC	≤ 24	79 (31.6)	14	65	0.259	0.732
	> 24	171 (68.4)	35	136		
Duration of LOH (hours)	≤ 24	39 (15.6)	9	30	0.354	0.518
	> 24	211 (84.4)	40	171		
Convulsions	Yes	169 (67.6)	35	134	0.408	0.611
	No	81 (32.4)	14	67		
Acidosis*	< 15	40 (16.0)	11	29	1.886	0.193
	≥ 15	210 (84.0)	38	172		
WBC (X 10^9/L)	> 10	74 (29.6)	14	60	0.031	0.865
	≤ 10	176 (70.40	35	141		
Neutrophils (%)	≤ 60	140 (56.0)	28	112	0.032	0.874
	> 60	110 (44.0)	21	89		
Lymphocytes (%)	≤ 40	138 (55.2)	25	113	0.431	0.526
	> 40	112 (44.8)	24	88		
PCV (%)	≥ 15	231 (92.4)	45	186	0.028	0.772
	< 15	19 (7.6)	4	15		
Platelets (X 10^9/L)	< 150	113 (45.2)	22	91	2.661	0.342
	150-450	127 (50.8)	27	100		
	≥ 450	10 (4.0)	0	10		
Sodium (mmol/L)	≥ 125	178 (71.2)	37	141	0.552	0.488
	< 125	72 (28.8)	12	60		
Potassium (mmol/L)	≤ 5.5	241 (96.4)	47	194	0.041	0.691
	> 5.5	9 (3.6)	2	7		
Cr mg/dL	≤ 1.5	236 (94.4)	48	188	1.460	0.315
	> 1.5	14 (5.6)	1	13		

***Baseline at admission; Resp-respiratory; LOC- Loss of consciousness; LOH-Length of hospitalization; WBC-white blood cells count; *bicarbonate less than 15 mmol/L.*

At follow-up, 24 (49.0%) of the 49 children with neurological complications at discharge had fully recovered, whereas 18 (36.7%) were still recovering (Table 4). The follow-up period after discharge from the hospital ranged from 2 to 66 days, with a median of 6.5 [interquartile range, 4.3–9] days). In addition, during follow-up after discharge, there was a significant relationship between recovery after neurological complications and sex (Table 4).

Discussion

Malaria continues to be a significant disease, disproportionately impacting Nigeria, with cerebral malaria being one of its common severe forms. This study examined the prevalence of cerebral malaria among overall admissions and among those with severe malaria, with rates of 3.4% and 30.0%, respectively. Our findings are similar to those of 3.7% and 4.3% prevalence of cerebral malaria among all hospitalized children in Nigeria and Cameroon, respectively.[10,17] In contrast to the prevalence obtained among the pediatric admissions in this study, a higher prevalence of 5.6% was observed among pediatric admissions in southwestern Nigeria,[18] possibly because of differences in the study population and season of the study. In addition, our observed prevalence of cerebral malaria was lower than that of 0.2% and 2.1% in pediatric admissions and severe malaria cases, respectively, in Mozambique.[19] The difference may be due to variations in the study population. All participants in our study had severe malaria, with slightly more than half of them being children aged 5 years and above. In contrast, nearly all children (91.4%) in the Mozambique study were under two years of age, and 73.0% had uncomplicated malaria. It is worth noting that despite the reported similar burden of cerebral malaria from total pediatric admission, a far higher proportion of cerebral out of all severe malaria cases (14.3%) was found in the study in Cameroun, with a larger percentage of under-five (70.0%).[17] Thus, the disparity from most of the aforementioned studies when compared to ours may be due to variations in age groups, immunogenicity of malaria parasites, genetic predisposition, and possibly malaria endemicity.[20,21] Variances in host immune factors, such as cytokine profiles, genetic polymorphisms, and acquired immunity, dictate population responses to infestation and differences in childhood cerebral metabolic crisis.[14] Populations with a more profound immunological response to severe malaria are at higher risk of cerebral malaria.

This study showed that hypoxemia, duration of loss of consciousness, duration of hospitalization, acidosis, white blood cell count, serum sodium, and serum creatinine were associated with hospitalization outcomes. These findings are comparable to those of a study conducted in southwestern Nigeria,[18] where poor outcomes were associated with white blood cell count, hematocrit, platelet count, and acute kidney injury. Similarly, a study in Malawi among 1663 children with cerebral malaria documented relationships between age, loss of consciousness, and acidosis with poor outcomes.[22] Also, in keeping with our observations, the authors documented a higher likelihood of neurological sequelae among younger age groups and those with longer durations of unconsciousness and higher likelihood of death associated with acidosis.[22]

The case fatality rate of 11.9% in our study was far lower than the 18.0% and 28.8% reported by studies in Nigeria and Uganda, respectively,.[18,23] The lower case fatality rate found in our study may be related to the higher proportion of children older than five years and possibly the hospital policy of having at least the first dose of intravenous artesunate freely available for children diagnosed with severe malaria. Research has documented that the earlier artesunate is administered to children with severe malaria, the better the outcomes.[21] This observation supports the need to make intravenous artesunate for severe malaria available free for children at pediatric hospitals or emergency points.

The predictors of hospitalization deaths were hypoxemia (AOR, 6.1), baseline serum creatinine greater than 1.5 mg/dl (AOR, 6.7), and the first 24 h of hospitalization (AOR, 5.9). In Malawi[22] a significant relationship was observed between acidosis and mortality, while a review of predictors of outcomes of cerebral by malaria Patel *et al*.[24] identified impaired consciousness, hypoxemia, metabolic acidosis, and acute kidney injury as predictors of mortality in severe malaria. The six-fold likelihood of mortality within the first 24 h in our patients is comparable to the substantial increase in mortality risk within the same timeframe observed in a multicenter study involving 7,765 children with severe malaria.[10] This finding suggests that the severity of the disease in patients may be higher in the first 24 h of admission and a need for closer monitoring during the early period of hospitalization.

The prevalence of neurological complications at discharge was 19.6%, half of whom recovered during the follow-up. This is slightly less than reports of a 23.1% and 22.0% prevalence of neurological complications among children with cerebral malaria in Malawi[25] and Nigeria[18] respectively. Similar to our observations, the studies also observed varying neurodisabilities, including motor, sensory, and language deficits, and seizures among survivors of cerebral malaria, re-enforcing the impact of cerebral malaria on the brain of children.[1825] In contrast, the

observed neurological complications in this study were far less than the 40.0% recorded in another Nigerian study,[26] probably due to differences in study sample and study location. This study had 284 cases of childhood cerebral malaria in Northern Nigeria compared with 20 cases studied in southwestern Nigeria.[26] This study shows that under-fives were associated with increased odds of neurological complications at discharge, while fever at presentation confers lower odds of neurological complications. Studies have documented higher likelihood of neurological complications in under 5 children compared to older children, probably a reflection of the increase susceptibility to neuronal damage.[16,22,26]

While this study has a relatively large sample size (284) of childhood cerebral malaria, there are some limitations. First, this was a single-center study and does not reflect the whole country. Also, 7 (14.3%) out of 49 children with neurological complications at discharge were lost to follow-up. In addition, we based our definition of cerebral malaria on the WHO definition criteria, which included coma lasting 30 minutes or more, evidence of *Plasmodium falciparum*, and the absence of any other plausible cause of encephalopathy. Worthy of note is the fact that additional features through cranial imaging and retinal changes on fundoscopic examination have been found to improve the diagnosis of childhood cerebral malaria.[7] However, in our facility, cranial imaging and fundoscopic examinations for retinal changes were not routinely carried out in children with cerebral malaria; hence, they were not included in the extracted data used for this study.

Conclusion

This study shows a high burden of cerebral malaria among Nigerian children, with unacceptably high mortality and neurological complications, especially among under-fives. Among children with cerebral malaria, the odds of death are increased in the presence of hypoxemia and elevated serum creatinine levels. There is a need to for studies that will improve outcomes (hospitalization deaths and neurological complications) in children with cerebral malaria.

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