Nurse Media Journal of Nursing
e-ISSN: 2406-8799, p-ISSN: 2087-7811
https://medianers.undip.ac.id
12(3):390-403, December 2022
https://doi.org/10.14710/nmjn.v12i3.45340

ORIGINAL RESEARCH

Non-comorbid Respiratory Factor and Work of Breathing in Pediatric COVID-19 Patient: How is Their Synergistic Correlation with the Level of Care?

Defi Efendi[1,2], Maria Dyah Kurniasari[3], Mega Hasanul Huda[4,5], Raudha Ilmi Farid[2], Yohanes Andy Rias[6], Yogi Prawira[7], Nina Dwi Putri[7], Ayuni Rizka Utami[1], Titik Ambar Asmarini[1,8], Pande Lilik Lestari[9], Pricilia Mais[10], Abram Babakal[10]

[1]*Department of Pediatric Nursing, Faculty of Nursing, Universitas Indonesia, Depok, West Java, Indonesia*
[2]*Neonatal Intensive Care Unit, Universitas Indonesia Hospital, Depok, West Java, Indonesia*
[3]*Department of Nursing, Faculty of Medicine and Health Science, Universitas Kristen Satya Wacana, Salatiga City Indonesia*
[4]*Institut Kesehatan Prima Nusantara Bukit Tinggi Sumatera Barat, Bukittinggi, West Sumatra*
[5]*Research and Development Center Hermina Hospital Group, Jakarta, Indonesia*
[6]*Faculty of Health and Medicine, Institut Ilmu Kesehatan Bhakti Wiyata Kediri, Kediri, Indonesia*
[7]*Department of Pediatrics, Dr. Cipto Mangunkusumo National Central Hospital, Faculty of Medicine, Univeristas Indonesia, Jakarta, Indonesia*
[8]*National Central of Army Hospital Gatot Soebroto, Central Jakarta, Indonesia*
[9]*Sanglah National Hospital, Denpasar, Bali Indonesia*
[10]*Prof. dr. R. D. Kandou National Hospital, Malalayang Satu Barat, North Sulawesi, Indonesia*

Article Info

Article History:
Received: 24 March 2022
Revised: 24 October 2022
Accepted: 23 November 2022
Online: 28 December 2022

Keywords:
COVID-19; level-of-care; non-comorbid respiratory; pediatric intensive care unit;; WOB

Corresponding Author:
Defi Efendi
Department of Pediatric Nursing, Faculty of Nursing, Universitas Indonesia, Depok, West Java
Email: defiefendi@ui.ac.id

Abstract

Background: Work of breathing (WOB) and non-comorbidities factors in the respiratory system are the two probable findings in pediatric COVID-19 patients. However, the association of those factors with level of care was not well reported.
Purpose: This study aimed to identify the relation between potential predictors including comorbidity, low nutritional fulfillment, infectious disease, shock, cough, O2 saturation reduction, abnormal blood gas analysis and sore throat with the level of care among pediatric COVID-19 patients. We also analyzed the synergistic correlation of non-comorbidities factors in the respiratory system and work of breathing to predict level of care in pediatric COVID-19 patients.
Methods: A cross-sectional study was conducted in the six referral hospitals from July to September 2020 in four provinces in Indonesia. An observation checklist was used to collect data from the medical records of pediatric patients with COVID-19, including medical diagnosis, demographic, and clinical manifestation. This study included 423 participants aged from 0 to 18. The multivariate logistic regression was performed to test the adjusted odds ratios (AORs) with the 95% confidence intervals (CIs) of the association between WOB, non-comorbid respiratory, and level of care. Moreover, dummy variables (2x2) were made to analyze synergistic correlation of non-comorbid respiratory disease and WOB. The AOR with the 95% CIs was applied in the association between the complication of non-comorbid respiratory diseases and high work of breathing with level of care among pediatric patients with COVID-19.
Results: Results showed that age, presence of comorbidity, nutritional fulfillment, infectious disease, shock, work of breathing, O2 saturation reduction, abnormal blood gas analysis, sore throat, and convulsive meningeal consciousness were significantly associated with the level of care (p<0.05). Pediatric patients with non-comorbid respiratory and increased work of breathing had a 15.59 times higher risk of requiring PICU care level (p<0.01). Meanwhile, pediatric patients who experienced both non-comorbid respiratory and increased work of breathing had a 5.76 times risk of requiring an intermediate level of care (p<0.05), and 9.32 times higher risk of requiring a PICU level of care (p<.05).
Conclusion: It was found that both non-comorbid respiratory and increased WOB had a significant relationship with the level of care for pediatric patients with COVID-19. Nurse should take into account those clinical findings to increase the awareness in monitoring clinical deterioration in pediatric COVID-19 patients.

How to cite: Efendi, D., Kurniasari, M. D., Huda, M. H., Farid, R. I., Rias, Y. A., Prawira, Y., Putri, N. D., Utami, A. R., Asmarini, T. A., Lestari, P. L., Mais, P., & Babakal, A. (2022). Non-comorbid respiratory factor and work of breathing in pediatric COVID-19 patient: How is their synergistic correlation with the level of care?. *Nurse Media Journal of Nursing, 12*(3), 390-403. https://doi.org/10.14710/nmjn.v12i3.45340

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in China, spreading to most countries and causing over 1,600,000 deaths globally (World Health Organization, 2020b). As the pandemic extends to low-middle income countries, there are rising concerns about the risk of severe coronavirus disease 2019 (COVID-19) in populations with high comorbidity prevalence, the effects on health and economies, and current health systems' capacity (Hopman et al., 2020). In particular, this threat was highly evident in Indonesia, where the prevalence of COVID-19 is estimated to be around 643,508, with a mortality rate of 3.0%. Interestingly, it further reported that 10.4% were pediatric patients with a mortality rate of 1.7 (Task Force for the Acceleration of Handling COVID-19, 2020). Moreover, during this pandemic, COVID-19 led to death in different age groups of pediatrics (Chang et al., 2020). A retrospective study revealed that the proportion of severe or critically ill cases was 7.3% of those aged 1-5 years and 4.2% for those aged 6-15 years (Dong et al., 2020). Consequently, the rising cases in pediatric may demand urgent attention. Pathak et al. (2020) triggered investigations that culminated in the establishment of the clinical characteristics regarding the comorbidity, severe or critical care urgently needs to be undertaken. This evidence highlights that the severe ill of COVID 19 among pediatric patients is a serious public health problem, particularly in Indonesia.

In term of severe illness of COVID-19 among pediatric patients, the investigation of the level of care that predicts disease might be of great benefit for healthcare professionals to accurately triage patients to mitigate mortality (Marin et al., 2020). Nurses and medical doctors are the frontline health care providers involved in triage and sorting patients with COVID-19 based on a history of the disease incidence. They can also use a case overview and approach from WHO's ABCDE (Airway, Breathing, Circulation, Disability, and Exposure) history (Gupta et al., 2021). In fact, children are mainly affected by infectious diseases, especially COVID-19, with many sign symptoms and a history of illness. However, these conditions have significantly increased the complexity and difficulty of preview and triage care.

Consequently, this has made the infection a substantial challenge for hospital outpatient triage staff (Zhang et al., 2020). No clinical study has investigated the triage care among children with COVID-19 in Indonesia. Thus, early preview triage care of suspected COVID-19 in children requires to examine, especially in Indonesia. Children with COVID-19 can be heterogeneous, with the most common clinical signs and symptoms such as sore throat, cough, fever, and headaches (Chang et al., 2020). Moreover, the critical disease usually with severe pneumonia, respiratory distress, had oxygen concentration less than 92%, autoinflammatory shock, and a high level of work of breathing (WOB) (Pathak et al., 2020; Sankar et al., 2020).

Among those heterogeneity signs and symptoms as well as the co-occurrence diseases, the high level of WOB is crucial for manifestations of acute respiratory failure. An elevated WOB score >4 was associated with increased severity of intubation and hypoxemia (Apigo et al., 2020). Hypoxemia was also independently associated with mortality in patients with COVID-19. Thus, due to the direct effects of COVID-19 that dictate the overall outcome, sensitive measures in the lungs or respiratory function changes would be reasonably reflect the outcome (Marin et al., 2020). These conditions have significantly increased the complexity of triage care (Zhang et al., 2020). However, no study has investigated the relationship between respiratory function and level of care in children with COVID-19, particularly Indonesians. Therefore, to address the gap, it is crucial to assess the factor of WOB in predicting the level of care among pediatric patients with COVID-19.

Fascinatingly, a systematic review study on COVID-19 describes that children with comorbidities is at a greater risk of severe COVID-19 and associated with a 2.81-fold increase in mortality compared with those who are without comorbidities (Tsankov et al., 2021). Previous studies report diabetes, hypertension, cardiovascular disease, Chronic Obstruction Pulmonary Disease (COPD), malignancy, immune-compromised state, obesity, sickle cell disease, chronic liver or kidney disease, thalassemia, cerebrovascular disease, co-existing infection from various sources were calculated as comorbid factor in pediatric population (CDC, 2020; Sanyaolu et al., 2020; Zhou et al., 2020). Children with comorbidities will be at an escalated risk for critical care and mortality rate during infection (Jain et al., 2020; Tsankov et al., 2021; World Health Organization (WHO), 2020a). Numerous clinical conditions such as diabetes, hypertension, cardiovascular disease, Chronic Obstruction Pulmonary Disease (COPD), chronic liver or kidney

disease, which have been classified as comorbid factors, have been well reported in pediatric population (CDC, 2020; Sanyaolu et al., 2020; Zhou et al., 2020). However, association among the presence of other co-occurrence diseases that is not categorized as comorbid diseases such as Acute Tonsillopharyngitis, Acute respiratory distress syndrome (ARDS), Acute Respiratory Infection, Community-Acquired Pneumonia (CAP) and the increased WOB were not clearly understood. Remarkably, other clinical findings which may be classified as non-comorbid factors in new COVID-19 cases continue to develop. Thus, assessing those factors on further pediatric COVID-19 patient conditions are urgently needed. To the best of our knowledge, no study has highlighted the character and risk factors related to level of care with non-comorbidities and clinical symptoms, especially WOB of children patients in Indonesia. Thus, this study aimed to identify the synergistic correlation of non-comorbidities factors in the respiratory system and WOB with the pediatric level of care in the COVID-19 unit. The synergistic correlation in this study is intended to analyze the interaction of non-comorbid respiratory factor and WOB with the level of care among pediatric patients with COVID-19.

2. Methods

2.1 Research design

A cross-sectional study was conducted in six referral hospitals from July to September 2020. Four provinces encompassed Jakarta, West Java, North Sulawesi, and Bali, with the highest confirmed case among provinces in Indonesia, were chosen. Figure 1 describes the participant's flowchart. Pediatric with mild case was assign as the control group, and those who were cared in the intermediate and intensive care level were the case group.

2.2 Setting and samples

The sample size was estimated using G-Power 3.1 software (El Maniani et al., 2016). The sample size was calculated by employing the effect size of the study based on a previous study with an effect size of 4.89 (Prata-Barbosa et al., 2020) for the level of care among patients with COVID-19. This previous study estimated the determinant factor of invasive mechanical ventilation in the PICU unit. The potential confounding factors were also considered, thus an alpha level (α) = (0.001) was utilized to lowered type I error and 80% power (1-ß) in a two-sided z-test (Cohen, 1988). The minimum sample size needed was 379 and considering an estimated 10% incompletion rate, a total of 423 participants were recruited for this study.

The study was conducted in six COVID-19 referral hospitals to ensure high variety in the pediatric level of care. The actual samples taken in this study using consecutive sampling were a secondary data of medical records with inclusion criteria: medical records of children aged ≤18 years; suspected (suspected) or confirmed (positive) COVID-19. As for the exclusion criteria, medical records suffering from data insufficiency were excluded from the study.

Participants were diagnosed with COVID-19 based on the WHO guidelines (World Health Organization, 2020). For simplicity's sake, the case definition used by the National Clinical Research Center for Child Health, Zhejiang University School of Medicine, whereby the case was classified as (1) suspected or probable case, and (2) confirmed case (Chen et al., 2020).

2.3 Measurement and data collection

A structured paper-based questionnaire was used to collect data from the medical records of pediatric patients in the six COVID-19 referral hospitals, Indonesia. Each questionnaire includes three section: (1) demographic data; (2) clinical manifestation; (3) existing diseases, and (4) level of care. The questionnaire was developed through a trial phase in three hospitals, to ensure the questionnaire was easy to understand by data collectors in each centre (Kouame, 2010). Before collecting data, nursing staffs from each centre were trained to use the questionaries. Existing data were tabulated by the research coordinator from each centre into a Google form sent to the principal investigator. Definition for major variables is described below.

2.3.1 COVID-19 status and level of care

COVID-19 status was determined by collecting samples using a real-time reverse-transcriptase polymerase-chain-reaction test (RTPCR) (Dong et al., 2020; Zimmermann & Curtis, 2020). To collect RTPCR sample, health care staffs were trained by the Ministry of Health Republic of Indonesia to ensure the quality of specimens meet a highly quality standard.

Ward level is usually associated with the level of patient illness severity (Garland et al., 2016). In terms of pediatric COVID-19 severity, it was classified as follows: asymptomatic infection, mild disease, moderate disease, severe disease, and critical illness (Buonsenso et al., 2020; The National Health and Health Commission of & China, 2020). The three types of ward level in line with the COVID-19 severity illness were used as follows: (a) isolation for clients with asymptomatic and mild disease, (b) intermediate level for moderate disease, and (c) intensive isolation for severe and critically ill cases (Carlotti et al., 2020; Mostafa et al., 2020).

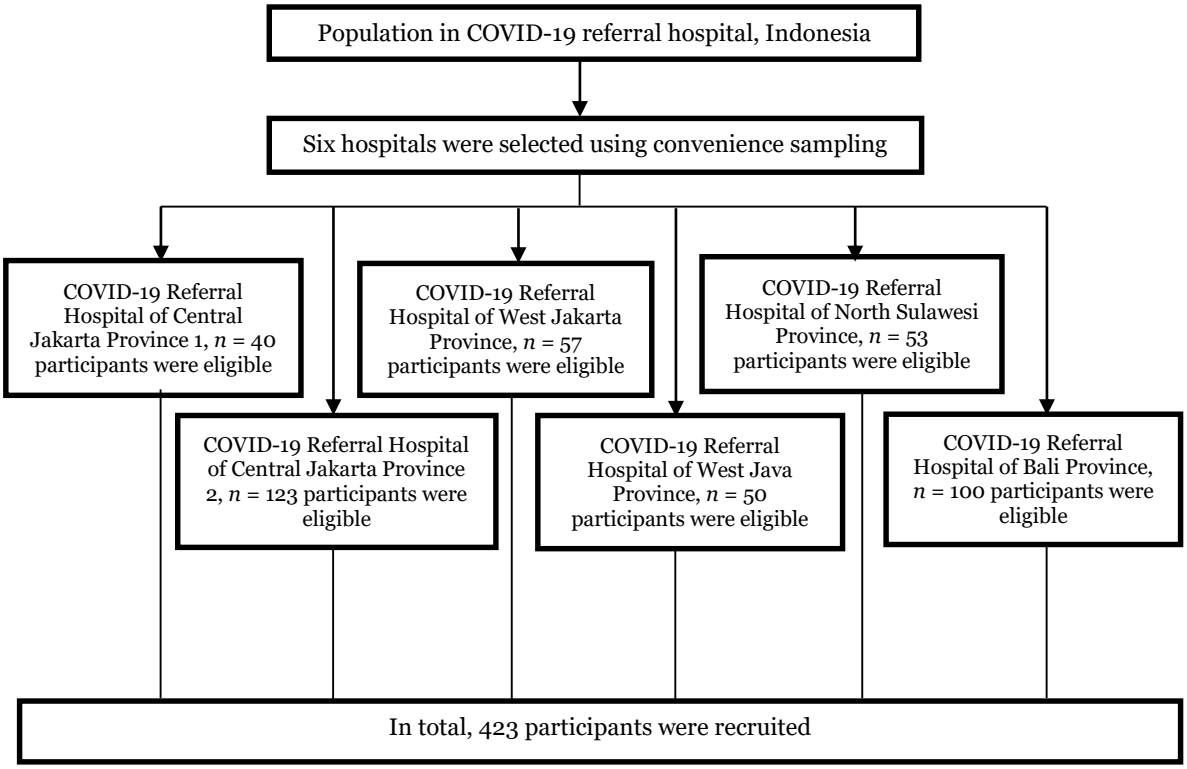

Figure 1. Flowchart of participants' recruitment

2.3.2 Demographic characteristics

The age classification was based on Ritchie (2020), divided into 0-9 years and 10-19 years. In addition, it is necessary to add subgroups to the classification of infants aged 0-1 year because the study found that severe COVID-19 cases in children aged ≤1 year are more likely admitted to ICU compared to the older (Bellino et al., 2020)

2.3.3 Presence of comorbid factors

Comorbidity is defined as the co-occurrence of more than one disorder in the same individual (Gulbech Ording & Toft Sørensen, 2013). Currently, there is no agreement on how to describe comorbidity in COVID-19; therefore, data on diabetes, hypertension, cardiovascular disease, Chronic Obstruction Pulmonary Disease (COPD), chronic liver or kidney disease, malignancy, immune-compromised state, obesity (body mass index (BMI) of 30 or higher, sickle cell disease, thalassemia, cerebrovascular disease, Co-existing infection (HIV, sepsis) from various sources were calculated (CDC, 2020; Sanyaolu et al., 2020; Zhou et al., 2020).

In this study, some patients have other respiratory system diseases beyond the list of comorbidities explained above. These diseases are classified as Non-Comorbid Respiratory Disease which includes Acute Tonsillopharyngitis, Acute respiratory distress syndrome (ARDS), Acute Respiratory Infection, Community-Acquired Pneumonia (CAP), pneumonia, bronchopneumonia, sinusitis, laryngomalacia, pharyngomalacia, mediastinal mass, acute adenolmphangitis, laryngeal granuloma, Healthcare-Associated Pneumonia (HCAP), subglottic stenosis, allergic rhinitis, respiratory failure, mastoiditis.

2.3.4 Clinical symptoms

Several studies have reported numerous clinical characteristics of pediatric patients with COVID-19 including: asymptomatic (Cai et al., 2020; Choi et al., 2020), fever (Cai et al., 2020; T. Chang et al., 2020), rhinorrhea (Hoang et al., 2020; Soltani et al., 2020), nasal congestion (Soltani et al., 2020), myalgia (Derespina et al., 2020; Hoang et al., 2020), fatigue (Hoang et al., 2020; Zimmermann & Curtis, s2020), sore throat (Soltani et al., 2020), shortness of breath, dyspnea (Derespina et al., 2020; Zimmermann & Curtis, 2020), abdominal pain (Cai et al., 2020; Choi et al., 2020), diarrhea (Hoang et al., 2020; Soltani et al., 2020), vomiting (Cai et al., 2020; Derespina et al., 2020), nausea, (Chang et al., 2020; Derespina et al., 2020), dizziness (Chang et al., 2020; Hong et al., 2020), poor feeding (Zimmermann & Curtis, 2020), and convulsion (Cai et al., 2020).

Work of breathing (WOB) has been defined as an effort to meet the body's ventilatory demand. In spontaneous breathing, it will represent by respiratory muscles work (Muñoz et al., 2019). Increased breathing definition commonly referred to as respiratory distress (Tulaimat et al., 2014). In this study, increased WOB was noted encompassed dyspnea, tachypnea, rhonchi, rales, grunting, chest wall retraction, nasal flaring, subcostal retraction, head bobbing, and paradox breathing (McCool D, 2012). One criterion above found in the patient, would be classified as an increase in WOB.

2.4 Data analysis

The X^2 test was used to analyze the distributions of participant characteristics. Continuous data for instances age has been categorized based on Our World in Data (Roser et al., 2020). The logistic regression analysis was utilized to examine the unadjusted (ORs) with the 95% confidence intervals (CIs) of the association between work of breathing, non-comorbid respiratory with the level of care among pediatric patients with COVID-19. The multivariate logistic regression test was performed to test the adjusted odds ratios (AORs) with the 95% confidence intervals (CIs) of the association between WOB, non-comorbid respiratory with level of care among pediatric with COVID-19 and controlling the covariates including no symptom, sore throat, seizures, abnormal blood gases, decreased oxygen saturation, shock, low nutritional fulfillment, and age.

Further, the synergistic correlation of WOB and non-comorbid respiratory was analyzed after creating four dummy variables for the following four (2x2) (Knol et al., 2007; Kurniasari et al., 2021). The adjusted odds ratio with the 95% confidence intervals (CIs) was applied in the association between the complication of non-comorbid respiratory diseases and high WOB with the level of care among pediatric with COVID-19. The covariates for cough, no symptoms, sore throat, seizures, abnormal blood gases, decreased oxygen saturation, shock, low nutritional fulfillment, and age were controlled, using p-value of <0.05, which was considered statistically significant. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) ver. 25.0 (Chicago, IL, USA).

2.5 Ethical considerations

The research protocol has been reviewed and approved by the Ethics Committee of the Faculty of Nursing, Universitas Indonesia (SK-266/UN2.F12.D1.2.1/ETIK 2020) and Faculty of Medicine Universitas Indonesia (No. KET-1000/UN2.F1/ETIK/PPM.00.02/2020) and conformed to the provisions of the Declaration of Helsinki.

3. Results

3.1 Sociodemographic characteristics and health status of participants

In total, 423 participants were included with age ranged from 0 to 18 years old. The participants were divided based on the level of care during hospitalization. Among 423 participants, most of them received the level of care in the ward. The majority of them (n=113) were >29 days ~ ≤12 months old, were boys (n=240). Most of the participants had no presence of infection disease (n=348) and a fever (n=264) (Table 1). Table 1 also provides bivariate analysis to select the potential variable that included in multivariate analysis.

Table 1. Sociodemographic characteristics and health status based on level of care (n=423)

Characteristics	Level of care			Total	*p*- value
	Ward (n=282) *n* (%)	Intermediate (n=89) *n* (%)	Critical (n=52) *n* (%)		
Age					
0 ~ ≤29 days old	4 (1.4)	0 (0)	5 (9.6)	9 (2.1)	0.01
>29 days ~ ≤12 months old	66 (23.4)	25 (28.1)	22 (42.3)	113 (26.7)	
>12 months ~ ≤3 years old	60 (21.3)	26 (29.2)	6 (11.5)	92 (21.7)	
>3 ~ ≤5 years old	30 (10.6)	8 (9)	4 (7.7)	42 (9.9)	
>5 ~ ≤12 years old	66 (23.4)	16 (18)	9 (17.3)	91 (21.5)	
>12 ~ ≤ 18 years old	56 (19.5)	14 (15.7)	6 (11.5)	76 (18)	
Gender					
Girl	121 (42.90)	40 (44.90)	22 (42.30)	183 (43.30)	0.93
Boy	161 (57.10)	49 (55.10)	30 (57.70)	240 (56.70)	
Covid status					0.31
Suspect	235 (83.3)	78 (87.6)	47 (90.4)	360 (85.1)	
Positive	47 (16.7)	11 (12.4)	5 (9.6)	63 (14.9)	
Presence of comorbidity					
No	115 (40.8)	19 (21.3)	10 (19.2)	144 (34)	0.001
Yes	167 (59.2)	70 (78.7)	42 (80.8)	279 (66)	
Low nutritional fulfillment					
No	255 (90.4)	66 (74.2)	44 (84.6)	365 (86.3)	0.000
Yes	27 (9.6)	23 (25.8)	8 (15.4)	58 (13.7)	
Congenital cardiac					0.09
No	277 (98.2)	84 (94.4)	49 (94.2)	410 (96.9)	
Yes	5 (1.8)	5 (5.6)	3 (5.8)	13 (3.1)	
COPD					
No	170 (60.3)	43 (48.3)	26 (50)	239 (56.5)	0.08
Yes	112 (39.7)	46 (51.7)	26 (50)	184 (43.5)	
Total non-comorbidity					
No	118 (41.88)	28 (31.5)	16 (30.8)	163 (38.3)	0.61
1 disease	112 (43.3)	42 (47.2)	19 (36.5)	183 (43.3)	
2 diseases	31 (11)	15 (16.9)	15 (28.8)	61 (14.4)	
3 diseases	11 (3.9)	4 (4.5)	2 (3.8)	17 (4)	
Infectious disease					
No	225 (79.8)	72 (80.9)	51 (98.1)	348 (82.3)	0.006
Yes	57 (20.2)	17 (19.1)	1 (1.9)	75 (17.7)	
Neurologic disease					
No	276 (98.2)	89 (100)	50 (96.2)	415 (98.3)	0.21
Yes	5 (1.8)	0 (0.0)	2 (3.8)	7 (1.7)	
Fever					
No	110 (39)	27 (30.3)	22 (42.3)	159 (37.6)	0.26
Yes	172 (61)	62 (69.7)	30 (57.7)	264 (62.4)	
Hematemesis, melena, petechia					
No	275 (97.5)	86 (96.6)	51 (98.1)	412 (97.4)	0.85
Yes	7 (2.5)	3 (3.4)	1 (1.9)	11 (2.6)	
Pain					
No	264 (93.6)	86 (96.6)	51 (98.1)	401 (94.6)	0.28
Yes	18 (6.4)	3 (3.4)	1 (1.9)	22 (5.2)	
Hemodynamic disorder					
No	250 (88.7)	81 (91)	50 (96.2)	381 (90.1)	0.23
Yes	32 (11.3)	8 (9)	2 (3.8)	42 (9.9)	
Shock					
No	267 (94.70)	83 (93.30)	36 (69.20)	386 (91.30)	<0.00
Yes	15 (5.30)	6 (6.70)	16 (30.80)	37 (8.70)	
Airway clearance					
No	161 (57.1)	39 (43.8)	25 (48.1)	225 (53.2)	0.07
Yes	121 (42.9)	50 (56.2)	27 (51.9)	198 (46.8)	

Table 1. Continued

Characteristics	Level of care			Total	*p*- value
	Ward (n=282) *n* (%)	Intermediate (n=89) *n* (%)	Critical (n=52) *n* (%)		
Cough					
No	139 (49.30)	43 (48.30)	36 (69.2)	218 (51.5)	0.02
Yes	143 (50.70)	46 (51.70)	16 (30.8)	205 (48.5)	
Work of breathing					
No	213 (75.5)	49 (55.1)	14 (26.9)	276 (65.2)	<0.00
Yes	69 (24.5)	40 (44.9)	38 (73.1)	147 (34.8)	
O_2 saturation reduction					
No	281 (99.6)	86 (96.6)	47 (90.4)	414 (97.9)	<0.00
Yes	1 (0.4)	3 (3.4)	5 (9.6)	9 (2.1)	
Abnormal blood gas analysis					
No	282 (100)	85 (95.5)	48 (92.3)	415 (98.1)	0.000
Yes	0 (0.00)	4 (4.5)	4 (7.7)	8 (1.9)	
Sore throat					
No	265 (94.00)	88 (98.90)	52 (100)	405 (95.70)	0.03
Yes	17 (6.00)	1 (1.10)	0 (0.00)	18 (4.30)	
Nasal congestion					
No	253 (89.7)	81 (91)	48 (92.3)	382 (90.3)	0.82
Yes	29 (10.3)	8 (9)	4 (7.7)	41 (9.7)	
Pharyngeal erythema					
No	279 (98.9)	88 (98.9)	52 (100)	419 (99.1)	0.75
Yes	3 (1.1)	1 (0.2)	0 (0)	4 (0.9)	
Diarrhea					
No	165 (58.5)	53 (59.6)	31 (59.6)	249 (58.9)	0.97
Yes	117 (41.5)	36 (40.4)	21 (40.4)	175 (41.1)	
Seizures					
No	267 (94.7)	85 (95.5)	40 (76.9)	392 (92.7)	0.000
Yes	15 (5.3)	4 (4.5)	12 (23.1)	31 (7.3)	
Non-comorbid respiratory					
No	173 (61.3)	42 (47.2)	25 (48.1)	240 (56.7)	0.02
Yes	109 (38.7)	47 (52.8)	27 (51.9)	183 (43.3)	

3.2 The association between the major determinant factors with the level of care

Results of the univariate analysis revealed that age, presence of comorbidity, nutritional fulfillment, infectious disease, shock, cough, work of breathing, O2 saturation reduction, abnormal blood gas analysis, sore throat, seizures and non-comorbid respiratory were significantly associated with the level of care ($p<0.05$) (Table 1). All the significant variables were included into the model using multiple linear regression models. The adjusted β coefficients and 95% CIs of the level of care are presented in Table 2. Participants with work of breathing were more likely to admit to intensive care compared to those who did not present work of breathing after adjustment the covariate and less likely to admit in the low level of care (inward). Additionally, the participants who had non-comorbid respiratory complications were more likely to receive intermediate as well as intensive care compared to those who did not have a non-comorbid respiratory complication. However, after adjusting the covariate, the association was no longer significant (Table 2).

3.3 Synergistic correlation of non-comorbid respiratory complication and work of breathing with the level of care

Table 3 shows the synergistic effect of non-comorbid respiratory complication and WOB among pediatric patients. Participants with the presence of both non-comorbid respiratory complication and WOB had synergistically significant to admit the intermediate and intensive level of care compared to those who did not present the symptoms. However, those who present the WOB without non-comorbid respiratory are more likely to admit the intensive care (Table 3).

Table 2. The major determinant factor of the level of careamong pediatric patients with COVID-19 (n=423)

Characteristic	Ward care		Intermediate care		Intensive care	
	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)
Work of Breathing						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	0.26 (0.17-0.40)** *p*=0.003	0.35 (0.22-0.57)** *p*=0.002	1.73 (1.07-2.79)* *p*=0.024	1.47 (0.87-2.49) *p*=0.545	6.52 (3.39-12.52)** *p*=0.003	9.82 (3.96-24.37)** *p*=0.004
Non-comorbid respiratory						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.75 (1.165-2.63)** *p*=0.005	0.76 (0.47-1.23) *p*=0.642	0.61 (0.38-0.98)* *p*=0.042	1.28 (0.76-2.16) *p*=0.705	0.67 (0.37-1.20) *p*=0.896	1.29 (0.61-2.71) *p*=0.353

Notes:
n: Total number of participants; %: Percent.
The OR was calculated with a binary logistic regression test.
The AOR was calculated by a multiple logistic regression test and adjusted for cough, no symptoms, sore throat, seizures, abnormal blood gases, decreased oxygen saturation, shock, low nutritional fulfillment age.
* Indicates a significant difference in values between groups at $p<0.05$.
** Indicates a significant difference in values between groups at $p<0.01$

Table 3. Synergistic correlation of non-comorbid respiratory complication and work of breathing on level of care among pediatric patient with COVID-19 (n=423)

Characteristic	Ward care		Intermediate care		Intensive care	
	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)
Without Non-comorbid respiratory and normal WOB	1.00	1.00	1.00	1.00	1.00	1.00
Non-comorbid respiratory and normal WOB	0.90 (0.49-1.65) *p*-value: .512	0.98 (0.51~1.91) *p*-value: .645	1. 03 (0.52-2.01) *p*-value: .802	0.92 (0.56~1.87) *p*-value: .921	1.31 (0.42-4.03) *p*-value: .465	1.22 (0.29~5.08) *p*-value: .704
Without Non-comorbid respiratory and increase WOB	0.27 (0.14-0.53) *p*-value: .345	0.38 (0.18-0.78) *p*-value: .832	0.95 (0.41-2.23) *p*-value: .032	0.74 (0.30-1.81) *p* value: .832	10.55 (4.28-25.97)* *p* value: .032	15.59 (5.11-47.00)** *p* value: .008
Non-comorbid respiratory and increase WOB	0.24 (0.14-0.41) *p*-value: .489	0.29 (0.16~0.54) *p*-value: .642	2.20 (1.25-3.85)* *p*-value: .045	1.92 (1.01~3.63)* *p*-value: .021	5.76 (2.54-13.08)* *p*-value: .022	9.32 (3.04~28.53)* *p*-value: .028

Notes:
n: Total number of participants; %: Percent.
The OR was calculated with a binary logistic regression test.
The AOR was calculated by a multiple logistic regression test and adjusted for cough, no symptoms, sore throat, seizures, abnormal blood gases, decreased oxygen saturation, shock, low nutritional fulfillment, and age.
* Indicates a significant difference in values between groups at $p<0.05$.
** Indicates a significant difference in values between groups at $p<0.01$.

4. Discussion

This study aimed to identify the synergistic association of non-comorbidities factors in the respiratory system and work of breathing (WOB) with the level of care of pediatric COVID-19 patient. This study found that both non-comorbid respiratory and increased WOB had a significant relationship with the level of care for pediatric patients with COVID-19. Data showed

pediatric patients with no non-comorbid respiratory and increased WOB had a 15.59 times higher risk of requiring PICU care level (p<0.01). These results indicate the highest risk of the overall results of this study. Meanwhile, pediatric patients who experienced both non-comorbid respiratory and increased WOB had a 5.76 times risk of requiring an intermediate level of care (p<0.05), and a 9.32 times higher risk of requiring a PICU level of care (p<0.05).

Patients with high-level WOB were more likely to admit intensive care after adjusting covariate. Based on this study, it was found that pediatric patients with increased WOB had 15.59 times higher risk of requiring intensive care levels. Where the increase in WOB is in line with the increase in the need for respiratory support. These results are in line with the study conducted by Shekerdemian et al. (2020) which found that 48 children with COVID-19 admitted to participating PICUs presented with respiratory symptoms (Shekerdemian et al., 2020). However, these results are in contrast to data from a study conducted by Swann et al., (2020), in which children admitted to critical care were more likely to have presented other clinical signs with diarrhea, conjunctivitis, and altered consciousness/confusion (Swann et al., 2020).

Pediatric patients with non-comorbid respiratory alone were not significantly related to the level of care. This is in line with a study conducted by Chen (2021) which examined respiratory tract infection which is one of the non-comorbid respiratory diseases in children during the COVID-19 pandemic. This study revealed that 73% of pediatric patients were 11% admitted to the ICU. Whereas adult patients who required ICU were likely higher than pediatric (19%) (Chen et al., 2021). Non-comorbid respiratory infections are common in COVID-19 patients in children. Of all research respondents, 56.7% had non-comorbid respiratory. Moreover, acute respiratory infections, ARDS, and pneumonia are among the most common manifestations of COVID-19 in children. This is in line with a study by Souza et al. (2020) which conducted research from a systematic review and metanalysis data from 38 studies (1124 cases) about the clinical manifestation of children with COVID-19 and found that 145 children (36.9%) were diagnosed with pneumonia and 43 children (10.9%) with upper airway infect were reported. Reduced lymphocyte count was reported in 12.9% of cases (Souza et al., 2020).

Pediatric COVID patients with increased WOB and without respiratory comorbidities showed significant correlate to the intensive care admission. In adults, the most common cause of ICU admission is an acute hypoxemic respiratory failure with or without severe hypercapnia due to acute respiratory distress syndrome (ARDS; 60-70%), followed by shock (30%), myocardial dysfunction (20-30%), and acute kidney injury (AKI; 10-30%) (Sun et al., 2020). Meanwhile, about 65-70% of children require treatment in the PICU, 40-60% of vasoactive drugs, and 15-25% require mechanical ventilation. (Gupta et al., 2021). Reports from China state that it takes an average of 8 days for dyspnea to develop and 9 days for pneumonia/pneumonitis to develop (Huang et al., 2020).

Other studies in line with this finding found that among the 66 symptomatic admitted children, 55% required respiratory support, and 17% required critical care. A total of 40 admitted patients had chest radiographs performed on admission, of which 25 (63%) had abnormal findings. Five out of 39 (13%) admitted patients tested with a respiratory pathogen panel had coinfection with an additional respiratory tract virus (Graff et al., 2021). However, a study conducted by Götzinger et al. (2020) found that significant risk factors for requiring ICU admission in multivariate analyses were being younger than one month, male sex, pre-existing medical conditions, and presence of lower respiratory tract infection signs or symptoms at presentation.

COVID-19 patients in children with non-comorbid respiratory and increased WOB synergistically significant with intermediate and intensive care. COVID-19 patients in children who experience both non-comorbid respiratory and increased WOB can occur in some patients with ARDS, pneumonia, or non-comorbid respiratory diseases that can interfere with the respiratory system and have manifestations of increased WOB. In a previous study comparing the main causes of adult and pediatric COVID-19 patients requiring intensive care, it was found that all the adults were admitted to intensive care due to ARDS (Girona-Alarcon et al., 2021).

Another study suggested that the main cause of adult COVID-19 patients requiring intensive care was multi-organ dysfunction syndrome (MODS) with ARDS (67%). Of the ICU admissions, 71% required mechanical ventilation, 35% vasoactive support, 17% renal replacement therapy, and 11% ECMO. Meanwhile, in pediatrics with COVID-19, the high-risk

pediatric population includes children with underlying conditions such as broncho-pulmonary hypoplasia, airway/lung anomalies, severe malnutrition, and congenital heart disease (Yang et al., 2020). This is in line with our findings. Moreover, our study provides more information regarding synergistic correlation of WOB and non-comorbid in the respiratory system.

5. Implications and limitations

Though non-comorbid respiratory has never been reported affecting the severity of pediatric patients with COVID-19, our study highlights its presence together with increased WOB, and this condition would likely increase the risk of the higher level of care. This study showed that nurses and doctors can perform more accurate triage of the patient's condition through a comprehensive assessment, one of which is through increased WOB. Accurate mapping of the level of care can also be useful in increasing the effectiveness and efficiency of patient care while in the hospital and impacting patient outcomes. Our existing data were taken from six COVID-19 referral in four provinces which may sufficiently represent COVID-19 cases in the Indonesian pediatric population. This study had several strengths, but it also had some limitations. Our study did not assess the biological marker of the diseases mechanism which is important to examine its relationship with the level of care among COVID-19 patients. Thus, further research involving the complex mechanism including biological aspect is highly recommended. Also, although our data represent the level of care among COVID-19 patients across Indonesia in a time, however, follow-up data in the longer time is also recommended to examine the outcome of patients during hospitalization.

6. Conclusion

In conclusion, it was found that both non-comorbid respiratory and increased WOB had a significant relationship with the level of care for pediatric patients with COVID-19. In particular, an increase in breathing is one of the most important clinical signs in increasing the level of care for pediatric patients with COVID-19. However, the existence of non-comorbid respiratory did not correlate significantly with a higher risk of level of care. These results suggest the crucial role of the pediatric nurse in detecting the increased work of breathing in pediatric COVID-19 admitted to the hospital.

Acknowledgment

The authors would like to thank Dr. Debie Dahlia, RN., for the support in conducting research, Dr. Astuti Yuni Nursasi, RN for the technical support, the study participants, and all Indonesian pediatric nurses who support the data collection process. This study was supported by the Faculty of Nursing Universitas Indonesia Grant No. NKB/UN.2.F12.D/HKP.01.03/2020

Author contribution

DE: Conceptualization, Methodology, Validation, Investigation, Resource, Data Curation, Supervision, Writing - Original Draft, and Writing - Review & Editing; MDK: Conceptualization, analyzed the data, data curation, and wrote the first draft of the manuscript; MHH: Conceptualization, analyzed the data, data curation, and Writing Original Draft; RIF: Investigation, Resource, Writing - Original Draft, and Writing - Review & Editing; YAR: Conceptualization, analyzed the data, data curation, and Writing Original Draft; YP: Conceptualization, methodology, and validation; NDP: Conceptualization, methodology, and validation; DW : Writing-Review and Editing; ARU: Conceptualization, and investigation; TAA: Conceptualization, and investigation; NC: Investigation; PLL: Investigation; AB: Investigation; PM: Investigation.

Conflict of interest

The authors declare no conflict of interest.

References

Apigo, M., Schechtman, J., Dhliwayo, N., Al Tameemi, M., & Gazmuri, R. J. (2020). Development of a work of breathing scale and monitoring need of intubation in COVID-19 pneumonia. *Critical Care, 24*(1), 4–6. https://doi.org/10.1186/s13054-020-03176-y

Bellino, S., Punzo, O., Rota, M. C., Del Manso, M., Urdiales, A. M., Andrianou, X., Fabiani, M., Boros, S., Vescio, F., Riccardo, F., Bella, A., Filia, A., Rezza, G., Villani, A., & Pezzotti, P. (2020). COVID-19 Disease severity risk factors for pediatric patients in Italy. *Pediatrics*, *146*(4), e2020009399. https://doi.org/10.1542/peds.2020-009399

Buonsenso, D., Parri, N., De Rose, C., Valentini, P., & Gemelli-pediatric COVID-19 team (2021). Toward a clinically based classification of disease severity for paediatric COVID-19. *The Lancet. Infectious diseases, 21*(1), 22. https://doi.org/10.1016/S1473-3099(20)30396-0

Cai, X., Ma, Y., Li, S., Chen, Y., Rong, Z., & Li, W. (2020). Clinical characteristics of 5 COVID-19 cases with non-respiratory symptoms as the first manifestation in children. *Frontiers in Pediatrics*, *8*, 258. https://doi.org/10.3389/fped.2020.00258

Carlotti, P., Carvalho, A. P. de, Carvalho, D., Brunow, W., Johnston, Rodriguez, C., Souza, I., Delgado, & Figueiredo, A. (2020). COVID-19 diagnostic and management protocol for pediatric patients. *Clinics*, *75*, 1–5. https://doi.org/10.6061/CLINICS/2020/E1894

CDC. (2020). *Coronavirus disease. People with certain medical conditions.* https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

Chang, T. H., Wu, J. L., & Chang, L. Y. (2020). Clinical characteristics and diagnostic challenges of pediatric COVID-19: A systematic review and meta-analysis. *Journal of the Formosan Medical Association, 119*(5), 982–989. https://doi.org/10.1016/j.jfma.2020.04.007

Chen, A. P. L., Chuang, C., Huang, Y. C., Wu, P. F., Huang, S. F., Cheng, N. C., Lin, Y. T., Chen, S. J., Huang, L. J., Lee, C. L., Chen, H. P., Chan, Y. J., & Wang, F. Der. (2021). The epidemiology and etiologies of respiratory tract infection in Northern Taiwan during the early phase of coronavirus disease 2019 (COVID-19) outbreak. *Journal of Microbiology, Immunology and Infection, 54*(5), 801–807. https://doi.org/10.1016/j.jmii.2021.05.006

Chen, Z. M., Fu, J. F., Shu, Q., Chen, Y. H., Hua, C. Z., Li, F. B., Lin, R., Tang, L. F., Wang, T. L., Wang, W., Wang, Y. S., Xu, W. Z., Yang, Z. H., Ye, S., Yuan, T. M., Zhang, C. M., & Zhang, Y. Y. (2020). Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. *World Journal of Pediatrics, 16*(3), 240–246. https://doi.org/10.1007/s12519-020-00345-5

Choi, S. H., Kim, H. W., Kang, J. M., Kim, D. H., & Cho, E. Y. (2020). Epidemiology and clinical features of coronavirus disease 2019 in children. *Clinical and Experimental Pediatrics, 63*(4), 125–132. https://doi.org/10.3345/cep.2020.00535

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Lawrence Erlbaum Associates.

de Souza, T. H., Nadal, J. A., Nogueira, R. J. N., Pereira, R. M., & Brandão, M. B. (2020). Clinical manifestations of children with COVID-19: A systematic review. *Pediatric Pulmonology, 55*(8), 1892–1899. https://doi.org/10.1002/ppul.24885

Derespina, K. R., Kaushik, S., Plichta, A., Conway, E. E., Jr, Bercow, A., Choi, J., Eisenberg, R., Gillen, J., Sen, A. I., Hennigan, C. M., Zerihun, L. M., Doymaz, S., Keenaghan, M. A., Jarrin, S., Oulds, F., Gupta, M., Pierre, L., Grageda, M., Ushay, H. M., Nadkarni, V. M., … Medar, S. S. (2020). Clinical Manifestations and Outcomes of Critically Ill Children and Adolescents with Coronavirus Disease 2019 in New York City. *The Journal of pediatrics, 226*, 55–63. https://doi.org/10.1016/j.jpeds.2020.07.039

Dong, Y., Mo, X., Hu, Y., Qi, X., Jiang, F., & Jiang, Z. (2020). Epidemiology of COVID-19 among children in China. *Pediatrics, 145*(6), 1-10. https://doi.org/https://doi.org/10.1542/peds.2020-0702

El Maniani, M., Rechchach, M., El Mahfoudi, A., El Moudane, M., & Sabbar, A. (2016). A calorimetric investigation of the liquid bi-ni alloys. *Journal of Materials and Environmental Science, 7*(10), 3759–3766. https://doi.org/10.1021/j150541a003

Garland, A., Ashton-Cleary, D., & Sinclair, R. (2016). Inpatient illness severity surveys provide essential data for planning capacity and managing patient flow in the acute hospital setting. *Journal of the Intensive Care Society, 17*(3), 196–201. https://doi.org/10.1177/1751143716628884

Girona-Alarcon, M., Bobillo-Perez, S., Sole-Ribalta, A., Hernandez, L., Guitart, C., Suarez, R., Balaguer, M., Cambra, F. J., & Jordan, I. (2021). The different manifestations of COVID-19 in adults and children: A cohort study in an intensive care unit. *BMC Infectious Diseases, 21*(1), 4–11. https://doi.org/10.1186/s12879-021-05786-5

Götzinger, F., Santiago-García, B., Noguera-Julián, A., Lanaspa, M., Lancella, L., Calò Carducci, F. I., Gabrovska, N., Velizarova, S., Prunk, P., Osterman, V., Krivec, U., Lo Vecchio, A., Shingadia, D., Soriano-Arandes, A., Melendo, S., Lanari, M., Pierantoni, L., Wagner, N., L'Huillier, A. G., … Riordan, A. (2020). COVID-19 in children and adolescents in Europe: A multinational, multicentre cohort study. *The Lancet Child and Adolescent Health, 4*(9), 653–661. https://doi.org/10.1016/S2352-4642(20)30177-2

Graff, K., Smith, C., Silveira, L., Jung, S., Curran-Hays, S., Jarjour, J., Carpenter, L., Pickard, K., Mattiucci, M., Fresia, J., McFarland, E. J., Dominguez, S. R., & Abuogi, L. (2021). Risk factors for severe COVID-19 in children. *Pediatric Infectious Disease Journal, 40*(4), E137–E145. https://doi.org/10.1097/INF.0000000000003043

Gulbech Ording, A., & Toft Sørensen, H. (2013). Concepts of comorbidities, multiple morbidities, complications, and their clinical epidemiologic analogs. *Clinical Epidemiology, 5*(1), 199–203. https://doi.org/10.2147/CLEP.S45305

Gupta, S., Angurana, S. K., & Kumar, V. (2021). Respiratory care in children with COVID-19. *Journal of Pediatric Intensive Care, 10*(4), 1-8. https://doi.org/10.1055/s-0041-1723036

Hoang, Ansel & Chorath, Kevin & Moreira, Axel & Evans, Mary & Burmeister-Morton, Finn & Burmeister Mccracken, Fiona & Naqvi, Rija & Petershack, Matthew & Moreira, Alvaro. (2020). COVID-19 in 7780 pediatric patients: A systematic review. *E-Clinical Medicine, 24,* 100433. https://doi.org/10.1016/j.eclinm.2020.100433

Hong, H., Wang, Y., Chung, H., & Chen, C. (2020). Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children. *Pediatrics and Neonatology, 61*(2), 131–132. https://doi.org/10.1016/j.pedneo.2020.03.001

Hopman, J., Allegranzi, B., & Mehtar, S. (2020). Managing COVID-19 in low- and middle-income countries. *JAMA, 323*(16), 1549–1550.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet, 395*(10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

Jain, S., Sen, S., Lakshmivenkateshiah, S., Bobhate, P., Venkatesh, S., Udani, S., Shobhavat, L., Andankar, P., Karande, T., & Kulkarni, S. (2020). Multisystem inflammatory syndrome in children with COVID-19 in Mumbai, India. *Indian Pediatrics, 57*, 1015–1019. https://doi.org/10.1016/j.ajem.2021.05.076

Knol, M. J., Tweel, I. Van Der, Grobbee, D. E., & Numans, M. E. (2007). Estimating interaction on an additive scale between continuous determinants in a logistic regression model. *International Journal of Epidemiology, 36,* 1111–1118. https://doi.org/10.1093/ije/dym157

Kouame, J. B. (2010). Using readability tests to improve the accuracy of evaluation documents intended for low-literate participants. *Journal of MultiDisciplinary Evaluation, 6*(14), 132–139. http://journals.sfu.ca/jmde/index.php/jmde_1/article/viewFile/280/283

Kurniasari, M. D., Karwur, F. F., Rayanti, R. E., Dharmana, E., Rias, Y. A., Chou, K. R., & Tsai, H.-T. (2021). Second-hand smoke and its synergistic effect with a body-mass index of >24.9 kg/m2 increase the risk of gout arthritis in Indonesia. *International Journal of Environmental Research and Public Health, 18*(8), 4324. https://doi.org/10.3390/ijerph18084324

Lee, J. H., Rehder, K. J., Williford, L., Cheifetz, I. M., & Turner, D. A. (2013). Use of high flow nasal cannula in critically ill infants, children, and adults: A critical review of the literature. *Intensive Care Medicine, 39*(2), 247–257. https://doi.org/10.1007/s00134-012-2743-5

Marin, B.G., Aghagoli, G., Lavine, K., Yang, L., Siff, E. J., Chiang, S. S., Salazar-Mather, T. P., Dumenco, L., Savaria, M. C., Aung, S. N., Flanigan, T., & Michelow, I. C. (2021). Predictors of COVID-19 severity: A literature review. *Reviews in Medical Virology, 31*(1), 1–10. https://doi.org/10.1002/rmv.2146

Mostafa, A. S., Abdalbaky, A., Fouda, E. M., Shaaban, H. H., Elnady, H. G., Hassab-Allah, M., Rashad, M. M., El Attar, M. M., Alfishawy, M., Hussien, S. M., Hamed, T., Hamed, D. H., & Sarhan, D. T. (2020). Practical approach to COVID-19: An Egyptian pediatric consensus. *Egyptian Pediatric Association Gazette, 68*(1), 1-8. https://doi.org/10.1186/s43054-020-00037-9

Muñoz, I. C., Hernández, A. M., & Mañanas, M. Á. (2019). Estimation of work of breathing from respiratory muscle activity in spontaneous ventilation: A pilot study. *Applied Sciences (Switzerland), 9*(10), 1-18. https://doi.org/10.3390/app9102007

Pathak, E. B., Salemi, J. L., Sobers, N., Menard, J., & Hambleton, I. R. (2020). Covid-19 in children in the united states: Intensive care admissions, estimated total infected, and projected numbers of severe pediatric cases in 2020. *Journal of Public Health Management and Practice, 26*(4), 325–333. https://doi.org/10.1097/PHH.0000000000001190

Prata-Barbosa, A., Lima-Setta, F., Santos, G. R. dos, Lanziotti, V. S., de Castro, R. E. V., de Souza, D. C., Raymundo, C. E., de Oliveira, F. R. C., de Lima, L. F. P., Tonial, C. T., Colleti, J., Bellinat, A. P. N., Lorenzo, V. B., Zeitel, R. de S., Pulcheri, L., Costa, F. C. M. da, La Torre, F. P. F., Figueiredo, E. A. das N., Silva, T. P. da, … de Magalhães-Barbosa, M. C. (2020). Pediatric patients with COVID-19 admitted to intensive care units in Brazil: a prospective multicenter study. *Jornal de Pediatria, 96*(5), 582–592. https://doi.org/10.1016/j.jped.2020.07.002

Roser, M., Ritchie, H., Ortiz-Ospina, E., & Hasell, J. (2020). *Coronavirus (COVID-19) cases - statistics and research - our world in data*. *In our world in data* (Vol. 2020, pp. 1–42).

Sankar, J., Dhochak, N. S., Kabra, S. ., & Lodha, R. (2020). COVID-19 in children: Clinical approach and management-correspondence. *Indian Journal of Pediatrics, 87*(11), 970–972. https://doi.org/10.1007/s12098-020-03374-0

Sanyaolu, A., Okorie, C., Marinkovic, A., Patidar, R., Younis, K., Desai, P., Hosein, Z., Padda, I., Mangat, J., & Altaf, M. (2020). Comorbidity and its impact on patients with COVID-19. *Comprehensive Clinical Medicine, 2*(8), 1069–1076. https://doi.org/10.1007/s42399-020-00363-4

Shekerdemian, L. S., Mahmood, N. R., Wolfe, K. K., Riggs, B. J., Ross, C. E., McKiernan, C. A., Heidemann, S. M., Kleinman, L. C., Sen, A. I., Hall, M. W., Priestley, M. A., McGuire, J. K., Boukas, K., Sharron, M. P., & Burns, J. P. (2020). Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. *JAMA Pediatrics, 174*(9), 868–873. https://doi.org/10.1001/jamapediatrics.2020.1948

Soltani, J., Sedighi, I., Shalchi, Z., Sami, G., Moradveisi, B., & Nahidi, S. (2020). Pediatric coronavirus disease 2019 (COVID-19): An insight from west of Iran. *Northern Clinics of Istanbul, 7*(3), 284–291. https://doi.org/10.14744/nci.2020.90277

Sun, M., Xu, G., Yang, Y., Tao, Y., Pian-Smith, M., Madhavan, V., Xie, Z., & Zhang, J. (2020). Evidence of mother-to-newborn infection with COVID-19. *British Journal of Anaesthesia, 125*(2), e245–e247. https://doi.org/10.1016/j.bja.2020.04.066

Swann, O. V., Holden, K. A., Turtle, L., Pollock, L., Fairfield, C. J., Drake, T. M., Seth, S., Egan, C., Hardwick, H. E., Halpin, S., Girvan, M., Donohue, C., Pritchard, M., Patel, L. B., Ladhani, S., Sigfrid, L., Sinha, I. P., Olliaro, P. L., Nguyen-Van-Tam, J. S., … Semple, M. G. (2020). Clinical characteristics of children and young people admitted to hospital with COVID-19 in United Kingdom: Prospective multicentre observational cohort study. *The BMJ, 370*(M3249), 1-14. https://doi.org/10.1136/bmj.m3249

Talarico, V., Nicoletti, A., Sabetta, L., Minchella, P., & Raiola, G. (2020). Preliminary epidemiological analysis on children and adolescents with novel coronavirus disease (2019-ncov) in acentral area of Calabria region. *Acta Biomedica, 91*(2), 232–233. https://doi.org/10.23750/abm.v91i2.9550

Task Force for the Acceleration of Handling COVID-19. (2020). *COVID-19 infographic* (26 October 2020). https://covid19.go.id/id/peta-sebaran

The National Health and Health Commission of, & China, P. R. of. (2020). *Diagnosis and treatment guidelines for 2019 novel coronavirus pneumonia* (draft version 5). http://www.nhc.gov.cn/yzygj/s76%0A53p/202002/3b09b894ac9b4204a79db5b89%0A12d4440.shtml

Tsankov, B. K., Allaire, J. M., Irvine, M. A., Lopez, A. A., Sauvé, L. J., Vallance, B. A., & Jacobson, K. (2021). Severe COVID-19 infection and pediatric comorbidities: A systematic review and meta-analysis. *International Journal of Infectious Diseases, 103*, 246–256. https://doi.org/10.1016/j.ijid.2020.11.163

Tulaimat, A., Gueret, R. M., Wisniewski, M. F., & Samuel, J. (2014). Association between rating of respiratory distress and vital signs, severity of Illness, intubation, and mortality in acutely 111 subjects. *Respiratory Care, 59*(9), 1338–1344. https://doi.org/10.4187/respcare.02650

World Health Organization (WHO). (2020a). *Public health surveillance for COVID-19*. Interim guidance. 7 August 2020 (Issue August, pp. 1–10). https://doi.org/10.1007/978-1-59745-326-4_13

World Health Organization (WHO). (2020b). *WHO Coronavirus Disease (COVID-19) dashboard*. https://covid19.who.int/

Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., Wu, Y., Zhang, L., Yu, Z., Fang, M., Yu, T., Wang, Y., Pan, S., Zou, X., Yuan, S., & Shang, Y. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. *The Lancet Respiratory Medicine, 8*(5), 475–481. https://doi.org/10.1016/S2213-2600(20)30079-5

Zhang, N., Deng, Y., Li, W., Liu, J., Li, H., Liu, E., & Zheng, X. (2020). Analysis and suggestions for the preview and triage screening of children with suspected COVID-19 outside the epidemic area of Hubei Province. *Translational Pediatrics, 9*(2), 126–132. https://doi.org/10.21037/tp.2020.03.08

Zhou, Y., He, Y., Yang, H., Yu, H., Wang, T., Chen, Z., Id, R. Y., & Liang, Z. (2020). Development and validation a nomogram for predicting the risk of severe COVID-19: A multi-center study in Sichuan, China. *PloS One, 863*, 1–14. https://doi.org/10.1371/journal.pone.0233328

Zimmermann, P., & Curtis, N. (2020). Coronavirus infections in children including COVID-19. An overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. *The Pediatric Infectious Disease Journal, 39*(5), 355–368. https://doi.org/10.1097/INF.0000000000002660