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Original Article

Determinants of COVID-19 severity and mortality in children: A retrospective and multicenter cohort study in Medan, Indonesia

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Abstract

This study investigated indicators of the severity and mortality of COVID-19 in children in Medan, Sumatera Utara Province, Indonesia. The aim of this study was to identify determinants of severity and outcome of children with COVID-19 as the lesson learned from the COVID-19 pandemic, particularly the limited health facilities in Indonesia. This retrospective cohort study was conducted in 2020, 2021, and 2022 at multiple centers. Inpatient and outpatient children confirmed to be SARS-CoV-2 positive were randomly recruited in the selected hospitals. Baseline data (demographic, clinical, laboratory and radiological data) were collected, and outcomes were classified as recovered/deceased (for the inpatient group) or returned to the hospital (for the outpatient group). Severity status was identified based on the Indonesia COVID-19 guidelines. The laboratory data were categorized according to international standards and data were analyzed using univariate analyzes followed by multivariate logistic regression. A total of 303 inpatient and 114 outpatient children were included in the analysis. Out of the total inpatient cases, nine patients died, with 2.9 mortality rate. Our final multivariate indicated that the presence of shortness of breath (SOB), anemia, and abnormal C-reactive protein (CRP) levels were significantly associated with the severity or the presence of emergency signs, while the presence of SOB and comorbidities were significantly associated with mortality in inpatient children with COVID-19. The presence of fever, cough, SOB, muscle ache and diarrhea were the reasons why the children were returned to the hospital from self-isolation at home among outpatient COVID-19 cases; however, the cough was the only significant factor in the final multivariate mode. This study highlights important determinants of COVID-19 severity and mortality in children, which should be considered during clinical decision-making in low-resource settings of healthcare centers in Indonesia.

Keywords: COVID-19, children, pandemic, determinant, risk factor

Introduction

The Indonesian Pediatric Society reported that the mortality rate of children with coronavirus disease 2019 (COVID-19) in Indonesia was 0.46–1.4%, which was higher not only among the Asia

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Pacific region but also in the world [1]. Indonesia was also one of the countries with the highest age-standardized case fatality rate of COVID-19 globally [2]. Previous studies in both Jakarta and Mataram in Indonesia revealed that age, nutritional status, and preexisting comorbid diseases are known to be the risk factors for severe and critical symptoms in hospitalized children with COVID-19 [3,4].

Information about children risk factors could inform clinical decision-making by identifying children who may benefit from closer monitoring [5]. In addition, identifying children who require emergency care or referral to higher type of health facilities is crucial for medical personnel in Indonesia's limited healthcare facilities, including primary and secondary healthcare centers. Although the number of health facilities, especially primary and secondary centers, has increased in recent years, efficient emergency care remains essential [6]. Additionally, primary and secondary healthcare centers are vital for preparing for future epidemics or pandemics [7]. Therefore, the aim of this study was to identify risk factors or determinants of the severity and outcome of children with COVID-19, which might be beneficial for primary and secondary healthcare system in Indonesia.

Methods

Study design and patients

A retrospective and multicenter cohort study was conducted at Bunda Thamrin, Murni Teguh, and Haji Adam Malik hospitals located in Medan, Indonesia. The three hospitals were appointed for COVID-19 management during the pandemic, according to the Governor of Sumatera Utara during the pandemic (instruction no.188.54/4/INST/2020). All laboratories and radiological facilities in the hospitals were nationally accredited. This study included inpatient and outpatient children with COVID-19 aged above 1-month-old and under 18 years old, confirmed by positive real-time polymerase chain reaction (RT–PCR) and registered in the medical records of the study location. Neonates and teenage girls who were pregnant were excluded from the study. Patients who were transferred to another hospital or who were discharged from the hospital by their own need were also excluded.

Data collection

The baseline demographic data, clinical signs and symptoms, laboratory and radiological examination results were recorded at the first admission of inpatient children. For outpatient children, only demographic data and clinical signs and symptoms were recorded with no laboratory or radiological examinations were conducted. The outcomes of the inpatient children were: (a) severity of the cases (classified as severe and non-severe case); and (b) mortality (classified as recovered or death). For outpatients, the outcome was classified as returned to hospital or remained in self-isolation. Returning to the hospital and symptoms after three days of taking the medication were monitored through direct calls or interviews with the parents or caregivers.

Study variables

On the first day of examination or admission (in the ward or the emergency room), the baseline sign and symptom data were collected, and the patients were followed up regarding the outcome. Data on age, sex, nutritional status, comorbid diseases, fever (fever for less than three days or persistent fever), cough (dry or productive cough), cephalgia, myalgia, diarrhea/watery stool, shortness of breath (SOB), oxygen saturation level, confusion/altered consciousness, abdominal pain, rash, rhinorrhea, anosmia, and sore throat were recorded based on the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) using the case record form (CRF) [8].

We used the 2020 Indonesia Ministry Health Office guidelines on children's anthropometric status (anthropometric status was calculated by weight per age for children <5 years old and body mass index (BMI) per age for children ≥5 years old) [9]. Children at risk of being overweight and obese were included in the overnutrition group, and children at risk of thinness, severe thinness, underweight and severe underweight were included in the malnutrition group.

The level of hemoglobin was classified as anemia or not anemia. The numbers of leucocyte, thrombocyte, neutrophil, and lymphocyte were categorized as low, normal or high. C-reactive protein (CRP) and D-dimer levels were categorized as normal or abnormal/high. Lastly, the neutrophil-to-lymphocyte ratio was categorized as low, normal, or high. All results were in accordance with the laboratory reference values of the Nelson textbook of the Pediatric 21st Edition [10]. The systemic immune-inflammation index (SII) ratio was calculated as (neutrophil×thrombocyte)/lymphocyte. The thrombocyte-to-lymphocyte (T/L) ratio was calculated based on the absolute thrombocyte and lymphocyte counts.

Radiological examination was performed using a chest X-ray (CXR) or chest computed tomography (CCT) scan. The results of the chest radiology examination were categorized as normal or abnormal (bilateral/unilateral interstitial patterns, focal consolidation, bronchial wall thickening, ground glass opacities, and other abnormalities) [11,12]. Parents who refused the radiology examination for any reason were categorized as having "no CXR or CCT result" and these cases were excluded from further analysis. According to the Indonesian COVID-19 guidelines [13-16], COVID-19 in children is categorized as asymptomatic, mild, moderate, severe, or critical. In this study, patients with asymptomatic, mild or moderate COVID-19 were classified as not severe.

Statistical analysis

Data entry and statistical analysis were performed using Excel (Microsoft Office 365, Redmond, WA) and SPSS version 25 (SPSS Inc., Chicago, USA). Descriptive statistics were used to summarize the data. Factors associated with the severity status of inpatient cases (severe and non-sever), the outcome of inpatient cases (recovered or deceased), and the outcome of outpatient children (returned to the hospital or remained in self-isolation) were assessed using Chi-squared test, Fisher's exact test, or independent Student t-tests as appropriate based on the variables. In the second stage, significant predictors with significant odds ratios were analyzed using stepwise logistic regression analysis.

Results

Characteristics, signs, symptoms and laboratory parameters of the patients

A total of 303 inpatient and 114 outpatient children were included in this study, as presented in **Table 1**. Approximately 66.3% of the inpatients and 90.4% of the outpatients were school-age children, and more than half of both inpatient and outpatient were girls. The total of 110 (36.3%) children were overnutrition and 25 were undernutrition (8.3%). Comorbid status was observed in 20 (6.6%) patients. The average observation days among the children with COVID-19 was 6.97 days for inpatient and three days for outpatient. The severe signs and symptoms were recorded in 28 (9.2%) inpatients and nine (2.9%) children did not survive. Among the outpatient children with COVID-19, 15 (13.2%) patients needed to return to the hospital.

Table 1. Characteristics of the children with COVID-19 (n=417)

Characteristics	Inpatient (n=303)		Outpatient (n=114)	
	Frequency	%	Frequency	%
Age (years)				
5–18	201	66.3	103	90.4
1–4	70	23.1	11	9.6
<1	32	10.6	0	0.0
Sex				
Boy	145	47.9	53	46.5
Girl	158	52.1	61	53.5
Nutritional status				
Normal	147	48.5	NA	NA
Overnutrition	110	36.3	NA	NA
Undernutrition	25	8.3	NA	NA
Comorbid diseases				
None	283	93.4	NA	NA
Yes	20	6.6	NA	NA
Observation (days)	6.97		3	
Severity				
Yes (severe and/or critical)	28	9.2	0	0.0

Characteristics	Inpatient (n=303)		Outpatient (n=114)	
	Frequency	%	Frequency	%
No (mild or moderate)	275	90.8	106	93.0
Asymptomatic	0	0.0	8	7.0
Outcome				
Recovered	275	90.8	NA	NA
Deceased	9	2.9	0	0.0
Returned to the hospital	NA	NA	15	13.2
Remained self-isolation	NA	NA	99	86.8

NA: not assessed

Fever was present in both inpatient and outpatient, with frequencies of 82.2% and 19.3%, respectively, and around 24.1% of the patients had persistent fever (>3 days). Most of the inpatient children complained of cough (71.9%) and 35.8% experienced productive cough. The majority of children did not complain of symptoms of headache, myalgia, diarrhea, SOB, altered consciousness, abdominal pain, rashes, anosmia, and sore throat. Low oxygen saturation levels (<93%) were observed in 29 (9.6%) patients. Among the patients, rhinorrhea was presented in at least one-third of each group (**Table 2**). In the outpatient group, fever (19.3%), productive cough (41.2%), rhinorrhea (36.6%), headache/cephalgia (8.8%), and diarrhea (1.8%) were some of the clinical signs and symptoms (**Table 2**).

Table 2. Signs and symptoms of children with COVID-19 (n=417)

Characteristics	Inpatient (n=303)		Outpatient (n=114)	
	Frequency	%	Frequency	%
Fever				
Yes	249	82.2	22	19.3
Yes, not persistent fever	189	75.9	NA	NA
Yes and persistent fever (>3 days)	60	24.1	0	0
No	54	17.8	92	80.7
Cough				
Yes	218	71.9	47	41.2
Yes, dry cough	140	64.2	0	0.0
Yes, productive cough	78	35.8	47	41.2
No cough	85	28.1	67	58.8
Headache/cephalgia				
Yes	22	7.3	10	8.8
No	281	92.7	104	91.2
Muscle ache/myalgia				
Yes	32	10.6	10	8.8
No	271	89.4	104	91.2
Diarrhea or watery stool				
Yes	36	11.9	2	1.8
No	267	88.1	112	98.2
Shortness of breath (SOB)				
Yes	56	18.5	0	0.0
No	247	81.5	114	100.0
Oxygen saturation level				
Not normal (<93%)	29	9.6	0	0.0
Normal (≥ 93%)	266	87.8	114	100.0
Altered consciousness				
Yes	13	4.3	0	0.0
No	290	95.7	114	100.0
Abdominal pain				
Yes	6	2.0	0	0.0
No	297	98.0	114	100.0
Rash at face, trunk, or extremities				
Yes	4	1.3	0	0.0
No	299	98.7	114	100.0
Rhinorrhea				
Yes	100	33.0	44	36.6
No	203	67.0	70	61.4
Anosmia				
Yes	25	8.3	0	0.0
No	278	91.7	114	100.0
Sore throat				
Yes	2	0.7	0	0.0
No	301	99.3	114	100.0

NA: not assessed

After three days of taking medication, the symptoms of the outpatient group were assessed (**Table 3**). Fever (43.9%), cough (15.8%), rhinorrhea (38.6%), sore throat (13.2%), headache (6.1%), anosmia (6.1%), and SOB (0.9%) were some of the symptoms identified by the parents after three days taking medication at home.

Table 3. Symptoms of outpatients children with COVID-19 after 3 days of medication (n=114)

Characteristics	Frequency	%
Fever		
Yes	50	43.9
No	64	56.1
Cough		
Yes	5	4.4
No	96	84.2
Yes, but less frequent	13	11.4
Headache		
Yes	7	6.1
No	107	93.9
Muscle ache		
Yes	4	3.5
No	110	96.5
Diarrhea or watery stool		
Yes	2	1.8
No	112	98.2
Shortness of breath (SOB)		
Yes	1	0.9
No	113	99.1
Rash		
Yes	0	0.0
No	114	0.0
Rhinorrhea		
Yes	44	38.6
No	70	61.4
Anosmia		
Yes	7	6.1
No	107	93.9
Sore throat		
Yes	15	13.2
No	99	86.8

A total of 18.8% of the inpatient children had anemia, while 62.7% and 79.5% of the inpatient children had normal leucocyte and thrombocyte counts, respectively. A total of 51.5% and 37.3% of the inpatient children had low neutrophil and lymphocyte counts, respectively, and 28.1% of the inpatient children had high neutrophil to lymphocyte (N/L) ratios. A total of 32.3% and 28.1% of the inpatient children had abnormal CRP and D-dimer levels, respectively. A total of 52.1% of the inpatient children with COVID-19 had radiological abnormalities (**Table 4**).

Table 4. Laboratory and radiological test results of inpatient children with COVID-19 (n=303)

Characteristics	Frequency	%
Hemoglobin		
Anemia	57	18.8
Normal	243	80.2
No result	3	1.0
Leucocyte		
Low	37	12.2
Normal	190	62.7
High	74	24.4
No result	2	0.7
Thrombocyte		
Low	26	8.6
Normal	241	79.5
High	34	11.2
No result	2	0.7
Neutrophil		
Low	156	51.5
Normal	52	17.2

Characteristics	Frequency	%
High	93	30.7
No result	2	0.7
Lymphocyte		
Low	113	37.3
Normal	53	17.5
High	135	44.6
No result	2	0.7
Neutrophil to lymphocyte (N/L) ratio		
Normal	216	71.3
High	85	28.1
No result	2	0.7
C-reactive protein (CRP)		
Normal	200	66.0
High/abnormal	98	32.3
No result	5	1.7
D-dimer		
Normal	194	64.0
High/abnormal	85	28.1
No result	24	7.9
Systemic immune-inflammation index (SII) ratio		
Mean	754.5	
Median	445.6	
Thrombocyte-to-lymphocyte (T/L) ratio		
Mean	11.5	
Median	7.9	
Chest X-ray and chest CT scan		
Normal	88	29.0
Abnormal	158	52.1
No CXR/CCT result	57	18.9

Univariate analysis of determinants of COVID-19 with severity and outcomes of inpatient cases

We did univariate analysis of demographic characteristics (age, sex, nutritional status, and comorbidity), clinical signs and symptoms to the severity status and the outcomes of hospitalized children. Our univariate analysis revealed that nutritional status (undernutrition) and age (<1 year old) were significantly associated (p<0.001) with severity, and the presence of comorbidities was significantly associated with outcome (**Table 5**). We also found that SOB, oxygen saturation level, abdominal pain, rhinorrhea, and sore throat were significantly associated with severity. Moreover, SOB and oxygen saturation level were the only two variables that were significantly associated with the outcome (**Table 5**).

Table 5. Univariate analysis showing the associations of inpatient's demography, clinical signs and symptoms on severity and outcome of inpatient COVID-19 cases

Characteristics	Severe case		*p*-value	Outcome		*p*-value
	No	Yes		Recovered	Deceased	
	n (%)	n (%)		n (%)	n (%)	
Age (years)						
5–18	188 (93.5)	13 (6.5)	<0.001*	185 (97.9)	4 (2.1)	0.073
1–4	64 (91.4)	6 (8.6)		63 (96.9)	2 (3.1)	
<1	23 (71.9)	9 (28.1)		27 (90)	3 (10)	
Sex						
Boy	129 (89.0)	16 (11.0)	0.302	128 (96.2)	5 (3.8)	0.594
Girl	146 (92.4)	12 (7.6)		147 (97.4)	4 (2.6)	
Comorbidity						
None	258 (91.2)	25 (8.8)	0.357	16 (84.2)	3 (15.8)	0.001*
Yes	17 (85)	3 (15)		259 (97.7)	6 (2.3)	
Nutritional Status						
Normal	135 (91.8)	12 (8.2)	<0.001*	136 (96.5)	5 (3.5)	0.273
Overnutrition	105 (95.5)	5 (4.5)		99 (98)	2 (2)	
Undernutrition	18 (72)	7 (28)		21 (91.3)	2 (8.7)	
Fever						
Yes, not persistent	174 (92.1)	15 (7.9)	0.110	171 (96.6)	6 (3.4)	0.805
Yes, persistent fever	56 (93.3)	4 (6.7)		54 (98.2)	1 (1.8)	
No fever	45 (83.3)	9 (16.7)		50 (96.2)	2 (3.8)	
Cough						

Characteristics	Severe case		*p*-value	Outcome		*p*-value
	No	Yes		Recovered	Deceased	
	n (%)	n (%)		n (%)	n (%)	
Yes, productive cough	67 (85.9)	11 (14.1)	0.172	71 (94.7)	4 (5.3)	0.274
Yes, dry cough	131 (93.6)	9 (6.4)		133 (98.5)	2 (1.5)	
No cough	77 (90.6)	8 (9.4)		71 (95.9)	3 (4.1)	
Muscle ache/myalgia						
Yes	32 (100)	0 (0)	0.056	31 (100)	0 (0)	0.286
No	243 (89.7)	28 (10.3)		244 (96.4)	9 (3.6)	
Headache/cephalgia						
Yes	22 (100)	0 (0)	0.120	18 (100)	0 (0)	0.428
No	253 (90)	28 (10)		257 (96.6)	9 (3.4)	
Diarrhea						
Yes	30 (83.3)	6 (16.7)	0.101	32 (97)	1 (3)	0.961
No	245 (91.8)	22 (8.2)		243 (96.8)	8 (3.2)	
Shortness of breath (SOB)						
Yes	36 (64.3)	20 (35.7)		49 (87.5)	7 (12.5)	
No	239 (96.8)	8 (3.2)	<0.001*	226 (99.1)	2 (0.9)	<0.001*
Saturation level						
Not normal (<93%)	14 (48.3)	15 (51.7)	<0.001*	22 (81.5)	5 (18.5)	<0.001*
Normal (≥ 93%)	253 (95.1)	13 (4.9)		245 (98.4)	4 (1.6)	
Altered consciousness						
Yes	11 (84.6)	2 (15.4)	0.434	12 (92.3)	1 (7.7)	0.341
No	264 (91)	26 (9)		263 (97)	8 (3)	
Abdominal pain						
Yes	4 (66.7)	2 (33.3)	0.040*	5 (100)	0 (0)	0.683
No	271 (91.2)	26 (8.8)		270 (96.8)	9 (3.2)	
Rash of face, trunk or extremities						
Yes	4 (100)	0 (0)	0.521	3 (100)	0 (0)	0.753
No	271 (90.6)	28 (9.4)		272 (96.8)	9 (3.2)	
Anosmia						
Yes	25 (100)	0 (0)	0.096	24 (100)	0 (0)	0.354
No	250 (89.9)	28 (10.1)		251 (96.5)	9 (3.5)	
Rhinorrhea						
Yes	99 (99)	1 (1)	0.001*	94 (98.9)	1 (1.1)	0.149
No	176 (86.7)	27 (13.3)		181 (95.8)	8 (4.2)	
Sore throat						
Yes	1 (50)	1 (50)		2 (100)	0 (0)	
No	274 (91)	27 (9)	0.046*	273 (96.8)	9 (3.2)	0.797

* Statistically significant at $p<0.05$

Our univariate analysis showed that laboratory parameters such as hemoglobin and CRP levels, thrombocyte, neutrophil, and lymphocyte counts and the N/L ratio were significantly associated with severity status. Hemoglobin levels, leucocyte, thrombocyte, neutrophil counts, and the N/L ratio were significantly associated with the outcome (**Table 6**).

Table 6. Univariate analysis of laboratory and radiological examination toward severity and outcome of inpatient COVID-19 cases

Characteristics	Severe case		*p*-value	Outcome		*p*-value
	No	Yes		Recovered	Deceased	
	n (%)	n (%)		n (%)	n (%)	
Hemoglobin						
Anemia	41 (71.9)	16 (28.1)	<0.001**	46 (86.8)	7 (13.2)	<0.001**
Normal	232 (95.5)	11 (4.5)		226 (99.1)	2 (0.9)	
Leukocyte						
Low	31 (83.8)	6 (16.2)	0.085	30 (88.2)	4 (11.8)	0.004**
Normal	178 (93.7)	12 (6.3)		176 (98.9)	2 (1.1)	
High	65 (87.8)	9 (12.2)		67 (95.7)	3 (4.3)	
Thrombocyte						
Low	21 (80.8)	5 (19.2)	<0.001**	19 (82.6)	4 (17.4)	<0.001**
Normal	228 (94.6)	13 (5.4)		224 (99.1)	2 (0.9)	
High	25 (73.5)	9 (26.5)		30 (90.9)	3 (9.1)	
Neutrophil						
Low	145 (92.9)	11 (7.1)	0.037*	144 (98)	3 (2)	0.038*
Normal	50 (96.2)	2 (3.8)		51 (100)	0 (0)	
High	79 (84.9)	14 (15.1)		78 (92.9)	6 (7.1)	

Characteristics	Severe case		*p*-value	Outcome		*p*-value
	No	Yes		Recovered	Deceased	
	n (%)	n (%)		n (%)	n (%)	
Lymphocyte						
Low	97 (85.8)	16 (14.2)	0.042*	98 (94.2)	6 (5.8)	0.169
Normal	51 (96.2)	2 (3.8)		51 (98.1)	1 (1.9)	
High	126 (93.3)	9 (6.7)		124 (98.4)	2 (1.6)	
N/L ratio						
Normal	204 (94.4)	12 (5.6)	0.002**	201 (98.5)	3 (1.5)	0.008**
High	70 (82.4)	15 (17.6)		72 (92.3)	6 (7.7)	
Mean	2.6	4.1	0.049*a	2.6	4.8	0.037*a
SD	3.1	3.7		3.1	4.3	
CRP						
Normal	187 (93.5)	13 (6.5)	0.047*	183 (97.9)	4 (2.1)	0.143
High	84 (85.7)	14 (14.3)		87 (94.6)	5 (5.4)	
D-dimer						
Normal	180 (92.8)	14 (7.2)	0.060	178 (97.8)	4 (2.2)	0.093
High	72 (84.7)	13 (15.3)		74 (93.7)	5 (6.3)	
SII ratio						
Mean	711.8	1187.8	0.067	725.4	862.2	0.092
Standard deviation	864.1	1269.4		1225.3	1159.3	
T/L ratio						
Mean	11.0	16.7	0.053	11,2	16,0	0.163
Standard deviation	10.0	14.4		9,9	12,7	
Chest X-ray and chest CT Scan						
Normal	86 (97.7)	2 (2.3)	0.060	83 (100)	0 (0)	0.099
Abnormal	138 (87.3)	20 (12.7)		151 (96.8)	5 (3.2)	

CRP: C-reactive protein; N/L: neutrophil to lymphocyte; SII: systemic immune-inflammation index; T/L: thrombocyte-to-lymphocyte
[a] Analyzed with independent t-test
* Statistically significant at $p<0.05$
** Statistically significant at $p<0.01$

Univariate analysis of determinants of COVID-19 outcomes of outpatient cases

Our univariate analysis of outpatient COVID-19 children showed that the presence of fever, cough, SOB, muscle ache and diarrhea were significantly associated with returning to the hospital (**Table 7**).

Table 7. Univariate analysis showing the associations of demography characteristics and symptoms with the outcome of outpatient COVID-19 cases

Characteristic	Returned to the hospital	Remained in isolation	*p*-value
	n (%)	n (%)	
Age			
5–18	13 (12.6)	90 (87.4)	0.637
1–4	2 (18.2)	9 (81.8)	
Sex			
Boy	7 (13.2)	46 (86.8)	1.000
Girl	8 (13.1)	53 (86.9)	
Fever			
Yes	15 (30.0)	35 (70)	<0.001**
No	0 (0.0)	64 (100)	
Cough			
Yes	4 (80.0)	1 (20)	<0.001**
No	1 (1)	95 (99)	
Yes, but less frequent	10 (76.9)	3 (23.1)	
Rhinorrhea			
Yes	5 (11.4)	39 (88.6)	0.869
No	10 (14.3)	99 (85.7)	
Shortness of breath (SOB)			
Yes	1 (100)	0 (0.0)	0.010*
No	14 (12.4)	99 (87.6)	
Headache			
Yes	1 (14.3)	6 (85.7)	1.000
No	14 (13.1)	93 (86.9)	
Muscle ache			
Yes	4 (100)	0 (0.0)	<0.001**
No	11 (10.0)	99 (90)	

Characteristic	Returned to the hospital	Remained in isolation	*p*-value
	n (%)	n (%)	
Diarrhea			
Yes	2 (100)	0 (0)	<0.001**
No	13 (11.6)	99 (88.4)	
Anosmia			
Yes	1 (14.3)	6 (85.7)	1.000
No	14 (13.1)	93 (86.9)	
Sore throat			
Yes	14 (14.1)	85 (85.9)	0.688
No	1 (6.7)	14 (93.3)	

* Statistically significant at $p<0.05$
** Statistically significant at $p<0.01$

Multivariable analysis of inpatients' variables to severity and mortality

Multivariable analysis assessing the factors associated with the severity and mortality of the inpatient COVID-19 cases was conducted. Our final model of the stepwise logistic regression analysis indicated that SOB, anemia, and abnormal CRP levels were significantly associated with severity (**Table 8**). SOB and the presence of comorbidities were the only two factors that significantly affected the inpatients' mortality (**Table 9**).

Table 8. Final model of multivariable analysis of inpatient variables to severity

Characteristics	Severe case		OR (95%CI)	*p*-value
	Yes	No		
	n (%)	n (%)		
Shortness of breath (SOB)			16.58 (5.38–51.12)	<0.001**
Yes	20 (35.7)	36 (64.3)		
No	8 (3.2)	239 (96.8)		
Hemoglobin			11.26 (3.49–36.38)	<0.001**
Anemia	16 (28.1)	41 (71.9)		
Normal	11 (4.5)	232 (95.5)		
C-reactive protein (CRP)				
Normal	13 (6.5)	187 (93.5)	6.01 (1.79–20.12)	0.004*
High	14 (14.3)	84 (85.7)		

* Statistically significant at $p<0.05$
** Statistically significant at $p<0.01$

Table 9. Final model of multivariable analysis of inpatient variables to mortality

Characteristics	Deceased		OR (95%CI)	*p*-value
	Yes	No		
	n (%)	n (%)		
Comorbidity			5.66 (1.14–27.98)	0.034*
Yes	6 (2.3)	16 (84.2)		
None	3 (15.8)	259 (97.7)		
Shortness of breath (SOB)			14.02 (2.78–71.09)	0.001**
Yes	7 (12.5)	49 (87.5)		
No	2 (0.9)	226 (99.1)		

* Statistically significant at $p<0.05$
** Statistically significant at $p<0.01$

Multivariable analysis of factor associated with outcome in outpatients

Our final model of multivariable analysis assessing factors associated with the outcome among of outpatient COVID-19 cases found a significant association between the persistent of cough and to return to the hospital, OR: 332.50; 95%CI: 34.63–3192.76 (**Table 10**).

Table 10. Final model of multivariable analysis of outpatients' variables to outcome

Characteristic	Outcome		OR (95%CI)	*p*-value
	Returned to the hospital	Stay isolation		
	n (%)	n (%)		
Cough			332.50 (34.63–3192.76)	<0.001
Yes	14 (77.8)	4 (22.2)		
No	1 (1)	95 (99)		

Discussion

Our study is so far the first study of children with COVID-19 in Medan, Indonesia, expressed in multivariable analysis based on a multi-center hospital approach. School-age children dominated the inpatient and outpatient groups with COVID-19, similar to other studies from Asian locations (Selangor, Negeri Sembilan of Malaysia, China, Iran), Latin America (Columbia), and the United States (Georgia) [17-21]. During the earlier part of the COVID-19 pandemic, many governments, including in Indonesia, had to close schools to prevent the spread of SARS-CoV-2, the virus responsible for COVID-19, in communities due to the possibility of transmission from school-age children [22,23]. However, reopening schools was not associated with significant increases in community transmission [24]. In Italy, during the second wave, school transmission remained uncertain, with the incidence of secondary infections at schools was <1%, clusters of ≥2 secondary cases in 5–7% of the analyzed schools, and the incidence among teachers was comparable to that among the population of similar ages [24,25]. In the middle of 2022, Indonesia started face-to-face classroom education for all school-age children, and the statistics showed no increase of more than 10,000 cases in August 2022 [26]. However, our study revealed that age, particularly under one year old, was significantly associated with severity. Similarly, two previous studies in Indonesia revealed that an infant age of less than one year was a determinant of the risk of mortality [1,27], and the risk of mortality in males was more significant than that in females [1,27,28]. According to our study, malnutrition and the presence of comorbidities are risk factors for mortality.

We found that SOB significantly contributed to the severity and outcome of COVID-19 cases in children. This sign is very important as an indicator, particularly for medical personnel at limited facilities providing care for children with this emergency sign. If children have SOB and morbidity, then mortality tends to occur [29,30]. Therefore, it is necessary for medical personnel to refer children to a more advanced type of hospital with intensive care facilities and certain pediatricians. Since the initial release in April 2020, Indonesia's national COVID-19 guidelines have included SOB as a symptom requiring careful monitoring due to its potential to become severe [13,14]. An international study by the ISARIC team comprising a cohort of 600,000 hospitalized COVID-19 patients (30,000 children) stated that SOB was one of the most common symptoms [31]. Almost all international criteria (Centers for Disease Control and Prevention (CDC), European Centre for Disease Prevention (ECDC), and World Health Organization (WHO) criteria) clearly include SOB or dyspnea as part of the COVID-19 case definition [32]. Our study revealed that 18.5% of the inpatient children had SOB and 9.6% of them had an abnormal oxygen saturation level, with both being statistically significant in the univariate analysis. The first Indonesian guideline (published in April 2020) and the second (published in August 2020) stated that an oxygen saturation level below 93% was the criterion for severe COVID-19 [13,14]. According to the third guideline (published in December 2020), an oxygen saturation level of less than 92% indicated severe COVID-19, and according to the fourth guideline (published in January 2022), severe COVID-19 was defined as an oxygen saturation level of less than 95% [15,16]. Our study used the first and second guidelines for defining oxygen saturation values for severe and critical COVID-19.

Our study revealed that children with comorbidities could affect the outcomes. A study reported that tuberculosis and HIV are the two main comorbidities in children with COVID-19 [33]. As a common respiratory disease in children, asthma is not the main comorbidity that causes increased morbidity or mortality in children who contract COVID-19. This might be explained by the lower expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) in asthmatic children, which behaves differently than that in asthmatic adults [34].

Our results also identified that abnormal CRP was revealed as a determinant for COVID-19 severity. Similarly, the studies indicated that high CRP levels acted as a severity predictor either in children or adults with COVID-19 [35-37]. In India, higher CRP result was significantly related to the presence of bacterial co-infections such as *Staphylococcus aureus* [38], but high suspicious for severe status of children with COVID-19 admitted to the ICU due to *S. pneumoniae*, and *H. influenzae* [39]. Unfortunately, in our study, we did not identify the bacterial co-infections.

Overall, signs of SOB, anemia, and abnormal CRP levels were identified as important predictors of disease severity and could serve as key indicators for the need for emergency care or district hospitals. Compared to adults, many children with COVID-19 are asymptomatic or express milder signs and symptoms [40], allowing them to isolate at home with their parents. Fever, productive cough, muscle ache, diarrhea, and SOB are likely useful indicators for parents to bring their isolated children back to the district hospitals. Despite the increase in available healthcare facilities in Indonesia over the last five years, Indonesia still faces limited health personnel and facilities compared to other countries in the Southeast Asia region [6,41]. Given the above number of healthcare facilities, Indonesia can use primary health care as the core for pandemic prevention, preparedness, response, and recovery, as guided by current studies [42,43]. SOB, anemia, and the presence of comorbidities can be easily identified by medical personnel in primary health care.

Indonesia must address the treatment and prevention of anemia in children regarding pandemic preparedness. Even before the current pandemic, anemia was a major problem for Indonesian children and has become a serious problem for adolescents, especially girls who menstruate. Based on the results of the 2013 and 2018 Indonesia Nationwide Basic Health Research (RISKESDAS), every 1 in 3 children under 5 years of age have anemia (prevalence: 38.5%; 95%CI: 36.6–40.4) [44,45], and the incidence of anemia in adolescents, particularly adolescent girls, can reach 61% [46,47]. Additionally, children in Turkey showed lower hemoglobin values in severe and critical cases of COVID-19 [48]. A multicenter study from hospitals in Oman also showed that anemia is a predictor of severe COVID-19 in children who required ICU care [49].

There are some limitations of this study. The possible effects of circulating variants of SARS-CoV-2 on clinical and laboratory manifestations during the study period were not analyzed. Additionally, field testing of our model is needed, and more clinical scenarios are needed for a more comprehensive understanding of the associations between variables. However, our study included multiple variables that were not measured in previous studies. By using demographic data and simple clinical and laboratory examination data, children who tend to have emergency signs or experience mortality can be easily identified and easily managed or referred by medical personnel in PHCs or by secondary medical personnel.

Conclusion

Our data indicated that the presence of SOB, anemia, and abnormal CRP level were associated with disease severity, while the presence of SOB comorbid were associated with mortality of hospitalized COVID-19 children. In addition, the presence of cough was associated with the return to the hospital among outpatients of COVID-19 in children. These important predictors for the severity and outcome of children with COVID-19 could be identified in limited healthcare facilities. Therefore, by using the clinical predictors generated from this study, it is expected to assist in clinical decision support in primary or secondary healthcare centers at the regency level in Indonesia.

Ethics approval

This study received ethical approval from the Ethics Commission of Universitas Sumatera Utara, Medan, Indonesia, No. 333/KEP/USU/2020. The authors received hospital approval before performing the data collection. For inpatient children, the requirement for patient consent was waived because this study was a secondary analysis of anonymized medical records, while informed consent for the outpatients was collected before the information was gathered.

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Competing interests

All the authors declare that there are no conflicts of interest

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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