Journal of Endocrinology, Tropical Medicine, and Infectious Disease (JETROMI) Vol. 05, No.4, 2023 / 198-207

JETROMI
Journal of Endocrinology, Tropical Medicine, and Infectious Disease

Factors Associated with the Severity of COVID-19 at H. Adam Malik Hospital, Medan, Indonesia

Dyana Destylya[1], Bintang Yinke Magdalena Sinaga[1*], Parluhutan Siagian[1], Putri Chairani Eyanoer[2]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara, Adam Malik Hospital, Medan, Indonesia
[2]Department of Community Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

ABSTRACT

Background: Several studies have shown an association among laboratory values, comorbidities, and the severity of COVID-19. This study aimed to find the factors associated with the severity of COVID-19 patients in Adam Malik Hospital.

Method: This is a descriptive study with a cross-sectional design. The subjects were COVID-19 patients from December 2020 to April 2021 whose data were in the form of secondary data obtained from their medical records. The inclusion criteria were patients diagnosed with COVID-19 based on RT-PCR while the exclusion criteria were incomplete medical record data. Statistical analysis was conducted via the following tests Kruskal Wallis Test, Kolmogorov Test, and Chi-Square based on the data category.

Results: A total of 110 subjects were enrolled in this study. Most subjects were male (55.45%) with age >40 years old (66.36%). The laboratory values of lymphocyte count, NLR, D-dimer, procalcitonin, ferritin, fibrinogen, and CRP were significantly associated with the severity of COVID-19. Also, there were several comorbidities statistically associated with the severity of COVID-19, including hypertension, diabetes mellitus, coronary artery disease, renal disease, and HIV ($p < 0.05$).

Conclusion: Lymphocyte count, NLR, CRP, procalcitonin, D-dimer, fibrinogen, ferritin, and comorbidities including diabetes mellitus, hypertension, HIV, coronary disease, and renal disease, were associated with the severity of COVID-19.

Keyword: COVID-19; Comorbid; Laboratory Value; Severity Level

ABSTRAK

***Latar Belakang**: Beberapa penelitian telah menunjukkan hubungan antara nilai laboratorium, komorbiditas, dan tingkat keparahan COVID-19. Penelitian ini bertujuan untuk menemukan faktor-faktor yang berhubungan dengan tingkat keparahan pasien COVID-19 di Rumah Sakit Adam Malik.*

*Corresponding author at: Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara, Adam Malik Hospital, Medan, Indonesia

E-mail address: bintang@usu.ac.id

DOI: https://doi.org/10.32734/jetromi.v5i4.14389
Journal Homepage: https://jetromi.usu.ac.id

***Metode**: Penelitian ini adalah studi deskriptif dengan desain potong lintang. Subjek penelitian adalah pasien COVID-19 periode Desember 2020 sampai April 2021 yang datanya berupa data sekunder dan diperoleh dari rekam medis. Kriteria inklusi adalah pasien yang terdiagnosis COVID-19 berdasarkan RT-PCR sedangkan kriteria eksklusi adalah data rekam medis yang tidak lengkap. Analisis statistik dilakukan melalui uji berikut Uji Kruskal Wallis, Uji Kolmogorov, dan Chi-Square berdasarkan kategori data.*

***Hasil**: Sebanyak 110 subjek terdaftar dalam penelitian ini. Sebagian besar subjek adalah laki-laki (55,45%) dengan usia >40 tahun (66,36%). Nilai laboratorium jumlah limfosit, NLR, D-dimer, prokalsitonin, feritin, fibrinogen, dan CRP secara signifikan terkait dengan tingkat keparahan COVID-19. Selain itu, terdapat beberapa komorbiditas yang secara statistik terkait dengan tingkat keparahan COVID-19, antara lain hipertensi, diabetes melitus, penyakit arteri koroner, penyakit ginjal, dan HIV (p <0,05).*

***Kesimpulan**: Jumlah limfosit, NLR, CRP, prokalsitonin, D-dimer, fibrinogen, feritin, dan komorbiditas termasuk diabetes mellitus, hipertensi, HIV, penyakit koroner, dan penyakit ginjal, dikaitkan dengan tingkat keparahan COVID-19.*

***Kata kunci**: COVID-19; Komorbid; Nilai Laboratorium; Tingkat Keparahan*

Received 16 November 2023 | Revised 29 November 2023 | Accepted 11 December 2023

1 Introduction

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).[1] The number of COVID-19 cases has been increasing rapidly, spreading all over the world, and on March 12, 2020, the WHO declared it a pandemic.[2] Several studies in various countries have found characteristics that are often found in COVID-19 patients, such as age, gender, comorbidities, clinical symptoms, and laboratory examination results. According to Liu et al, 2020, in Wuhan Central Hospital, more progressive cases were found at the age of 66 years, while stable patients were at a younger age.[3] According to Li et al, 2020 in a meta-analysis conducted, it was found that the percentage of men was 60% greater than women.[4] According to Xu, in 2020 several research reports on patients with COVID-19 found that 100% of the 25 COVID-19 patients who died had co-morbidities such as hypertension (16/25, 64%), diabetes (10/25, 40%), heart disease (8/25, 32%), renal disease (5/25, 20%), cerebral infarction (4/25, 16%), Chronic Obstructive Pulmonary Disease (COPD) (2/25, 8%), malignant tumors (2/25, 8%) and acute pancreatitis (1/25, 4%).[5]

Chen et al, 2020, found 36% with elevated D-Dimer, 6% with elevated procalcitonin, 63% patients with elevated ferritin levels, and 86% patients with elevated CRP levels.[6] According to Wang, 2020 based on the results of research at Qiandongnan Hospital, China, CRP levels and the extent of lesions in the lungs are associated with the severity of COVID-19.[7] The study aimed to find the factors associated with the severity of COVID-19 patients, and the correlation between laboratory parameters, comorbidities, and the disease severity in COVID-19 patients

2 Methods

This study is a descriptive study with a cross-sectional design using the data on the medical records of COVID-19 patients treated in the isolation room of Adam Malik Hospital. The study was conducted over 5 months, from December 2020 to April 2021 at Adam Malik Hospital, Medan, Indonesia. This research has been approved by the Health Research Ethics Commission (KEPK) Faculty of Medicine, Universitas Sumatera Utara, Medan. The subjects consist of 110 COVID-19 patients who met the inclusion criteria patients diagnosed with COVID-19 based on RT-PCR. The exclusion criteria were incomplete medical records. This study uses two variables. The dependent variable is the severity of the disease. The independent variables include age, gender, results of laboratory tests such as levels of lymphocytes, neutrophil-lymphocyte ratio (NLR), D-Dimer, C Reactive Protein (CRP), procalcitonin (PCT), fibrinogen and ferritin, and existing comorbidities such as diabetes mellitus, hypertension, Human Immunodeficiency Virus (HIV), heart disease, kidney disease, cancer, other lung diseases such as tuberculosis (TB) and pregnancy status.

Statistical analysis

Statistical analysis was performed using the Kruskal Wallis, Kolmogorov, and Chi-Square tests based on data categories by using SPSS version 21. A 95% confidence interval (CI) was calculated. p-values less than 0.05 were considered significant.

3 Results

Data were taken retrospectively from medical record data of patients who met the inclusion criteria (a diagnosis of COVID-19 based on positive RT-PCR) from December 2020 to April 2021. The results showed that there was more male than female patients; most patients were over 40 years old; and that hypertension was the most frequent/common comorbidity. In addition, most of the patients had one comorbidity and the severity of the disease (COVID-19) was most likely moderate (Table 1).

Table 1 Demographic Characteristics of COVID-19 Patients

Characteristics	Total	Percentage (%)
Gender		
Male	61	55.5
Woman	49	44.5
Age (year)		
>40	73	66.4
<40	37	33.6
Comorbid		
Hypertension	43	38
Diabetes Mellitus	21	18
Coronary Disease	21	18
Kidney Disease	12	11
Pregnancy	10	9
Cancer	3	3
HIV	2	2
Tuberculosis	1	1
Number of co-morbidities		
Without comorbid	33	30
1 Comorbid	43	39
2 Comorbid	17	15.5
> 2 Comorbid	17	15.5
Disease severity		
Moderate	76	69
Severe	17	15.5
Critical	17	15.5

The mean lymphocyte count in all the COVID-19 patients is within the normal value (1.79 10^3/µL ± 2.75), whereas NLR, CRP, PCT, D-dimer, Fibrinogen, and Ferritin have a higher mean than the normal value (Table 2).

Table 2 Characteristics of Laboratory Values

Parameter	Mean ± SD	Median (Min-Max)	Normal value
Lymphocyte(10^3/µL)	1.79 ± 2.75	1.30 (0.30 – 29)	1.5 – 3.7
NLR (10^3/µL)	8.01 ± 11.17	3.70 (0.61 – 65.02)	< 7
CRP (mg/dl)	0.95 ± 0.62	0.70 (0.70 – 2.80)	< 0.7
PCT (ng/ml)	1.86 ± 8.25	0.06 (0 – 50.65)	< 0.1
D-dimer (ng/ml)	931.29±1,133.12	416 (100– 4,483)	< 500
Fibrinogen (mg/dl)	467.11 ± 165.38	438.50 (142 – 900)	150 – 400
Ferritin (ng/ml)	941.61±1,174.65	597.50 (7.32– 10,621)	15 – 150

The age of COVID-19 patients is statistically correlated with the severity level of COVID-19. The mean age of patients with critical severity is higher than that of the severe level, and the mean age of patients with severe levels is higher than that of the moderate level (p=0.004) (Table 3).

Table 3 Age of Respondents (in years) Based on COVID-19 Disease Severity

Severity	Mean ± SD (yr)	Median (Min-Max)	p-value
Moderate	46.92± 15.71	48 (19 -79)	0.004
Severe	56.47 ± 14.76	58 (30 – 79)	
Critical	58.50 ± 9.35	60 (32 – 73)	

The mean value of lymphocyte count decreases with increasing disease severity while neutrophil-lymphocyte ratio, fibrinogen, and ferritin patients increase with increasing disease severity. The mean value of D-dimer, CRP, and procalcitonin is lower in moderate severity compared to severe and critical COVID-19 patients. There was an association between the laboratory value of lymphocytes, the ratio of neutrophils to lymphocytes, D-dimer, CRP, procalcitonin, fibrinogen, and ferritin with the severity of the disease ($p<0.05$) (Table 4).

Table 4 Laboratory Values Based on COVID-19 Disease Severity

Parameter	Severity	Mean ± SD	Median (Min-Max)	P-Value
Lymphocyte (10^3/µL)	Moderate	2.13± 3.24	1.59(0.64 – 29)	**0.001**
	Severe	1.41± 0.92	1.19(0.30 – 3.38)	
	Critical	0.72± 0.33	0.57(0.34 – 1.26)	
NLR (10^3/µL)	Moderate	3.70± 3.39	2.75(0.61 – 22.82)	**0.001**
	Severe	8.87± 8.24	6.48 (1.71 – 36.83)	
	Critical	25.21± 17.05	18.79 (4.60 – 65.02)	
D- dimer (ng/ml)	Moderate	624± 763	340 (100 – 4,001)	**0.001**
	Severe	1,750±1,661	950 (290– 4,483)	
	Critical	1,435± 1,318	799 (190 – 4,001)	
Fibrinogen (ng/ml)	Moderate	429±138.64	409 (142 – 900)	**0.006**
	Severe	541± 172.29	535 (275 – 900)	
	Critical	551.88± 211	494.50 (201 - 900)	
CRP (mg/dl)	Moderate	0.82± 0.35	0.69 (0.01- 2.8)	**0.002**
	Severe	1.39± 0.95	0.70 (0.69 – 2.80)	
	Critical	1.08± 0.90	0.70 (0.7 – 2.80)	
PCT (ng/ml)	Moderate	0.72± 5.19	0.04 (0.01– 45.08)	**0.001**
	Severe	5.49± 14.84	0.15 (0.02– 50.66)	
	Critical	3.19± 9.56	0.31 (0.02– 40.73	
Ferritin (ng/ml)	Moderate	620.53±597.89	364.60 (7.32 – 2,001)	**0.001**
	Severe	1,191.83±794.16	1,125 (83.16 – 2,001	
	Critical	2,043± 2,212	1,893 (207–10,621)	

The most common comorbidities found in critically ill patients based on this study were hypertension, diabetes, heart disease, and kidney disease. Also, there was an association between the following comorbid diabetes mellitus, hypertension, kidney disease, heart disease, and HIV, and the severity of the disease ($p<0.05$) (Table 5).

Table 5 The Association Between Comorbidities and the Severity of COVID-19

Comorbid	Severity			p-value
	Moderate	Severe	Critical	
Hypertension	23 (53.5%)	8(18.6%)	12(27.9 %)	**0.015**
DM	9 (42.9%)	9(42.9%)	3(14.2%)	**0.001**
Heart Disease	10 (47.7%)	3(14.2 %)	8(38.1%)	**0.010**
Kidney Disease	2 (16.7%)	3(25%)	7(58.3%)	**0.001**
Cancer	2 (66.7%)	0(0%)	1(33.3%)	0.600
HIV	0 (0%)	2(100%)	0(0%)	**0.004**
Pregnancy	9 (90%)	0	1(10%)	0.254
Tuberculosis	1 (100%)	0	0	0.790

4 Discussion

In this study, the frequency of male sex was higher, namely 61 male patients (55.45%). This is by Liu et al who found that more COVID-19 diagnosis was found in men (55.4%). The X chromosome contains a high density of immune-related genes; therefore, generally, there is a stronger innate and adaptive immune response in women than in men. It is influenced by sex chromosomes and sex hormones, including estrogen, progesterone, and androgens as well as the production of steroid hormones.[8]

As for this study, the age of the COVID-19 patients is related to the severity of the disease. Aging causes many physiological changes in the immune system which, in turn, cause a progressive decrease in the ability of the immune system to fight new and latent infections thereby influencing the course of the disease.[9]

This study found an association between lymphocyte value and COVID-19 severity; lymphocyte value decreased along with increasing severity. Liu et al, showed that the number of lymphocytes decreased in most patients, and the absolute value of lymphocytes was associated with the severity of COVID-19. Continuous stimulation by the virus can lead to T cell exhaustion, resulting in decreased immune function and worsening of the patient's condition. Studies have shown a decrease in all lymphocyte subsets, including total T cells, CD4+ and CD8+ T cells, memory and regulatory T cells, and B cells, in COVID-19 infection.[10]

In this study, NLR value was associated with COVID-19 severity, and NLR was increasing with increasing severity. The NLR was significantly increased in COVID-19 patients. The study by Nalbant et al showed that the N/L ratio is an independent biomarker for the severity of COVID-19 patients.[11] According to Qin et al. NLR was higher in critical COVID-19 patients and NLR > 4 was a predictor for ICU admission.[12]

This study found D-dimer value was lower in moderate COVID-19 patients than in severe and critical. Yu et al stated that an increase in D-dimer indicated an increased risk of abnormal blood clotting. Elevated D-dimer may be an indirect manifestation of the inflammatory reaction;

because inflammatory cytokines can cause an imbalance of coagulation and fibrinolysis in the alveoli, which can activate the fibrinolytic system and further increase D-dimer levels.[13]

Guan et al, declared that the liver overreacted during the acute inflammatory phase of COVID-19 and secreted several reactants such as fibrinogen, C-reactive protein (CRP), ferritin, and many cytokines. The secretion of these reactants is the body's defense mechanism against invading pathogens[14]. Our study found an association between CRP and severity of COVID-19, CRP value was lower in moderate severity than in severe and critical patients. In line with Zavareh et al, serum CRP levels can be used as an important indicator of the progression and severity of COVID-19.[15]

This study showed an increase in the median procalcitonin values of moderate, severe, and critical COVID-19 patients, 0.04 ng/mL, 0.15 ng/mL, and 0.31 ng/mL respectively. According to Feng et al, procalcitonin levels increased dramatically in response to a cytokine storm with increased concentrations of interleukin (IL)-1β, Tumor Necrosis Factor (TNF)-α, and IL-6, gamma-induced interferon protein-10, and macrophage inflammatory protein 1-α; most of which were significantly increased in severe and critical COVID-19 cases.[4]

This study found mean fibrinogen value was higher than the normal value and associated with COVID-19 severity level. Based on the study of Nugroho et al, it was found that the average fibrinogen was higher in critically ill patients compared to non-severe cases by more than 500[16]. In this study, the mean values of ferritin in moderate, severe, and critical severity were 620.53 ng/ml, 1,191.83, and 2,043 ng/mL. The highest value in the critical level was 10,621 ng/mL. In the Carubbi et al study, hyperferritinemia was associated with an inflammatory state in SARS-CoV-2 infection. Ferritin is useful as a parameter for predicting disease severity and the severity of cytokine storms. A complex feedback mechanism between ferritin and cytokines in the control of pro-inflammatory and anti-inflammatory mediators may exist because cytokines can induce ferritin expression, but ferritin can induce pro- and anti-inflammatory expression.[17]

This study showed the most frequent comorbidity found was hypertension, followed by diabetes mellitus and heart disease. A significant association was found between the comorbidity of hypertension, diabetes mellitus, heart disease, kidney disease, and HIV, and the severity of COVID-19. Liang et al, stated that hypertension was significantly associated with independent risk for predicting the severity and mortality of COVID-19 patients.[18] According to Wang et al, this could be due to SARS-CoV-2 infection in patients with diabetes triggering higher stress conditions and greater release of hyperglycemic hormones such as glucocorticoids and catecholamines, leading to elevated blood glucose and abnormal glucose variability.[19] A study by Zhou et al mentioned pre-existing cardiovascular disease engendered greater severity in COVID-19. This is because coronary heart disease has also been found to be associated with acute cardiac events and poor outcomes in influenza and other respiratory viral infections.[20]

Patients with kidney disease have decreased innate and adaptive immunity, which may contribute to an increased risk of infection. This led to the finding of more severe COVID-19 infections in patients with chronic kidney disease comorbidity. In addition, acute kidney disease is also frequently reported in the initial series of patients with COVID-19.[21] The COVID-19 pandemic has significantly impacted individuals with Human Immunodeficiency Virus (HIV), interfering with critical health services for HIV prevention, treatment, and care. The severity of COVID-19 in HIV individuals is strongly related to the presence of comorbidities that increase the risk of severity in COVID-19 patients in the absence of HIV.[22] In this study, a significant association was found between HIV and the severity of COVID-19 disease, but the number of subjects who had HIV in this study was only 2 (1.82%) out of the total number of study subjects. So, this is a limitation of this study.

In this study, there was no significant association between the presence of pregnancy, cancer, and tuberculosis with the severity of COVID-19. This may be due to the small number of COVID-19 patients in this study who had pregnancy, cancer, and tuberculosis. According to Hapshy et al, there was a lack of adequate data and literature on coronavirus in pregnancy. There is limited evidence regarding the risk of infection with COVID-19 in the peripartum and antepartum period. However pregnant females should be classified as a high-risk population. A recent study showed older age and underlying medical conditions were associated with an increased risk of moderate-to-severe or critical COVID-19 illness among pregnant women.[23]

The limitation of cancer patients during the pandemic could be due to the reduced number of visits to cancer patients during the pandemic. This can be caused by medical services for cancer patients who have not fully recovered during the pandemic, which can affect cancer patients' visits to the hospital.[24]

TB patients who have lung damage due to sequelae of TB or chronic obstructive pulmonary disease may have a more severe outcome if infected with COVID-19.[25,26] This study found that 1 person (1.3%) of COVID-19 patients was hospitalized with comorbid tuberculosis (TB). It was not found in the severe and critical category. There was no significant association between the presence of comorbid tuberculosis and the severity of COVID-19 when the patient entered the inpatient room, but this may be because only 1 tuberculosis patient was analyzed. Current evidence on TB-COVID-19 coinfection indicates that patients are more likely to suffer severe illness or death than COVID-19 patients.[27]

There are some limitations to this study. The results of this study were obtained from patient medical records from December 2020 to April 2021, during which time the number of cases was decreasing in Indonesia, especially in March and April. The data were only those taken when the patient was admitted to the hospital without any data from the follow-up treatment. This study

was conducted on hospitalized COVID-19 patients, so there is no data on patients who were asymptomatic and had mild symptoms.

Therefore, a comparative analysis of laboratory values and comorbidities involving asymptomatic and mildly symptomatic patients cannot be performed. Also, the number of patients with comorbid pregnancy, tuberculosis, cancer, and HIV was small to analyze the association with COVID-19 severity.

5 Conclusion

There was an association between age, lymphocyte count, NLR, CRP, procalcitonin, D-dimer, fibrinogen, ferritin, and some comorbid like diabetes mellitus, hypertension, HIV, heart dis, ease and kidney disease with the severity of COVID-19.

Further research is needed to determine the factors associated with COVID-19 severity with a prospective study design and a larger population involving all levels of disease severity.

REFERENCES

[1] World Health Organization, "Coronavirus Disease (Covid-19) Situation Reports," World Health Organization, 2020. [Online]. Available: Https://Www.Who.Int/Emergencies/Diseases/Novel-Coronavirus-2019/Situation-Reports. [Accessed: 16-Nov-2023].

[2] World Health Organization, "Clinical Management Of Severe Acute Respiratory Infection (Sari) When Covid-19 Disease Is Suspected: Interim Guidance, 13 March 2020," World Health Organization, 2020. [Online]. Available: https://Www.Who.Int/Europe/Publications/I/Item/Who-2019-Ncov-Clinical-2020-4. [Accessed: 16-Nov-2023].

[3] S. Liu, H. Luo, Y. Wang, L. E. Cuevas, D. Wang, S. Ju, et al., "Clinical Characteristics And Risk Factors Of Patients With Severe Covid-19 In Jiangsu Province, China: A Retrospective Multicentre Cohort Study," Bmc Infect Dis, 2020;20(1):1–9.

[4] X. Li, M. Geng, Y. Peng, L. Meng, And S. Lu, "Molecular Immune Pathogenesis And Diagnosis Of Covid-19," J Pharm Anal, 2020;10(2):102–8.

[5] Y. Feng, B. Xu, J. Feng, And J. Xianyu, "Association Of Procalcitonin And The Severity Of Covid-19 : A Meta-Analysis 2020," 2021;7:166–74.

[6] W. Chen, K. I. Zheng, S. Liu, Z. Yan, C. Xu, And Z. Qiao, "Plasma Crp Level Is Positively Associated With The Severity Of Covid-19," Ann Clin Microbiol Antimicrob, 2020;19:1–7.

[7] C. Wang, P. W. Horby, F. G. Hayden, And G. F. Gao, "A Novel Coronavirus Outbreak Of Global Health Concern," The Lancet, 2020;395(10223):470–3.

[8] G. Sharma, A. S. Volgman, And E. D. Michos, "Sex Differences In Mortality From Covid-19 Pandemic: Are Men Vulnerable And Women Protected?," Jacc Case Rep, 2020;2(9):1407–10.

[9] V. Bajaj, N. Gadi, A. P. Spihlman, S. C. Wu, C. H. Choi, And V. R. Moulton, "Aging, Immunity, And Covid-19: How Age Influences The Host Immune Response To Coronavirus Infections?," Front Physiol, 2021;11:1–23.

[10] X. Qing Liu, S. Xue, J. Bo Xu, H. Ge, Q. Mao, X. Hui Xu, et al., "Clinical Characteristics And Related Risk Factors Of Disease Severity In 101 Covid-19 Patients Hospitalized In Wuhan, China," Acta Pharmacol Sin, 2021.

[11] A. Nalbant, T. Kaya, C. Varim, S. Yaylaci, A. Tamer, And H. Cinemre, "Can The Neutrophil/Lymphocyte Ratio (Nlr) Have A Role In The Diagnosis Of Coronavirus 2019 Disease (Covid-19)?," Rev Assoc Med Bras, 2020;66(6):746–51.

[12] C. Qin, L. Zhou, Z. Hu, S. Zhang, S. Yang, Y. Tao, et al., "Dysregulation Of Immune Response In Patients With Covid-19 In Wuhan, China," Ssrn Electronic Journal, 2020.

[13] Z. Feng, Q. Yu, S. Yao, L. Luo, W. Zhou, X. Mao, et al., "Early Prediction Of Disease Progression In Covid-19 Pneumonia Patients With Chest Ct And Clinical Characteristics," Nat Commun, 2020;11(1):1–9.

[14] W. Guan, Z. Ni, Y. Hu, W. Liang, C. Ou, J. He, et al., "Clinical Characteristics Of Coronavirus Disease 2019 In China," New England Journal Of Medicine, 2020;382(18):1708–20.

[15] M. Sharifpour, S. Rangaraju, M. Liu, D. Alabyad, F. B. Nahab, C. M. Creel-Bulos, et al., "C-Reactive Protein As A Prognostic Indicator In Hospitalized Patients With Covid-19," Plos One, 2020;15(11):1–5.

[16] J. Nugroho, A. Wardhana, E. P. Mulia, I. Maghfirah, D. A. Rachmi, M. Q. A'yun, et al., "Elevated Fibrinogen And Fibrin Degradation Product Are Associated With Poor Outcome In Covid-19 Patients: A Meta-Analysis," Clin Hemorheol Microcirc, 2021;77(2):221–31.

[17] F. Carubbi, L. Salvati, A. Alunno, F. Maggi, E. Borghi, R. Mariani, et al., "Ferritin Is Associated With The Severity Of Lung Involvement But Not With Worse Prognosis In Patients With Covid-19: Data From Two Italian Covid-19 Units," Sci Rep, 2021;11(1):1–11.

[18] Y. Liang, M. L. Wang, C. S. Chien, A. A. Yarmishyn, Y. P. Yang, W. Y. Lai, et al., "Highlight Of Immune Pathogenic Response And Hematopathologic Effect In Sars-Cov, Mers-Cov, And Sars-Cov-2 Infection," Front Immunol, 2020;11:1–11.

[19] A. Wang, W. Zhao, Z. Xu, And J. Gu, "Timely Blood Glucose Management For The Outbreak Of 2019 Novel Coronavirus Disease (Covid-19) Is Urgently Needed," Diabetes Res Clin Pract, 2020;162:

[20] C. Wu, X. Chen, Y. Cai, J. Xia, X. Zhou, S. Xu, et al., "Risk Factors Associated With Acute Respiratory Distress Syndrome And Death In Patients With Coronavirus Disease 2019 Pneumonia In Wuhan, China," Jama Intern Med, 2020;180(7):934–43.

[21] A. Rao, S. Ranka, C. Ayers, N. Hendren, A. Rosenblatt, H. M. Alger, et al., "Association Of Kidney Disease With Outcomes In Covid-19: Results From The American Heart Association Covid-19 Cardiovascular Disease Registry," J Am Heart Assoc, 2021;10:12.

[22] R. W. Eisinger, A. M. Lerner, and A. S. Fauci, "Human Immunodeficiency Virus/Aids In The Era Of Coronavirus Disease 2019: A Juxtaposition Of 2 Pandemics," J Infect Dis, 2021;224(9):1455–461.

[23] R. R. Galang, S. M. Newton, K. R. Woodworth, I. Griffin, T. Oduyebo, C. L. Sancken, et al., "Risk Factors For Illness Severity Among Pregnant Women With Confirmed Severe Acute Respiratory Syndrome Coronavirus 2 Infection-Surveillance For Emerging Threats To Mothers And Babies Network, 22 State, Local, And Territorial Health Departments, 29 March," Clin Infect Dis, 2021;73:S17–S23.

[24] A. G. Lai, L. Pasea, A. Banerjee, G. Hall, S. Denaxas, W. H. Chang, et al., "Estimated Impact Of The Covid-19 Pandemic On Cancer Services And Excess 1-Year Mortality In People With Cancer And Multimorbidity: Near Real-Time Data On Cancer Care, Cancer Deaths And A Population-Based Cohort Study," BMJ Open, 2020;10(11):1–9.

[25] B. Y. Sinaga And C. P. Sinulingga, "Pulmonary Tuberculosis With Covid-19 Coinfection: A Case Report | International Journal Of Medical Reviews And Case Reports," Int J Med Rev Case Rep, 2022;6(9):62–5.

[26] B. Yinke, M. Sinaga, J. P. Sinaga, and P. Siagian, "Multidrug-Resistant Tuberculosis And Covid-19 Coinfection with Diabetes Mellitus in Medan, Indonesia: A Case Report," Open Access Maced J Med Sci, 2022;10:187–90.

[27] W. M. Song, J. Y. Zhao, Q. Y. Zhang, S. Q. Liu, X. H. Zhu, Q. Q. An, et al., "Covid-19 and Tuberculosis Coinfection: An Overview of Case Reports/Case Series And Meta-Analysis," Front Med (Lausanne), 2021;8:1–13.