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Research Article

Clinical Severity and Predictors of Outcome among Children and Adolescents Hospitalized with Covid-19

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Abstract

Objectives: To analyze the clinical, demographic, and epidemiological spectrum and their association with clinical severity and predictors of outcome, in children hospitalized with COVID-19, in a public reference hospital for COVID-19 in a State in Northeastern Brazil, between April 2020 and April 2021. **Method:** A retrospective cross-sectional study was conducted by analyzing the electronic medical records of children and adolescents. In the statistical analysis, we adopted a significance level of 5% and employed the chi-square test and Fisher's exact test. **Results:** Of the 165 patients seen in the emergency room with clinically suspected COVID-19, 117 were admitted and confirmed by rapid serologic test or RT-PCR for SARS-CoV-2. The median age was 3 years 5 months. The weight-for-age in children under 10 years of age was adequate in 64.1% of them. The predominant symptoms were cough, fever, and dyspnea. There was pneumonia diagnosis in 53.8% of patients, and interstitial pulmonary infiltrate was the most frequent alteration (50.4%). There was an association between ethnicity (black or brown) and greater severity of the disease. Asthma was the most prevalent comorbidity, followed by diabetes mellitus, both were statistically associated with disease severity. The favorable outcome of hospital discharge within 14 days was associated with adequate weight. **Conclusions:** Black and brown ethnicity and the comorbidities of asthma and diabetes mellitus were determinants of severity while age-appropriate weight was a predictor of favorable outcome in COVID-19.

Keywords: COVID-19; SARS-CoV-2; Comorbidity; Severity; Pneumonia.

Introduction

Since the World Health Organization (WHO) declared a pandemic for Corona Virus Disease 2019 (COVID-19) on March 11, 2020 [1], raised both concern and commitment from the global scientific community. Within this context, in 2022, Brazil had the third-highest number of cases and the second-highest number of deaths in the world [2].

The COVID-19 is caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), that since late 2020, has exhibited continuous convergent evolution, characterized by the generation of sets of mutations that impact the transmissibility and antigenicity of the virus, phenotypic changes and propagation [3]. These mutations were classified according to the WHO, in variant of concern (VOC) and Variant of interest (VOI). In the VOCs group, were initially sequenced: Alpha variants (B.1.1.7), initially identified in the United Kingdom and Brazil in December 2020, Beta (B.1.351), discovered in South Africa, Gamma (B. .1.1.28.1), originating in Brazil (Manaus) and Delta (B.1.617.2), identified in India [3].

In Brazil, from January 2020 to May 2021, changes in the frequency of dominant lineages were recorded, according to data from the Genomic Fiocruz Network [4]. The confirmation of records of cases of Covid-19 caused by the Beta variant only occurred at the end of April 2021[5] and caused by the Delta Variant only in the second half of May 2021[6]. SARS-CoV-2 colonizes the upper airways and nasopharyngeal cavity [7,8]. It can be transmitted by a symptomatic infected individual or an asymptomatic carrier and is highly contagious. Respiratory droplets are the main route of transmission, but transmissibility by contact and the digestive tract may be possible as well [8]. The incubation period is around 1 to 14 days, and the diagnostic confirmation of SARS-CoV-2 infection is done by detection of viral nucleic acid, viral antigens, or serological tests [8].

The initial response to infection occurs via the innate immune system through the participation of Toll-like receptors (TLR) 3, 4, and 7, resulting in the production of several cytokines with antiviral effects, such as interferons and the inflammatory cytokine interleukin-6. This is followed by an adaptive immune response, important for viral clearance, with the participation of CD4, CD8, and B T-lymphocytes and antibodies [8,9]. In the pediatric setting, most statistical reports designate children as a relatively protected group, having lower infection and hospitalization rates [10]. Less than 10% of pediatric cases require admission to the Intensive Care Unit (ICU), and the pediatric mortality rate has been less than 1% [11]. Given the broad spectrum of manifestations and severity of COVID-19, in different pandemic periods, the present study aims to analyze clinical, epidemiological, demographic characteristics and their associations with disease severity and predictors of outcome in children hospitalized in a public reference hospital for COVID-19 in the State, in the first year of the pandemic.

Methods

We analyzed the clinical, demographic, and epidemiological profile of pediatric patients hospitalized with a clinical laboratory diagnosis of COVID-19, using a retrospective cross-sectional study that analyzed the electronic medical records of children and adolescents admitted between April 1, 2020, and April 1, 2021, to a public pediatric referral hospital for the disease, in a State in northeastern Brazil.

The data collected were age, gender, ethnicity, weight, symptoms, previous contact with COVID-19 patients, days of hospitalization, pneumonia, and the presence of comorbidities (previous chronic diseases). The age group classification adopted in the general description included infant (<2 years), preschool (≥ 2 and <6 years), school (≥ 6 and <12 years), and adolescent (≥12 years and < 19 years). However, for purpose of analyzing disease severity and outcome, we adopted the division of ≤ 6 years and > 6 years.

We classified the clinical severity of the disease based on Dong et al. [11]: mild cases (cold symptoms and/or digestive symptoms such as diarrhea, vomiting, and abdominal pain), moderate (frequent fever and cough, followed by pneumonia, without hypoxemia or fatigue), and severe (fever and early cough, with/without gastrointestinal symptoms, dyspnea, cyanosis, saturation below 92%, or use of accessory muscles). For statistical analysis, mild and moderate cases were grouped together and considered non-severe. We divided the clinical evaluation of patients into favorable outcome (hospital discharge in 14 days or less) and unfavorable outcome (discharge in more than 14 days or death). Data collection was carried out after obtaining the approval of the research ethics committee, of the Hospital Universitario Onofre Lopes, from Universidade Federal do Rio Grande do Norte (4.886.243), for which a waiver of informed consent was granted according to the required criteria.

The data underwent exploratory descriptive and inferential analysis with a significance level of 5%, using the chi-square test and Fisher's exact test [10]. For data treatment, SPSS (IBM) version 22 was used.

Results

Of 165 children and adolescents who were admitted to the emergency department of a referral pediatric hospital with suspected COVID-19 between April 1, 2020, and April 1, 2021,

154 were hospitalized and 117 had diagnostic confirmation by RT-PCR or rapid serological test for COVID-19, these being the study's subject (Figure 1).

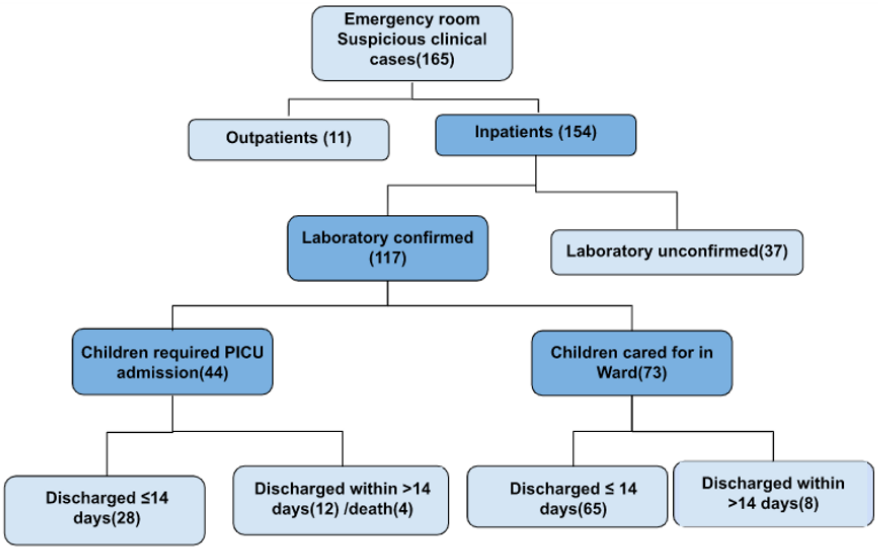

Figure 1: Flowchart of admission and outcome of patients admitted with COVID-19; Source: Modified from Kazi et al. [12]

The median age was 3 years 5 months, with interquartile ranges from 1 year 7 months (P25) to 8 years 8 months (P75). A slight majority were male (57.3%), in the infant to preschool age group (54.7%), of black or brown ethnicity (51.3%), and of age-appropriate weight under 10 years of age (64.1%). Less than one-third of the patients (29.1%) the contact with a sick person was reported (Table 1).

VARIABLES		N	%
Gender	Female	50	42.70
	Male	67	57.30
Age Group	Infant	45	38.50
	Preschool	19	16.20
	School	37	31.60
	Adolescent	16	13.70
Ethnicity/population	White	27	23.10
	Black	03	2.60
	Brown	57	48.70
	NR	30	25.60
Weight for age	Very low weight	04	3.42
<10 years (WHO)	Low weight	05	4.27
	Appropriate weight	75	64.10
	High weight	13	11.11
	NA	20	17.09
Contact with patient	No	83	70.90
	Yes	34	29.10

Table 1: Demographic and epidemiological data of pediatric inpatients with COVID-19; NR: Not mentioned in the medical record. NA: WHO classification not applicable (patients >10 years of age).

The main signs and symptoms presented were cough (73.5%), fever (71.8%), dyspnea (63.2%), tachypnea (51.3%), and the use of accessory respiratory muscles (48.7%), with flu-like symptoms (runny nose, sneezing, and nasal obstruction) present in only 31.6% of the patients (Figure 2).

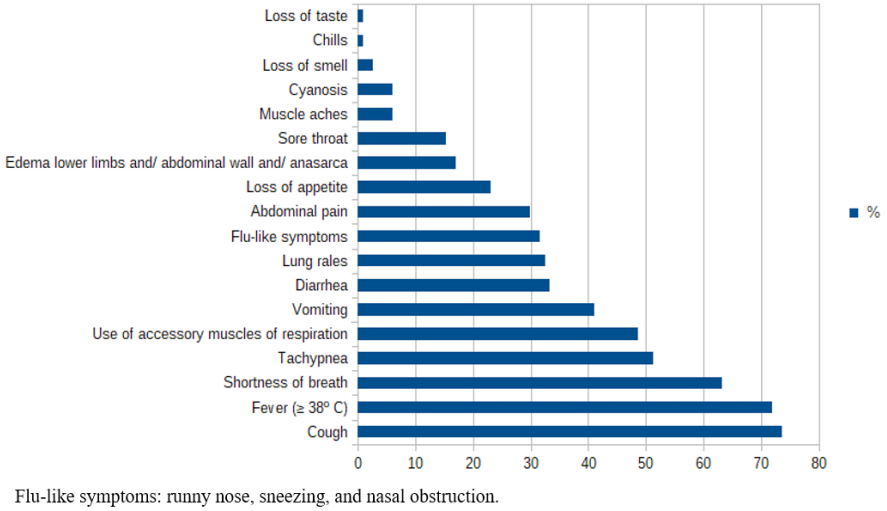

Figure 2: Clinical symptoms of pediatric patients hospitalized with COVID-19.

Laboratory diagnosis was confirmed in 117 patients, 61% of whom were diagnosed by rapid serological test and 39% by RT-PCR. The chest X-ray or CT scan report was recorded in 70 out of 117 patients, of which 7 were normal and 63 presented the following alterations: interstitial infiltrate (50.43%), consolidation/opacification (2.85%), homolateral pulmonary veiling (1.42%), and pulmonary hyperinflation (1.42%).

In the clinical severity classification, of the 117 patients studied, 97 (82.9%) were severe. Analyzing the association between disease severity (non-severe [mild and moderate cases] *vs*. severe) and the variables of sex, age, ethnicity, and weight, only ethnicity (black and brown populations) was significantly associated with severity (p = 0.00) (Table 2).

VARIABLES		SEVERITY				X^2	*p*-value
		Not Severe		Severe			
		N	%	N	%		
Gender	Female	8	16.00	42	84.00	0.074	0.49
	Male	12	17.90	55	82.10		
Age	Up to 6 years	14	18.40	62	81.60	3.269	0.60
	Over 6 years	6	14.60	35	85.40		
Ethnicity/population	White	1	3.70	26	96.30	30.941	0.00*
	Black and brown	4	6.70	56	93.30		
	NR	15	50.00	15	50.00		
Weight**	Inadequate weight	4	18.20	18	81.80	0.003	0.95
	Appropriate weight	14	18.70	61	81.30		

Table 2: Analysis between COVID-19 disease severity and demographic data;* Significant at the 5% level. NR: Not recorded. ** <10 years of age.

One or more comorbidities were present in 51 out of 117 patients hospitalized with COVID-19 (43.6%), in the following decreasing order of prevalence: asthma (26), neurological diseases (13), other chronic conditions (sickle cell anemia, ichthyosis, arthrogryposis, and cancer) (8), congenital heart disease (4), obesity (3), diabetes (3), other congenital malformations (3), prematurity (2), cystic fibrosis (1), and an inborn error of immunity (1). Most of the severe patients had 1 or more comorbidities; patients with severe cases included all those with diabetes mellitus, 96.2% of the asthma patients, 84.6% of the patients with neurological diseases, 75% of those with congenital heart disease, the patient with cystic fibrosis, and the patient with the inborn error of immunity. A statistically significant association was found between disease severity and asthma ($p = 0.03$) and diabetes mellitus ($p = 0.05$) (Table 3).

COMORBITIES	**SEVERITY**				**X^2**	***p*-value**
	Not Severe		**Severe**			
	N	**%**	**N**	**%**		
Prematurity	1	50.00	1	50.00	1.555	0.31
Neurological disease	2	15.40	11	84.60	0.03	0.61
Congenital heart disease	0	0.00	4	100.00	0.854	0.46
Asthma	1	3.80	25	96.20	4.14	0.03*
Obesity	1	33.30	2	66.70	0.573	0.43
Diabetes mellitus	0	0.00	3	100.00	0.635	0.05*
Cystic Fibrosis	0	0.00	1	100.00	0.208	0.82
Inborn error of immunity	0	0.00	1	100.00	0.208	0.82
Congenital malformations (other)	1	33.,30	2	66.70	0.573	0.43
Other pre-existing chronic conditions**	2	25.00	6	75.00	0.379	0.41

Table 3: Disease severity and comorbidities in pediatric patients with COVID-19;*Significant at the 5% level. **Sickle cell anemia, ichthyosis, arthrogryposis, and cancer.

The duration of hospitalization, whose median was 7 days, was divided between those who were discharged within 14 days of hospitalization (79.4%), which was considered a favorable outcome, and those discharged from the hospital after 14 days (17.9%), which was considered an unfavorable outcome. There was no significant association between the favorable or unfavorable outcomes and the age of the patients, if ≤ 6 years or > 6 years, but the weight was significantly associated ($p = 0.01$) with this clinical outcome (Table 4). The severe acute respiratory syndrome (SARS) was present in 76% of patients and death in 3.4%. No case of multisystem inflammatory syndrome of children (MIS-C) related to COVID-19 was reported.

Variables		Outcome				X^2	*p*-value
		Favorable (discharge within 14 days)		Unfavorable (discharge over 14 days)			
		N	%	N	%		
Age	Up to 6 years	60	78.90	16	21.10	0.39	0.84
	Over 6 years	33	80.50	8	19.50		
**Weight	Inadequate	13	59.10	9	40.90	6.22	0.01*
	Adequate	63	84.00	12	16.00		
Comorbidities	No	51	77.30	15	22.70	0.46	0.50
	Yes	42	82.40	9	17.60		
X-Ray/CT Pneumonia	No	4	57.10	3	42.90	2.28	0.32
	Yes	51	81.00	12	19.00		
	Not registered	38	80.90	9	19.10		

Table 4: Analysis of outcome predictors related to hospital discharge; *Significant at the 5% level. **Weight <10 years old.

Discussion

Reports of new infections from the SARS-CoV-2 are still on the rise. The number of cumulative cases of Covid-19 in the Brazil, reported to WHO, increased a lot from April 2020 to April 2022 and slowed down for 2023[13]. This study was carried out in a period during which the Wuhan and Alpha virus variants dominated [3].

All the inpatients had a positive laboratory diagnosis for COVID-19, with more than half of these diagnoses performed by rapid serological test and 39% by RT-PCR. The rapid serological test detects the presence of anti-viral antibodies IgM and IgG, and it is the most affordable test with immediate results. RT-PCR detects viral RNA, and while a positive result is highly specific to the presence of the virus, the sensitivity is not well determined and can be affected by the timing of the test, sample collection, and laboratory techniques [14]. RT-PCR has less sensitivity, especially during the viral incubation phase, and a high false negative rate of about 68% [15].

The hospital admissions for COVID-19 were most common in the infant and preschool age group (up to 6 years). The highest rates of hospitalization for COVID-19 have been associated with children under 1 year of age, although hospitalization of infants may not reflect a greater disease severity [16] or worse prognosis [17]; rather, this rate may be relative to a lower judgmental threshold for admission [10].

The lack of significant difference found between the sexes, also has been observed in several studies [11,17]. The weight categorization for the current study was based on the WHO's anthropometric weight-for-age index for children under 10 years of age [18]. The weight was appropriate for the children's age for most children under 10 years old. It is known that there are better parameters for weight assessment among children, such as weight-for-stature among those aged 0-5 years and body mass index among those over 10; however, the hospital records did not include the patients' heights.

Although this study analyzed cases of children and adolescents hospitalized during the pandemic's peak year, from 2020 to 2021, the reference of previous contact with people with COVID-19 occurred in less than one-third of the patients. Unlike this, other study of children and adolescents hospitalized with COVID-19 between March and April 2020, which found that most of them (52%) had previous contact with family members with COVID-19 symptoms, 18% of whom had diagnostic proof [19]. It is possible that these differences are related to the different realities of the populations studied, such as access to and availability of health services. Children with COVID-19 are usually asymptomatic or have mild to moderate disease [16]. However, there are cases that progress to severe pneumonia, SARS, and even multiple organ dysfunction [19].

The most reported symptoms in the current study were cough, fever, and dyspnea, the latter of which may have justified the hospitalization, especially since there was a predominance of children under 6 years of age. At the beginning of the pandemic, when early Sar-CoV-2 variants (VOCs) like Alpha variant prevailed, the fever, chills and cough were the most frequently reported symptoms in children and adolescents [6]. Flu-like symptoms (runny nose, sneezing, and/or nasal obstruction) were mentioned less frequently among the patients, which may be attributed to the fact that the children were no longer in the initial phase of the disease at the time of admission, when these indications of upper airway infection prevail. In addition, it was during the dominance of the Delta and Omicron variants, around April 2021, that nasal congestion, headache, sneezing, sore throat, altered sense of smell and croup-like symptoms occurred most commonly [20].

In the imaging diagnosis, which was performed by simple chest radiography or CT scan, pneumonia was present in 90% of the cases reported. Among the radiological findings, interstitial infiltrate was the predominant finding, followed by consolidation. A similar finding was reported in prospective study [21]. In the early phase of coronavirus pneumonia, plain chest radiography shows small irregular opacities and interstitial changes, especially in the periphery of the lungs. Severe cases may develop multiple bilateral ground-glass opacities and lung consolidations [8]. A systematic review and meta-analysis of studies on lung imaging in a pediatric population with COVID-19 found that more than one-third of the patients had normal chest CT results and that only 27.7% (95% CI: 19.9%–35.6%) presented bilateral lesions. Among the most typical findings were ground-glass opacity (37.2%, 95% CI: 29.3%–45%) and pneumonic consolidations or infiltrates (22.3%, 95% CI: 17.8%–26.9%). Imaging changes among children were less severe than in adults, and neither increased perihilar marks nor hyperinflation was reported [22].

Severe clinical cases were defined if they presented fever and early cough, with/without gastrointestinal symptoms, dyspnea, cyanosis, saturation below 92%, or use of accessory muscles [11] and corresponded to 82.9% out of 117 patients. In this group was included all cases diagnosed as SARS due to COVID-19. According to the National Epidemiological Bulletin 44, through epidemiological week 53 on December 27, 2020, there were 14,638 confirmed cases of SARS hospitalization due to COVID-19 among patients aged 0-19 years, accounting for 2.5% of the SARS cases due to COVID-19 in Brazil in 2020 [23].

Although hospitalization of patients clinically classified as mild is not expected [21], the early age and the presence of risk factors such as digestive symptoms, signs of dehydration, comorbidities, or vulnerable social status may have justified the hospitalization of non-severe patients in the present study (17.1%). No association between clinical severity and age, was found. The median age was 3 years 5 months and most were up to 6 years old. A French national prospective surveillance of children hospitalized with SARS-CoV-2 infection reported higher rate of severe forms of COVID-19 and number of deaths (7 out of 397 cases), in children over 10 years old and only 3 (3/7) deaths were under 6 years old [21]. However, there was a significant association between clinical severity and ethnicity, i.e., critically ill patients were predominantly of brown or black ethnicity. A North American study found a disproportionate effect of COVID-19 according to racial and ethnic groups, with rates of hospitalization and death 2.5 times higher in children from less represented racial groups (black and Hispanic) than in non-Hispanic whites [24]. This result was probably related to health determinants influenced by unfavorable socioeconomic status which has relevance for the population predominantly assisted in public hospitals.

Published studies on pediatric patients with chronic diseases prior to COVID-19 have shown that prior disease plays an important role in the development of severe forms of COVID-19, accounting for 50-80% of ICU admissions and increased risk of Invasive mechanical ventilation [17]. In the present study, almost 50% of the patients presented comorbities. The asthma and diabetes mellitus were significantly associated with disease severity. Asthma is one of the most common chronic diseases in childhood, with a prevalence in children and adolescents in Brazil ranging from 10.1% to 31.2% from 2003 to 2012 [25]. However, studies show that people with asthma do not appear to be at increased risk of acquiring COVID-19 [26].

In a cross-sectional study of 4,302 COVID-19 inpatients (<18 years) in 800 USA hospitals, found an association between comorbidities and disease severity, with the highest risk of severe disease being among those with diabetes mellitus (RR 2.38; 95% CI, 2.06–2.76) [19]. Among other comorbidities present in the patients with severe disease, we highlight the case of a 5-year-old

boy with the inborn error of immunity (IEI) - Chediak-Higashi syndrome (with clinical and genetic diagnostic test) who had a favorable outcome being discharged from the hospital in less than 14 days. He is currently in the third month after bone marrow transplant for correction of his underlying disease. Although there is a fear that patients with IEI may have a very poor prognosis due to the presence of immune dysregulation, studies have shown that, in general, most patients with IEI have mild forms of COVID-19 or are asymptomatic [27].

Although this is a study of predominantly critically ill patients, 82% of them had a favorable outcome, regarding the length of hospital stay i.e., they were discharged within 14 days. Most children and adolescents with COVID-19 have a good prognosis, with a mean hospital stay of 12.9 days [28]. No case of multisystem inflammatory syndrome of children (MIS-C) related to COVID-19 was reported. It is a severe complication following SARS-CoV-2 infection. Its main characteristics are fever and multiple organ dysfunction—in particular, cardiac dysfunction and severe shock—due to the patient's hyper inflammatory state [11].

Of the 4 deaths (3.4%) in the present study, all had comorbidities. The statutory notification system of this State, reported that through August 2022, 33 COVID-19-related deaths were among those aged 0-14 years with a lethality of 0.11% in people aged 0-19 years [29]. Age-appropriate weight in children under 10 years of age was a predictor of favorable outcome, regarding the length of hospital stay. Although it did not present a significant relationship with the severity of the disease, children with inadequate weight needed more days of hospitalization for their complete recovery.

In conclusion, ethnicity (black and brown) and the presence of the comorbidities asthma and diabetes mellitus were determinants of COVID-19 severity, with asthma being the most prevalent comorbidity. On the other hand, age-appropriate weight in children under 10 years of age was a predictor of favorable clinical outcome. This is a retrospective study, therefore, it has limitations inherent to data collected from medical records.

We hope that this study during the first year of the pandemic, could contribute to comparative studies in different periods in which new variants are in force.

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Author Contributions

Vera M Dantas[1] Participated in the conception and design of the study, data analysis and interpretation, article writing.

Vanessa S L Dantas[2] Participated in the conception and design of the study, data acquisition, article writing and preparing figures.

Claudia R S Maia[3] Participated in the critical review of the relevant intellectual content.

Barbara M F C Faria[4] Participated in the critical review of the relevant intellectual content.

Raissa A S Brandão[5] Participated in the critical review of the relevant intellectual content.

Authors Declaration

All authors were involved in the final approval of the version to be submitted.

An institution with which the work is associated: Federal University of Rio Grande Do Norte – Department of Pediatrics.

The authors declare that there are no conflicts of interest.

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