Aswan University Medical Journal, volume 3 / No.2/ December 2023 (157-168) Online ISSN: **2735-3117**

ORIGINAL ARTICLE

The predictive value of laboratory biomarkers in defining COVID-19 severity.

Ebtsam Abd Kareem, Hassan Abdelrazzak*, Shazly Ahmed

Department of Chest Diseases, Faculty of Medicine, Aswan University

ABSTRACT

Keywords: COVID-19- Ferritin- NLR- SARSCoV-2- D- dimer

***Corresponding author:**

Hassan Abdelrazzak Mohamed

Email: ahsn6607@gmail.com

Mobile: 01144636078

Background: The COVID-19 outbreak poses a serious hazard to human health. We aimed to correlate between the severity of clinical presentation and laboratory results. **Material and methods:** All COVID-19 positive cases that were admitted to Aswan University Hospitals were prospectively collected and classified into either severe or non-severe COVID-19 cases . All the demographic, clinical characteristics, HRCT results and the basic laboratory biomarkers at time of admission were collected including [WBC, absolute neutrophil count, absolute lymphocyte count, CRP, D-dimer, NLR and ferritin]. **Results:** The severe case group (n=71) had considerably higher mean levels of WBCs, absolute neutrophils, absolute lymphocytes, CRP, D-dimer, NLR and ferritin than the non-severe case group (n=137) (p <0.0001 considerably). However, CRP and serum ferritin are considered the independent risk factors for COVID-19 severity (p= 0.009 & 0.033 respectively). Moreover, at a cut-off point (5.73), the sensitivity of NLR ratio to predict the case severity was low (43%) but higher specificity (93.2%). Similarly, at a cut-off point of (1.56), the sensitivity and specificity of D-dimer were (60.6% and 78.1% respectively). **Conclusions:** Increased NLR (> 5.73), and D-dimer level (> 1.56 mg\L), CRP (> 86.5 mg/L and serum Ferritin >256.5 at time of admission can be simple available prognosticators for severe COVID-19 contagion.

INTRODUCTION

The COVID-19 outbreak poses a serious risk to human well-being **(WHO, 2020).** The clinical presentations of COVID-19 vary from asymptomatic cases to mild, moderate, and severe forms rapidly progressing to hospital admission, septicemia, or even decease in 4–15% of cases **(Wang et al, 2020).** So, it is critical to classify the COVID-19 illness and its severity as early as possible.

Along with the disease course, COVID-19 cases may be roughly classified into 2 clusters; [asymptomatic or mild cases that usually recover and severe cases that proceed to multi-organ failure, principally respiratory failure, necessitating admission to the intensive care unit (ICU). **[(Wang et al, 2020) (Guan et al, 2020)].**

Numerous laboratory bio-markers are used primarily for COVID-19 contagion assessment or diagnosis; however, their accuracy to evaluate contagion severity and prognosis along with the levels at which they are alarming results are still to be appraised **(Knight et al, 2020).**

Currently, the usual technique for proving COVID-19 is the real-time polymerase chain reaction (RT-PCR). Other laboratory investigations include leucopenia, lymphopenia, low platelet count, high serum CRP, and ferritin **[(Wu et al, 2020 a) (Habibzadeh et al, 2020)].**

We aimed to correlate between the severity of clinical presentation and hematological [CBC including: lymphocyte count, neutrophil to lymphocyte ratio] and immunological (CRP, serum ferritin, D-Dimer) laboratory results of COVID-19 cases and estimate the precise cut-off value for those indicators.

PATIENTS AND METHODS

Design:

it is a prospective observational study

Settings:

Inclusion criteria: patients with PCR positive for COVID-19 who were admitted to COVID-19 isolation department and COVID-19 isolation ICU in Aswan University Hospital during the period from January 2021 to January 2022.

Exclusion criteria: patients with PCR positive for COVID-19 less than 18 years old, patients who had laboratory and radiological findings suspicious of COVID-19 but negative PCR results and pregnant females.)

Ethical approval

The study protocol was approved by the ethical committee of the Faculty of Medicine, Aswan University (IRB no: 521/3/21).

All eligible patients had subjected to:

1- **Demographic and clinical characteristics**: comprising age, gender, site of admission, presenting complains, the clinical severity of the cases and comorbid disorders. We classified the Clinical severity of COVID-19 illness according to **WHO, (2021)** into: [Asymptomatic or pre-symptomatic contagion, mild, moderate, severe, and critical illness].

2- **The outcomes measures of the patients** (ICU admittance, decease, recovery, prerequisite for invasive or non-invasive mechanical ventilation or referral).

3- **Laboratory data** comprising [complete blood count (Sysmex XN-1000-Japan), C-reactive protein (CRP) (Beckman Coulter AU480), D dimer, serum ferritin (Vidas–Biomerieux-France)], & kidney functions.

4- **High resolution CT chest**:
HRCT was accomplished on all the study cohort using standard protocol through Toshiba 160- slice CT scanner, aquilion TM prime, Japan. Non-contrast scans *were captured at*

full inspiration from the apex to the base of the lung in supine patients. the following criteria were emphasized: Ground-glass opacities (GGO), and consolidation. For the radiological classification of COVID-19 we used the CORAD score as shown in Figure (2).

CO-RADS* Level of suspicion COVID-19 infection		
		CT findings
CO-RADS 1	No	normal or non-infectious abnormalities
CO-RADS 2	Low	abnormalities consistent with infections other than COVID-19
CO-RADS 3	Indeterminate	unclear whether COVID-19 is present
CO-RADS 4	High	abnormalities suspicious for COVID-19
CO-RADS 5	Very high	typical COVID-19
CO-RADS 6	PCR +	

Figure (1): COVID-19 CO-RADS classification (WHO, 2020),

This study included 208 confirmed COVID - 19 cases with positive PCR. **Based on this the clinical severity of the cases as illustrated in Figure (2) (WHO, 2020)**, The study cohort was divided into:

- **Severe cases group**: including severe and critical case COVID-19 (n= 71).
- **Non severe cases group:** including the asymptomatic, mild and moderate cases (n=137).

	Mild	Moderate	Severe	Critical
Adult	• Symptomatic • Meets case definition • No evidence of pneumonia or hypoxia	• Clinical signs of pneumonia (febrile, cough, dyspnoea, tachypnoea) • Saturations ≥ 90% in air	Signs of pneumonia and any of: • respiratory rate > 30 breaths/min • severe respiratory distress • Saturations < 90% in air	• ARDS • Sepsis • Septic shock
Child		• Clinical signs of non-severe pneumonia (cough or dyspnoea + tachypnoea with or without recessions)	Signs of pneumonia and any of: • Central cyanosis • Saturations < 90% in air • Severe respiratory distress (e.g. grunting, very severe recessions) • Any red flag: inability to take oral intake/breastfeed, lethargy, loss of consciousness, seizures • Tachypnoea (breaths/min): < 2 months: ≥ 60 2–11 months: ≥ 50 1–5 years: ≥ 40	

Figure (2): The clinical severity of COVID-19 (WHO, 2020),

Statistical analysis

The data was analyzed by SPSS (statistical package for social science) version 26.0 on IBM compatible computer (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered significant.

RESULTS

This study included 208 confirmed COVID-19 cases with positive PCR, presenting at the Quarantine section in Aswan University Hospital.

Table (1): Socio-demographic and baseline clinical characteristics of the studied cohort (N=208).

		N=208
Age (Y)	Mean ± SD	58.4 ± 17.5
Gender N (%)	Male Female	96 (46.2 %) 112 (53.8 %)
DM N (%)		51 (24.5 %)
Hypertension N (%)		145 (69.7 %)
Chronic kidney disease N (%)		9 (4.3 %)
Chronic lung disease N (%)		16 (7.7 %)
Chronic cardiac disease N (%)		77 (37 %)
CVD N (%)		13 (6.2 %)
Smoking status N (%)	Non-smoker Mild smoker Moderate smoker Heavy smoker	144 (69.2 %) 8 (3.8%) 11 (5.3 %) 45 (21.6 %)
Symptoms		
Fever N (%)		155 (74.5 %)
Dyspnea N (%)		146 (70.2 %)
Cough N (%)		124 (59.6 %)
Rhinorrhea N (%)		38 (18.3 %)
Diarrhea N (%)		40 (19.2 %)
Headache N (%)		82 (39.4 %)
Fatigue N (%)		81 (38.9 %)
Duration of symptoms (days)	Mean ± SD	4.4 ± 2.2

Management	Invasive ventilation Non-invasive ventilation O_2 therapy	23 (11.1 %) 101 (48.6 %) 84 (40.4 %)
Clinical Severity	Severe Non- severe	71 (34.1 %) 137 (65.9 %)
Outcome	Death Recovery	82 (39.4 %) 126 (60.6 %)

Socio-demographic and baseline clinical characteristics of the studied cohort were illustrated in Table (1).

Table (2): Relation between both Laboratory and radiological data and the clinical cases severity of the study population (N=208)

		COVID-19 Clinical Severity		
		Severe (n=71)	**Non- severe (n= 137)**	P value
Hemoglobin (g/dl)	Mean ± SD	11.2 ± 2.2	12.9 ± 1.9	<0.0001
WBCs (10^3/ul)	Mean ± SD	14.0 ± 6.4	10.2 ± 5.4	<0.0001
Absolute neutrophils (10^3/ul)	Mean ± SD	69.6 ± 27.5	46.9 ± 37.4	0.001
Absolute lymphocytes (10^3/ul)	Mean ± SD	7.7 ± 4.5	7.3 ± 8.6	0.032
NLR	Mean ± SD	13.2 ± 0.3	4.5 ± 0.5	<0.0001
CRP (mg/dl)	Mean ± SD	75.6 ± 49.7	50.8 ± 29.9	<0.0001
D-dimer (mg/l)	Mean ± SD	4.57 ± 8.371.9	1.81 ± 2.5	<0.0001
Serum ferritin (ng/ml)	Mean ± SD	538.4 ± 338.2	404.6 ± 336.3	<0.0001
Radiological data				
GGO		71 (100 %) 0	132 (96.4 %) 5 (3.6 %)	0.103
Consolidation		23 (32.4 %) 48 (67.6%)	27 (19.7 %) 110 (80.3 %)	0.042

Table (2) disclosed that the severe cases had considerably higher mean levels of WBCs, absolute neutrophils, absolute lymphocytes, CRP, D-dimer, NLR, and ferritin than the non-severe cases (p<0.0001 considerably).

Table (3): Binary logistic regression analysis for independent risk elements for the case severity.

	S.E.	P value	ß	95% CI	
				Lower	Upper
WBCs	0.033	0.115	1.053	0.987	1.124
Absolute neutrophils	0.015	0.078	1.015	0.998	1.031
Absolute lymphocytes	0.038	0.165	0.948	0.879	1.022
NLR	0.396	0.491	1.313	0.605	2.852
CRP	0.005	0.009	1.013	1.003	1.023
D-dimer	00	0.082	1.000	1.000	1.000
Serum ferritin	0.001	0.033	1.001	1.000	1.002
Consolidation	0.391	0.063	0.484	0.225	1.040

SE = standard error, CI = confidence interval

CRP and serum ferritin are considered independent risk factors for COVID-19 severity (p= 0.009 & 0.033 respectively) as illustrated in Table (3).

Table (4): Accuracy of the hematological markers to predict the severity of COVID-19 among the studied cases (N= 208)

	WBCs	Absolute neutrophils	Absolute lymphocytes	NLR
AUC	0.687	0.644	0.591	0.333
SE	0.040	0.040	0.039	0.039
P value	<0.0001	0.001	0.032	<0.0001
95% CI	0.609 – 0.766	0.567 – 0.722	0.514 – 0.668	0.256 – 0.410
Cut-off point	13.7	74.5	1.73	5.73
Sensitivity	52.1%	76.1%	90.1%	43%
Specificity	79.6%	55.5%	27.0%	93.2%

AUC: area under curve, SE = standard error, CI = confidence interval

Table (4) displayed the diagnostic accuracy of the hematological markers to predict the severity of COVID-19 among the studied cases where at a cut-off point (13.710^3/ul), the sensitivity and specificity of WBCs to forecast the clinical severity of COVID-19 were (52.1% and 79.6% respectively). Similarly, at a cut-off point of (74.510^3/ul), the sensitivity and specificity of absolute neutrophil count to predict severity were (76.1% and 55.5% respectively). However, at a cut-off point ($1.73\ 10^3$/ul), the sensitivity of absolute lymphocyte counts to predict severity was (90.1%) but low specificity (27.0%). Moreover, at a cut-off point (5.73), the sensitivity of the NLR ratio to predict the case severity was low (43%) but higher specificity (93.2%).

Table (5): Accuracy of the immunological markers to predict the severity of COVID-19 among the studied cases (N= 208)

	CRP	**D-dimer**	**Serum ferritin**
AUC	0.668	0.732	0.656
SE	0.040	0.036	0.038
P value	<0.0001	<0.0001	<0.0001
95% CI	0.590 – 0.747	0.662 – 0.803	0.581 – 0.731
Cut-off point	86.5	1.56	256.5
Sensitivity	39.4%	60.6%	90.1%
Specificity	86.9%	78.1%	38.0%

AUC: area under curve, SE = standard error, CI = confidence interval

Table (5) disclosed the diagnostic accuracy of the immunological markers to forecast the severity of COVID-19 among the studied cases where at a cut-off point of (86.5 mg/l), the sensitivity of CRP to predict severity is (39.4%) but high specificity (86.9%). Similarly, at a cut-off point of (1.56 mg/l), the sensitivity and specificity of D-dimer to forecast severity were (60.6% and 78.1% respectively). Furthermore, at a cut-off point of (256.5 ng/ml), the sensitivity of serum ferritin to predict severity was high (90.1%) but low specificity (38.0%).

DISCUSSION

The COVID-19 outbreak poses a serious risk to human well-being **(WHO, 2020).** So, it is crucial to identify the COVID-19 illness and its severity as early as possible. This study included 208 confirmed COVID-19 cases with positive PCR, [of them 71 cases (34.1 %) were admitted to ICU presenting at the Quarantine section in Aswan University Hospital during the period from January 2021 to January 2022.

As anticipated, the most common symptom among the studied cohort was fever (74.5%), followed by 70.2% dyspnea, while 59.6% had a cough which is in harmony, with numerous studies [**(Chen et al., 2020) (Guan et al., 2020) (Wu et al., 2020) b].** A recent systematic review summarized that fever and cough were the most common complaints in COVID-19 cases under the age of 20 years with other complaints infrequent **(Viner et al., 2021).**

Complete blood count is one of the essential widely available investigations for COVID-19 infection diagnosis and severity assessment **(Cavezzi et al., 2020). In this study**, we found

that severe cases had considerably higher levels of WBCs, absolute neutrophils, absolute lymphocyte count, & NLR ($p<0.0001$ considerably).

Lymphopenia & leukocytosis were also proposed to be risk elements for severe COVID-19 contagion and worse outcomes **[(Yamada et al., 2020) (Huang et al., 2020) a].** A recent meta-analysis summarized that leukocytosis and lymphopenia were allied with severe disease **(Huang et al., 2020 b).** Lymphopenia was previously used as a predictive biomarker in other communicable disorders such as influenza. Association between lymphopenia and severe illness may be the sequel of direct contamination of the lymphocyte, destruction of the lymphatic tissue, lymphocytic apoptosis owing to inflammation, or some metabolic troubles such as lactic acidosis triggering lymphocytes inhibition **(Tan et al., 2020 a).** In this study, in harmony with **Hashem et al., (2021)** in spite of being allied with severe COVID-19 contagion, neither lymphopenia nor leukocytosis was a substantial hazard element by multivariate regression analysis. Furthermore, the optimal WBC cut-off point to predict the clinical severity of COVID-19 was [13.7 10^3/ul] with (79.6%) sensitivity but (52.1%) specificity. Similarly, the optimal cut-off point of absolute neutrophil count to predict severity was [74.5 10^3/ul], with sensitivity (76.1%) nevertheless (55.5%) specificity. Besides, the optimal cut-off point of absolute lymphocyte count to predict severity was [1.73 10^3/ul] with (90.1%) sensitivity but (27.0%) specificity.

The neutrophil-to-lymphocyte ratio (NLR) is an anxiety and immune element. For COVID-19, the increased neutrophil count may specify the degree of the inflammatory feedback, and the reduced lymphocytes estimate the degree of immune disparity. These relations are augmented by the concept of NLR **(Zahorec et al., 2020).** The normal values of NLR in adults range from 1.0 to 2.3. The cut-off value of NLR that could forecast unfortunate COVID-19 contagion fluctuates widely among studies. It varies between 3.1 and 9 **(Wang et al, 2021). In this study**, the optimal cut-off point that could predict severe COVID-19 contagion was [5.73]. A previous study found a statistically considerable strong relation of in-hospital decrease with NLR > 3.1 **(Asem et al., 2021).** The non-existence of a single general explanation for severe COVID-19 contagion and the fluctuating outcome measures used in diverse studies might clarify this wide range and variances. However, there is accordance about the value of raised baseline NLR in forecasting severe COVID disease.

Regarding inflammatory biomarkers associated with the COVID-19 contagion, **in this study**, we found that severe cases had considerably higher levels of CRP, D dimer & ferritin. several meta-analysis studies disclosed higher concentrations of C-reactive protein (CRP) among patients with severe COVID-19 infection **[(Henry et al., 2020) (Tan et al., 2020 b) (Elshazli et al., 2020)]. In this study,** higher levels of CRP were found in severe COVID-19 cases. moreover, by applying multivariate regression analysis, it was established to be a forecaster of severity ($p= 0.009$) in contrast to **Hashem et al., (2021).**

SARS-CoV-2 virus can affect coagulation and hemostasis by diverse measures involving both abnormal bleeding hazard and thrombo-embolism. Consequently, all main coagulation biomarkers disorders were displayed in COVID-19 cases specifically higher serum D-dimer level, longer prothrombin time (PT), and lower platelet counts **(Danwang et al., 2020).** Elevated levels of D-dimer may help in competent diversity between mild and severe cases of COVID-19 infection **(Zhang et al., 2020)** and may be used as a mirror for the documentation of disease evolution toward unfavorable outcomes or even decrease **(Bashash et al., 2020).** The optimal D-dimer level that could forecast a worse prognosis varies among studies between > 1 mg/L to >

2.14 mg/L **(Zhou et al., 2020 b).** In this study, D-dimer > [1.56 mg\L] found to be a subtle forecaster for severe COVID-19 infection

Serum Ferritin is an acknowledged inflammatory biomarker in COVID-19. A recent metanalysis summarized that Hyper-ferritinaemia was found to be allied with more severe illness and worse COVID-19 sequel. Consequently, serum ferritin level can aid as a significant prognostic biomarker in the management of COVID-19 cases. However, in the presence of other comorbidities, serum ferritin levels are required to be taken carefully **(Kaushal et al., 2022).** This agreed with our results., Besides, we found that serum ferritin was considered an independent hazard factor for COVID-19 severity (p= 0.033). Moreover, the optimal cut-off point of serum ferritin to predict severe COVID-19 infection was [256.5 (ng/ml)] with (90.1%) sensitivity but (38.0%) specificity.

However, this study had numerous limitations including the following: First: the retrospective design of the study. Second: the changing treatment protocol and admission policy during the study period. Third: it's a single-center study with a small number of patients to identify the outcome. Fourth: the follow-up laboratory data and linear changes in association with the clinical condition of the patients were not evaluated and the other bio-markers such as IL-6 level, LDH, CK-MB, troponin, and procalcitonin were not assessed. Finally, the inter-observer bias is presented in the CT interpretation.

CONCLUSIONS

Increased NLR (> 5.73), D-dimer level (> 1.56 mg\L), CRP (> 86.5 mg/L and serum Ferritin (>256.5 ng/ml) at the time of admission can be simply available prognosticators for severe COVID-19 contagion. Upcoming studies are desired to appraise the linear variation of NLR, CRP, Ferritin, and D-dimer with disease progression.

Abbreviations

COVID- 19: Corona virus disease 2019

CRP: C-reactive protein

Hb: Hemoglobin

ICU: Intensive care unit

NLR: Neutrophil-to-lymphocyte ratio

SARS CoV-2: Severe acute respiratory syndrome coronavirus 2

WHO: World Health Organization

AUC: Area under curve

SE = Standard error

CI = Confidence interval

HRCT: High resolution CT chest:

REFERENCES

- Asem N, Hassany M, Taema K, Masoud H, Elassal G, Kamal E, Amin W, Abdelbary A, Baki AA, Zaky S, Abdalmohsen A. Demographic and clinical features associated with in-hospital mortality in Egyptian COVID-19 patients: A retrospective cohort study. medRxiv. 2021 Mar 25:2021-03.

- Bashash D, Abolghasemi H, Salari S, Olfatifar M, Eshghi P, Akbari ME. Elevation of D-dimer, but not Pt and aPTT, reflects the progression of covid-19 toward an unfavorable outcome: a meta-analysis. IJBC . 2020 Jun 10;12(2):47-53.

- Cavezzi A, Troiani E, Corrao S (2020) COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. Clin Pract 10(2):1271
- Chen Q, Zheng Z, Zhang C, Zhang X, Wu H, Wang J, et al. (2020). Clinical characteristics of 145 patients with coronavirus disease 2019 (COVID-19) in Taizhou, Zhejiang, China. Infection, 48(4), 543-551.
- Danwang C, Endomba FT, Nkeck JR, Wouna DL, Robert A, Noubiap JJ. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). Biomarker research. 2020 Dec;8(1):1-3.
- Elshazli RM, Toraih EA, Elgaml A, El-Mowafy M, El-Mesery M, Amin MN, Hussein MH, Killackey MT, Fawzy MS, Kandil E. Diagnostic and prognostic value of hematological and immunological markers in COVID-19 infection: A meta-analysis of 6320 patients. PloS one. 2020 Aug 21;15(8):e0238160.

- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020 Apr 30;382(18):1708-20.

- Habibzadeh P, Stoneman EK. The novel coronavirus: a bird's eye view. The international journal of occupational and environmental medicine. 2020 Apr;11(2):65.
- Hashem MK, Khedr EM, Daef E, Mohamed-Hussein A, Mostafa EF, Hassany SM, Galal H, Hassan SA, Galal I, Amin MT, Hassan HM. Prognostic biomarkers in COVID-19 infection: value of anemia, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and D-dimer. The Egyptian Journal of Bronchology. 2021 Dec;15(1):1-9.
- Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G (2020) Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a metaanalysis. Clin Chem Lab Med (CCLM) 58(7):1021–1028.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497–506 (a).
- Huang G, Kovalic AJ, Graber CJ. Prognostic value of leukocytosis and lymphopenia for coronavirus disease severity. Emerging infectious diseases. 2020 Aug;26(8):1839 (b).
- Kaushal K, Kaur H, Sarma P, Bhattacharyya A, Sharma DJ, Prajapat M, Pathak M, Kothari A, Kumar S, Rana S, Kaur M. Serum ferritin as a predictive biomarker in COVID-19. A systematic review, meta-analysis and meta-regression analysis. Journal of Critical Care. 2022 Feb 1; 67:172-81.

- Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, Dunning J, Fairfield CJ, Gamble C, Green CA, Gupta R. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. bmj. 2020 Sep 9;370.

- Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, Jiang X, Li X. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. Journal of medical virology. 2020 Jul;92(7):856-62 (a).
- Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, Wang Q, Miao H. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal transduction and targeted therapy. 2020 Mar 27;5(1):33 (b).

- Viner RM, Ward JL, Hudson LD, Ashe M, Patel SV, Hargreaves D, Whittaker E. Systematic review of reviews of symptoms and signs of COVID-19 in children and adolescents. Archives of disease in childhood. 2021 Aug 1;106(8):802-7.

- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. jama. 2020 Mar 17;323(11):1061-9.

- Wang S, Fu L, Huang K, Han J, Zhang R, Fu Z. Neutrophil-to-lymphocyte ratio on admission is an independent risk factor for the severity and mortality in patients with coronavirus disease 2019. Journal of Infection. 2021 Feb 1;82(2):e16-8.
- World Health Organization. Living guidance for clinical management of COVID-19: living guidance, 23 November 2021. World Health Organization; 2021.

- World Health Organization. WHO. WHO Director-General's opening remark at the media briefing on COVID 19. 11 March 2020, [Internet]. Genebra: World Health Organization; 2020 [cited 2020 Jun 10].

- Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, et al. (2020). Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA internal medicine, 180 (7), 934-943 (a).

- Wu J, Huang J, Zhu G, Wang Q, Lv Q, Huang Y, Yu Y, Si X, Yi H, Wang C, Liu Y. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. BMJ Open Diabetes Research and Care. 2020 Jun 1;8(1):e001476 (b).

- Yamada T, Wakabayashi M, Yamaji T, Chopra N, Mikami T, Miyashita H, Miyashita S. Value of leukocytosis and elevated C-reactive protein in predicting severe coronavirus 2019 (COVID-19): A systematic review and meta-analysis. Clinica chimica acta. 2020 Oct 1; 509:235-43.
- Zahorec R, Hulin I, Zahorec P. Rationale Use of Neutrophil-to-lymphocyte ratio for early diagnosis and stratification of COVID-19. Bratislavske Lekarske Listy. 2020 Jan 1;121(7):466-70.

- Zhang JJ, Dong X, Cao YY, YuanYD, Yang YB, Yan YQ, et al. (2020). Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy, 75(7), 1730-1741.
- Zhou Y, Yang Q, Chi J, Dong B, Lv W, Shen L, et al. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: a systematic review and meta-analysis. Int J Infect Dis. 2020; 99:47–56.