Jurnal RSMH Palembang
Journal Homepage: http://jurnalrsmh.com/index.php/JRP

Analysis of Risk Factors Associated with Survival COVID-19 Confirmed Patients

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ARTICLE INFO

Keywords:
COVID-19
Mortality
Risk factors
Survival

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/JRP.v4i1.41

ABSTRACT

Background: COVID-19 is a pandemic that occurs in all parts of the world and can cause worsening health conditions and even death. Several factors are suspected to aggravate risk factors that can worse clinical conditions and cause death in COVID-19 patients. Risk factors such as age, gender, and the presence or absence of chronic disease are often associated with increased mortality in COVID-19 patients. This study aimed to determine the relationship between factors that affect the survival of COVID-19 patients, such as age, gender, diabetes mellitus, hypertension, heart disease, kidney disease, lung disease, smoking history, alcohol history, and obesity. **Methods:** An analytical description study of 66 participants was conducted for bivariate and multivariate analysis. **Results:** The results showed that aged more than 45 years(p=0,001; OR 6,111; 95% CI: 2.102-17.769), male (p=0,003; OR 5.417; 95% CI: 1.862-15.756), diabetes mellitus (p=0,000; OR 36.000; 95% CI: 7.194-180.151), heart disease (p=0,003; OR 9.286; 95% CI: 1.894-45.522), kidney disease (p=0,001; OR 8.953; 95% CI: 2.192-33.686) dan lung disease (p=0,002; OR 7.632; 95% CI: 1.943-29.971), smoker (p=0,003; OR 4.846; 95% CI: 1.683-13.955), dan obesity (p=0,005; OR 4.875; 95% CI: 1.600-14.855) influenced the patient's survival. **Conclusion:** Risk factors from age, gender, diabetes mellitus, heart disease, kidney disease, lung disease, smoking, alcoholism, and obesity influence the survival of confirmed COVID-19 patients. Among these factors, the most influential is diabetes mellitus.

1. Introduction

The viral pandemic that is currently sweeping the world has attracted a lot of attention due to the increasing number of cases. The World Health Organization (WHO) finally officially established COVID-19 as the name of the disease caused by the virus, which stands for coronavirus disease that was discovered in 2019.[1] The worldwide mortality rate due to COVID-19 until November 2020 exceeded 1.2 million with the highest number of deaths occurring in the United States with 230,996 deaths.[2] The mortality rate of COVID-19 patients in Indonesia is the highest in Asia and ranks 12th in the world with a mortality rate of 0.34 per 100,000 population or 3.4 percent.[3] Deaths due to COVID-19 in Indonesia are still too high compared to the world average. Other data states that positive confirmed cases of COVID-19 in Indonesia reached 808,340 on January 8, 2021 with a death rate of 2.9%.[4]

Several factors are thought to be aggravating risk factors that can worsen clinical conditions and cause death in these COVID-19 patients. Risk factors such as age, gender, and the presence or absence of chronic diseases are often associated with increased mortality in COVID-19 patients. Old age is considered

to be more susceptible to infectious diseases and there is a decrease in immunity as a result of degenerative processes in the anatomy and physiology of the body. In addition, in older people, the lung lining is less elastic and the inflammatory effects are more insidious, leading to organ damage.[5] Higher chronic comorbidities in men, such as heart disease, hypertension, lung disease and smoking, are also associated with higher COVID-19 mortality rates in men.[6] Comorbidities that can aggravate the clinical manifestations of COVID-19 disease include diabetes, geriatric-related diseases, autoimmune diseases, kidney disease, heart disease, hypertension, and pulmonary disease or pneumonia.[4] The more comorbidities a COVID-19 patient has, the 6.5-fold higher risk of death compared to those without comorbidities.[3] Other risk factors in the development of disease worsening until death in COVID-19 patients are associated with lifestyle factors such as smoking, physical activity, obesity, and excessive alcohol intake.[7]

Dr. Mohammad Hoesin General Hospital Palembang is a national referral center for the Sumatra region, including a COVID-19 service and referral center. According to medical record data from Dr. Mohammad Hoesin General Hospital Palembang in 2020, the number of COVID-19 isolation inpatients who died with confirmed positive COVID-19 was 145 people. Data on the number of COVID-19 patients in January 2021 obtained from 7 isolation inpatient rooms in January were 207 people, with the number of patients who died was 4 people. Meanwhile, in February, the number of patients totaled 236 people and 42 people died. Research on risk factors associated with the cause of death of COVID-19 patients at Dr. Mohammad Hoesin General Hospital Palembang has never been done. Based on this consideration, the researcher will examine how the analysis of the risk factors of age, gender, diabetes mellitus, hypertension, heart disease, kidney disease, lung disease, smoking history, alcohol history, and obesity) that affect the survival of confirmed COVID-19 patients.

2. Methods

The research conducted was descriptive analytic research using a cross-sectional design with a quantitative approach. Based on the calculation results, the minimum sample required is 66 people. The inclusion criteria in this study were patients confirmed positive for COVID-19 during the period March to August 2020, aged ≥ 18 years, and recorded in hospital medical records. Meanwhile, the exclusion criteria are patients whose medical record data is incomplete in filling. The sampling technique used was non-probability with retrospective sampling. Data analysis of this study included univariate analysis, bivariate analysis, and multivariate analysis with logistic regression.

3. Results

Univariate analysis

Univariate analysis in this study included categorical variable analysis. Variable analysis included age, gender, diabetes mellitus, hypertension, heart disease, kidney disease, lung disease, smoking history, alcohol history, and obesity.

Based on the analysis in Table 1, it is known that the number of patients aged ≥ 46 years is 35 people (53%) and 38 people (57.6%) are male. Patient distribution based on comorbid diseases is known to be 26 people (39.4%) suffering from diabetes mellitus, 31 people (47%) have hypertension, 15 people (22.7%) suffer from heart disease, 19 people (28.8%) have kidney disease, and as many as 18 people (27.3%) suffer from lung disease. Most patients were smokers, 29 people (43.9%), alcohol drinkers were only 9 people (13.6%), and most were not obese, 42 people (63.6%).

Table 1. Distribution of Respondent Characteristics at Dr. Mohammad Hoesin General Hospital Palembang March - August 2020 (n = 66).

Patient Characteristics	Frequency(n)	Percentage (%)
Age		
≥ 46 years	35	53
< 46 years	21	47
Gender		
Male	38	57,6
Female	28	42,4
Diabetes Mellitus		
Yes	26	39,4
No	40	60,6
Hypertension		
Yes	31	47
No	35	53
Heart Disease		
Yes	15	22,7
No	51	77,3
Kidney Disease		
Yes	19	28,8
No	47	71,2
Lung Disease		
Yes	18	27,3
No	48	72,7
Smoker		
Yes	29	43,9
No	37	56,1
Alcoholism		
Yes	9	13,6
No	57	86,4
Obesity		
Yes	24	36,4
No	42	63,6
TOTAL	66	100

Bivariate analysis

Bivariate analysis in this study was conducted to explain whether there was a relationship between each independent variable (age, gender, diabetes mellitus, hypertension, heart disease, kidney disease, lung disease, smoking history, alcohol history, and obesity) on the dependent variable (patient survival). The analysis test used is the chi square test with the conditions of the chi square test fulfilled, namely the form of the 2x2 contingency table and there are no cells that have an expected frequency below five.

Table 2 shows that the survival of patients aged ≥ 46 years is lower with a percentage of deaths of 71.4% and has a significant relationship (p = 0.001; α = 0.05). In addition, male gender showed lower survival with a mortality percentage of 68.4% and had a significant relationship (p = 0.003; α = 0.05). Patients with diabetes mellitus had a lower survival rate with a mortality rate of 92.3% and a significant association (p = 0.000; α = 0.05). In addition, the survival of patients with hypertension had a mortality percentage of 58.1% which was almost the same as those without hypertension, namely 45.7%. The statistical test results showed that there was no relationship between hypertension and survival (p = 0.337; α = 0.05).

Table 2. Analysis of the relationship between risk factors and patient survival confirmed COVID-19 March - August 2020 (N = 66).

Variables	Group	Survival				p-value	OR
		No		Yes			95 % CI
		n	%	n	%		
Age	≥ 46 Years	25	71,4	10	28,6	0,001*	6,111
	< 46 Years	9	29,0	22	71,0		2.102-17.769
Gender	Male	26	68,4	12	31,6	0,003*	5.417
	Female	8	28,6	20	71,4		1.862-15.756
Diabetes mellitus	Yes	24	92,3	2	7,7	0,000*	36.000
	No	10	25	30	75		7.194-180.151
Hypertension	Yes	18	58,1	13	41,9	0,337	1.644
	No	16	45,7	19	54,3		0.620-4.360
Heart disease	Yes	13	86,7	2	13,3	0,003*	9.286
	No	21	41,2	30	58,8		1.894-45.522
Kidney disease	Yes	16	84,2	3	15,8	0,001*	8.953
	No	18	38,3	29	61,7		2.192-33.686
Lung disease	Yes	15	83,3	3	16,7	0,002*	7.632
	No	19	39,6	29	60,4		1.943-29.971
Smokers	Yes	21	72,4	8	27,6	0,003*	4.846
	No	13	35,1	24	64,9		1.683-13.955
Alcohol consumers	Yes	7	77,8	2	22,2	0,151	3.889
	No	27	47,4	30	52,6		0.743-20.356
Obesity	Yes	18	75	6	25	0,005*	4.875
	No	16	38,1	26	61,9		1.600-14.855

Table 2 also states that patients suffering from heart disease have a lower survival with a percentage of death of 86.7% and has a significant relationship (p = 0.003; α = 0.05). In addition, patients with concomitant kidney disease showed a lower survival with a mortality percentage of 84.2% and had a significant relationship (p = 0.001; α = 0.05). Patients with concomitant pulmonary disease had a lower survival rate with a mortality rate of 83.3% and a significant association (p = 0.002; α = 0.05). In addition, the survival of smoker patients had a mortality percentage of 72.4% and had a significant relationship (p 0.003; α = 0.05).

Table 2 shows that the survival of patients with a history of alcohol was lower, with a mortality rate of 77.8%. The statistical test results showed that there was no association between alcohol consumption and survival (p = 0.151; α = 0.05). In addition, patients with obesity showed a lower survival with a mortality percentage of 75% and had a significant association (p = 0.005; α = 0.05).

Multivariate analysis

Multivariate analysis in this study was used to determine the most dominant factors in survival in patients with confirmed COVID-19. In this study, the multivariate analysis used is logistic regression because the dependent variable is categorical.

Table 3. Final logistic regression modeling of survival factors in COVID-19 confirmed patients.

Variables	OR (95% CI)	ρ value
- Gender	0,093 (0,010-0,855)	0,036
- DM	0,004 (0,000-0,104)	0,001
- Heart disease	0,078 (0,007-0,919)	0,043
- Lung disease	0,020 (0,001-0,405)	0,011
- Smoking	0,047 (0,004-0,573)	0,017
Constant	412,151	0,001

Table 3 shows that the factor most associated with survival in COVID-19 patients is diabetes mellitus with a variable p-value of 0.001. Followed by the lung disease variable with a p-value of 0.011, the smoker variable with a p-value of 0.017, then the gender variable with a p-value of 0.036 and finally the heart disease variable with a p-value of 0.043. The risk of death of COVID-19 patients in patients with diabetes mellitus is 63.20%.

4. Discussion

Age

The results of this study are in line with research in Mexico which aims to describe the main clinical characteristics of COVID-19 and the contribution of chronic comorbidities to COVID-19, the results show that case fatality rates increase with age Thus, age is one of the major independent risk factors for COVID-19 patient mortality.[8]

Recent evidence suggests that while younger subjects may be more susceptible to infection, lower angiotensin converting enzyme-2 (ACE2) levels in older patients may promote more severe clinical behavior of COVID-19. Furthermore, patients with more aggressive clinical behavior of COVID-19 are more common in older age groups and may progress to ARDS. In line with studies conducted in Italy, ARDS was observed in the majority of patients (96.8% of cases) dying in the hospital.[9] Notably, ARDS has been found to be higher in the elderly as well as in subjects with acute impairment of cardiac, hepatic and renal function. Older adults are more likely to become seriously ill from COVID-19. More than 80% of COVID-19 deaths occur in people over 65 years old, and more than 95% of COVID-19 deaths occur in people over 45 years old.[10]

Gender

COVID-19 patients who died were more male than female in 41 out of 47 countries with an overall COVID-19 case fatality ratio approximately 2.4 times higher in males.[11] Male COVID-19 patients have three times the risk of requiring intensive care unit (ICU) admission (OR = 2.84; 95% CI = 2.06, 3.92) and a higher likelihood of death (OR = 1.39; 95% CI = 1.31, 1.47) compared to females.[12] In addition, a study in Mexico that aimed to determine the survival of COVID-19 patients with multicomorbid results showed that patients without comorbidities, younger people and women were more likely to survive.[13]

Research on COVID-19 patients in Wuhan City using survival analysis, also found that the high risk of death of severe COVID-19 patients was associated with old age, male gender, and comorbidities.[14] Sex differences in the innate and adaptive immune systems are thought to be the cause. In the adaptive

immune system, women have higher numbers of CD4+ T cells, more cytotoxic activity of strong CD8+ T cells, and increased immunoglobulin-producing B cells compared to men and are thus presumed to have better resistance.[15] Women produce more type 1 interferon (IFN), a potent antiviral cytokine, at receptor 7 that senses viral RNA than men which is important for the initial response in COVID-19.[16]

Another biological factor can be attributed to angiotensin-converting enzyme (ACE2) concentrations where blood levels in men are higher than women. ACE 2 facilitates SARS-CoV-2 virus entry and human-to-human transmission and allows the coronavirus to infect healthy cells. Estradiol may affect the expression of ACE2 by favoring ACE2 located on chromosome X147 which may make it susceptible to escape X inactivation in females thus aiding a stronger immune system in females.[17]

Diabetes mellitus

COVID-19 patients with diabetes ranked as the second largest number of comorbidities.[18,19] Data obtained from the Indonesian COVID-19 Task Force showed diabetes mellitus as the second most common comorbid condition (35.6%) after hypertension (49.9%). COVID-19 patients with diabetes mellitus have a worse prognosis after infection.[20] The increased risk of death is 8.3 times greater than those without diabetes mellitus.[21] The risk of additional length of stay and the possibility of ICU treatment is also almost three times higher in these patients.[19]

Research in Italy found that 36% of deaths in COVID-19 patients were related to diabetes mellitus previously suffered by the patient.[9] The comorbidity of diabetes mellitus in COVID-19 patients is allegedly able to stimulate the occurrence of hyperglycemia conditions in patients which can further modulate immune and inflammatory responses, resulting in an increase in disease severity and even the possibility of death in these patients.[21] Hyperglycemia stimulates viral proliferation through the production of mitochondrial oxygen species and activation of hypoxia-induced factors.[22] In addition, diabetes mellitus causes a decrease in adaptive immunity by inhibiting neutrophil chemotaxis, phagocytosis, and killing of intracellular microbes. In the early stages of the disease, abnormal values of cytokines, including interleukin 6 (IL-6) in serum, are higher in severe cases than in mild cases, which is reflected in the laboratory features of COVID-19 patients with diabetes. IL-6 is produced by macrophages and TH2 cells that fight infection and autoimmunity by inducing B lymphocyte proliferation and promoting T lymphocyte proliferation and activation.[23]

Inflammatory storms or cytokine storms due to viral invasion lead to increased activation of the monocyte macrophage system characterized by a significant increase in serum ferritin often found in diabetic patients which ultimately leads to rapid COVID-19 damage.[24] Excessive systemic inflammatory response can lead to systemic endothelial impairment (endotheliopathy) and hypercoagulable state which increases the risk of systemic macrotrombosis and microthrombosis. The manifestation of macrotrombosis can be venous thromboembolism (e.g. deep vein thrombosis and pulmonary embolism) or arterial thromboembolism (e.g. stroke). Microthrombosis plays a role in the process of ARDS and multi-organ failure.[25]

Hypertension

The results of this study are in line with a UK study aimed at examining the relationship between preinfection blood pressure control and COVID-19 outcomes where no relationship was found between blood pressure control and outcomes in COVID-19 patients. In that study, the primary outcome was death within 28 days of COVID-19 diagnosis. Multivariable logistic regression was used to examine the association between blood pressure control and outcomes. The results showed that out of 4277

patients, 877 died within 28 days. Individuals with uncontrolled stage 1 hypertension had lower odds of COVID-19 death (odds ratio, 0.76 [95% CI, 0.62-0.92]) compared to patients with well-controlled hypertension.[26] The absence of an association between hypertension and the risk of death in COVID-19 patients may be due to other risk factors, such as end-organ damage or pre-existing cardiovascular disease.[27] This supports a poor prognosis in COVID-19 patients, not because of hypertension in patients but because of other disease conditions that these patients have.

Heart disease

The results of this study are in line with a UK study that aimed to provide a comprehensive review of the clinical course of COVID-19, its comorbidities, and mechanistic considerations for future therapies. The results revealed that COVID-19 mainly affects the lungs, causing interstitial pneumonitis and acute respiratory distress syndrome (ARDS), also affecting multiple organs, especially the cardiovascular system. The risk of severe infection and death increased with increasing age and male gender. Mortality increases in association with comorbidities of cardiovascular disease, diabetes, chronic lung disease and cancer.[28]

Although the main target of SARS-CoV-2 is the respiratory tract, cardiovascular mechanisms can be involved in many other ways.[29] SARS-CoV-2 infection is developed by the activation of spike proteins by the angiotensin-converting enzyme 2 (ACE2) receptor in humans to trans-membrane protease serine-2 (TMPRSS2).[30] Angiotensin-converting enzyme catalyzes the regulation of angiotensin II (Ang II) and therefore plays a key role in cardiorenal and circulatory strain control. Overactivity of the renin-angiotensin framework contributes to cardiovascular damage. ACE2 is known to limit the movement of the renin-angiotensin framework by converting Ang II into the vasodilator Ang I-7. Furthermore, ACE2 can adjust cardiac contractility, inhibit cardiovascular Ang II levels, and support apoptotic qualities triggered by direct hypoxia highlighting work for ACE2 inferred peptides in cardiovascular capacity guidelines.[31]

Renin-angiotensin overactivity is involved in the pathophysiology of persistent cardiovascular damage. Viral diseases can severely affect the cardiovascular system, causing widespread harm from severe coronary conditions, myocardial despair triggering cardiovascular damage, or arrhythmias and myocarditis/pericarditis.[32] Patients with cardiovascular diseases including heart failure are particularly defenseless against infectious diseases of the upper and lower respiratory tract causing even more serious harm to them.[33]

Kidney disease

These results are in line with research conducted retrospectively on 419 COVID-19 patients with end stage renal disease (ESRD) who were admitted to New York hospitals in the period March 1 to May 27, 2020 where it was found that COVID-19 patients with ESRD had a higher hospital mortality rate than patients who did not have ESRD comorbidities (31.7% vs 25.4%), OR 1.38, 95% CI 1.12-1.70).[34] Patients with ESRD have a decreased immune system and carry significant comorbid conditions that are currently considered risk factors for COVID-19 severity, such as diabetes mellitus, heart disease, and obesity.[5]

Those with kidney disease have a greater risk of mortality compared to those without kidney disease.[35] In-hospital mortality rates for patients with renal disorders are significantly higher, including elevated baseline serum creatinine, elevated baseline BUN, proteinuria, hematuria, and AKI ($P < 0.001$).[36] Renal disease patients often have elevated creatinine values. Elevated baseline serum creatinine indicates higher leukocyte counts, lower lymphocyte and platelet counts, coagulation pathway abnormalities,

prolonged activated partial thromboplastin time and higher D-dimer. In addition, the percentage of patients with elevated procalcitonin, and aspartate aminotransferase and lactose dehydrogenase levels were also higher in patients with elevated baseline serum creatinine.[36]

Lung disease

People living with lung diseases such as chronic obstructive pulmonary disease (COPD), asthma, pulmonary fibrosis and lung cancer are at greater risk of serious illness if infected. The virus focuses its attack on structures and tissues involved with the respiratory system. The resulting complications not only lead to severe pneumonia, but also ARDS (acute respiratory distress syndrome) which prevents lung tissue from getting enough oxygen. Lung diseases that have a higher risk of COVID-19 complications include asthma and chronic obstructive pulmonary disease, which includes chronic bronchitis or emphysema.

One lung disease that is a factor in increasing the severity of COVID-19 is Chronic Obstructive Pulmonary Disease (COPD). A study of 1590 COVID-19 patients in China showed that COPD patients with COVID-19 were 2,681 times more likely to worsen, be admitted to the ICU or use mechanical ventilation, and even die, which would be more aggravated if they were older and also had a history of smoking (95% CI 1,424-5,048; p=0.002). In addition, 62.5% of severe cases occurred in patients with a history of COPD (compared to only 15.3% in non-severe cases) and 25% of patients who died were COPD patients (compared to only 2.8% in survivors).[37] Another study found similar, if statistically weaker, differences in COPD rates between ICU and non-ICU hospitalizations (8.3% versus 1.0%; p=0.054), severe and non-severe cases (4.8% versus 1.4%; p=0.026), and between non-survivors and survivors (7% versus 1%; p=0.047).[38]

A receptor on the cell surface called Angiotensin converting enzyme 2 (ACE2) on the body makes it easier for SARS-CoV-2 to enter and adhere to cells.[39] The strong binding affinity based on biochemical interaction studies and crystal structure analysis between the spike proteins (which are shaped like spikes that stick to the surface) of the SARS-CoV virus and human ACE2 will help the SARS-CoV virus enter the host cell. The SARS-CoV-2 virus can recognize the human ACE2 receptor more efficiently, leading to a higher ability of SARS-CoV2 to transmit from human to human (39). ACE2 expression in COPD patients is significantly increased. In addition, the blood flow in COPD patients contains less oxygen, as well as COVID-19 patients when invading the lungs. If COPD patients are infected with COVID 19, they will be at greater risk of breathing difficulties and more susceptible to pneumonia or lung failure.[30]

Smoking history

Smoking can increase the risk of negative health effects, including severe illness and death, among those infected with COVID-19, as well as lung disease. A metanalysis study showed the risk of COVID-19 disease severity doubled in patients who smoked, experienced severe symptoms and were 2.5 times more likely to be admitted to the ICU, require mechanical ventilation, or die compared to non-smokers. (OR 1.98 95% CI).[40] Smoking can increase the ACE2 receptor, which has been recognized as the "entry point" of the SARS-CoV-2 virus to various organs. The effects of smoking on ACE 2 expression may increase susceptibility to COVID-19.[41]

Alcohol consumption

This study is not in line with previous research that aimed to explore the relationship between alcohol consumption and the risk of SARS-CoV-2 infection and serious clinical outcomes in patients with COVID-19. The study used a sample of 12,937 participants aged 50-83 years and showed that

alcohol consumption was not associated with the risk of SARS-CoV-2 infection, but frequent drinking (HR=1.565, 95%CI 1.012-2.419; q=.079), especially heavy drinking (HR=2.071, 95%CI 1.235-3.472; q=.054), was associated with a higher risk of death (42).[42]

The discrepancy between the results of this study and previous studies may be due to the insufficient sample size with alcohol history (9 patients out of 66 patients), which is not representative of the sample size. Acute and chronic alcohol abuse has an adverse impact on innate and adaptive immune responses, which may result in decreased resistance to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections and promote the development of COVID-19 disease.

Obesity

The results of this study are in line with a study that aimed to describe the main clinical characteristics of COVID-19 in the main social security institutions in Mexico, as well as the contribution of chronic comorbidities to COVID-19. The results showed that case fatality increased in the presence of obesity.[8] New data report more severe symptoms and even a negative prognosis for obese patients. A growing body of evidence links obesity to COVID-19 and a number of mechanisms from attenuation of immune system activity to chronic inflammation are implicated. Lipid peroxidation creates reactive lipid aldehydes which in patients with metabolic disorders and COVID-19 will affect their prognosis.[43]

5. Conclusion

The survival of COVID-19 confirmed patients is influenced by age, gender, diabetes mellitus, heart disease, kidney disease, lung disease, smokers, alcohol consumption, and obesity. The limitation in this study is that the research is retrospective so it is a little difficult to identify confounding factors.

6. References

1. Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, et al. Extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. The COVID-19 Resource Centre - inc. 2020;(1):19–21.
2. Monárrez-Espino J, Zubía-Nevárez CI, Reyes-Silva L, Castillo-Palencia JP, Castañeda-Delgado JE, Van-Oostdam ASH, et al. Clinical factors associated with COVID-19 severity in mexican patients: Cross-sectional analysis from a multicentric hospital study. Healthc. 2021;9(7).
3. World Health Organization [WHO]. Coronavirus. 2021; Available from: https://www.who.int/health-topics/coronavirus#tab=tab_1
4. Kementerian Kesehatan Republik Indonesia. Dua pasien positif Covid-19 dirawat di RSPI Sulianti Saroso [Internet]. 2020.Availablefrom:https://www.kemkes.go.id/article/view/20030200009/dua-pasien-positif-covid-19-dirawat-di-rspi-sulianti-saroso.html
5. Docherty AB, Harrison EM, Green CA, Hardwick H, Pius R, Norman L, et al. Features of hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. 2020.
6. Dehingia N, Raj A. Sex differences in COVID-19 case fatality: Do we know enough? Lancet Glob Heal [Internet]. 2021;9(1):e14–5. Available from: http://dx.doi.org/10.1016/S2214-109X(20)30464-2
7. Hamer M, Kivimäki M, Gale CR, Batty GD. Lifestyle risk factors, inflammatory mechanisms, and COVID-19 hospitalization: A community-based cohort study of 387,109 adults in UK. 2020;(January).

8. Escobedo-de J, Rasc A, Gonz E, Fern E, Borja-bustamante P, Santill A. Hypertension , diabetes and obesity , major risk factors for death in patients with COVID-19 in Mexico. 2021;(January).
9. Istituto Superiore di Sanità. Characteristics of SARS-CoV-2 patients dying in Italy. Report based on available data on March 30th, 2021 [Caratteristiche dei pazienti deceduti positivi all'infezione da SARS-CoV-2 in Italia]. 2021;1–11. Available from: https://www.epicentro.iss.it/coronavirus/sars-cov-2-decessi-italia
10. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients : A comparison with young and middle-aged patients. 2020;(January).
11. Sharma G, Volgman AS, Michos ED. Sex differences in mortality from COVID-19 pandemic. JACC Case Reports [Internet]. 2020;2(9):1407–10. Available from: https://doi.org/10.1016/j.jaccas.2020.04.027
12. Peckham R. COVID-19 and the anti-lessons of history. Lancet [Internet]. 2020;395(10227):850–2. Available from: http://dx.doi.org/10.1016/S0140-6736(20)30468-2
13. Bustos-Vázquez E, Padilla-González E, Reyes-Gómez D, Carmona-Ramos MC, Monroy-Vargas JA, Benítez-Herrera AE, et al. Survival of covid-19 with multimorbidity patients. Healthc. 2021;9(11):1–11.
14. Xinhuanet. China detects large quantity of novel coronavirus at Wuhan seafood market. 2020 Jan 27; Available from: http://www.xinhuanet.com/english/2020-01/27/c_138735677.htm
15. Ghazeeri G, Abdullah L, Abbas O. Immunological differences in women compared with men: overview and contributing factors. Am J Reprod Immunol. 2011;66(3):163–9.
16. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun [Internet]. 2020;11(1):1–10. Available from: http://dx.doi.org/10.1038/s41467-020-19741-6
17. Fawzy MS, Ashour H, Allah A, Shafie A, Ben N, Dahman H, et al. The role of angiotensin - converting enzyme 2 (ACE2) genetic variations in COVID - 19 infection : a literature review. Egypt J Med Hum Genet [Internet]. 2022;6. Available from: https://doi.org/10.1186/s43042-022-00309-6
18. Lukman A, Sri N, Ferdiana A. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information . 2020;(January).
19. Roncon L, Zuin M, Rigatelli G, Zuliani G. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information . 2020;(January).
20. Jian Shang, Qian Wang, Haiping Zhang, Xiaoyue Wang JW, Xiaoyue Wang JW, Youqin Yan, Yadong Gao, Jie Cheng, Ziang Li JL. The relationship between diabetes mellitus and COVID-19 prognosis: A retrospective cohort study in Wuhan, China. Elsevier Inc [Internet]. 2020;(January):2–5. Available

from:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7254017/pdf/main.pdf
21. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 2020;31(6):1068-1077.e3.
22. Sada K, Nishikawa T, Kukidome D, Yoshinaga T, Kajihara N, Sonoda K, et al. Hyperglycemia induces cellular hypoxia through production of mitochondrial ROS followed by suppression of aquaporin-1. PLoS One. 2016;11(7):1–16.
23. Tanaka T, Narazaki M, Kishimoto T. Patterns (DAMPs), which are released from damaged or dying cells in noninfectious inflammations such as burn or trauma, directly or indirectly promote inflammation. During sterile surgical operations, an increase in serum IL66 levels precedes elevation of. 2014;6(Kishimoto 1989):1–16.
24. Li Z, Wu M, Yao J, Guo J, Liao X, Song S, et al. Caution on kidney dysfunctions of COVID-19 patients. medRxiv. 2020;1–25.
25. Fahmy OH, Daas FM, Salunkhe V, Petrey JL, Cosar EF, Ramirez J, et al. Is microthrombosis the main pathology in coronavirus disease 2019 severity?—A systematic review of the postmortem pathologic findings. Crit Care Explor. 2021;3(5):e0427.
26. Sheppard JP, Nicholson BD, Lee J, McGagh D, Sherlock J, Koshiaris C, et al. Association between blood pressure control and coronavirus disease 2019 outcomes in symptomatic patients with hypertension: An observational cohort study. Hypertension. 2021;(March):846–55.
27. Salazar MR. Is hypertension without any other comorbidities an independent predictor for COVID-19 severity and mortality ? 2021;232–4.
28. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-berg FM, et al. COVID-19 and the cardiovascular system : implications for risk assessment , diagnosis , and treatment options. 2020;1666–87.
29. Xiong T, Redwood S, Chen M, Prendergast B. Coronaviruses and the cardiovascular system : acute and long-term implications. 2020;1798–800.
30. Markus Hoffmann, Hannah Kleine-Weber, Simon Schroeder, ..., Marcel A. Mu¨ ller, Christian Drosten SP hlmann, Correspondence. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. 2020;(January).
31. Crackower MA, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, et al. Angiotensin-converting enzyme 2 is an essential regulator of heart function. 2020;417(June 2002).
32. Faconti L, Chowienczyk PJ, Shah AM. Cardiovascular disease , heart failure and COVID-19. 2020;5–7.
33. Corrales-medina VF, Musher DM, Shachkina S, Chirinos JA. Acute pneumonia and the cardiovascular system. Lancet [Internet]. 2013;381(9865):496–505. Available from: http://dx.doi.org/10.1016/S0140-6736(12)61266-5
34. Ng JH, Hirsch JS, Wanchoo R, Sachdeva M, Sakhiya V, Hong S, et al. Outcomes of patients with end-stage kidney disease hospitalized with COVID-19. 2020;2507(February):1–9.
35. Wang HE, Gamboa C, Warnock DG, Muntner P. Chronic kidney disease and risk of death from infection. Am J Nephrol. 2011;34(4):330–6.
36. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int [Internet]. 2020;97(5):829–38.

Available from: https://doi.org/10.1016/j.kint.2020.03.005
37. Guan W-j, Liang W-h, Zhao Y et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Pneumologie. 2020;74(10):640.
38. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (covid-19) outbreak in china: Summary of a report of 72314 cases from the chinese center for disease control and prevention. JAMA - J Am Med Assoc. 2020;323(13):1239–42.
39. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from wuhan: An analysis based on decade-long structural studies of SARS coronavirus. J Virol. 2020;94(7):1
40. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med [Internet]. 2020;8(4):420–2. Available from: http://dx.doi.org/10.1016/S2213-2600(20)30076-X
41. Brake SJ, Barnsley K, Lu W, McAlinden KD, Eapen MS, Sohal SS. Smoking upregulates angiotensin-converting enzyme-2 receptor: A potential adhesion site for novel coronavirus SARS-CoV-2 (Covid-19). J Clin Med. 2020;9(3):841.
42. Xiude Fan, Zhengwen Liu, Kyle L Poulsen, Xiaoqin Wu, Tatsunori Miyata, Srinivasan Dasarathy, Daniel M Rotroff LEN. Alcohol consumption is associated with poor prognosis in obese patients with COVID-19: Amendelian randomization study using UK Biobank. 2020;026938.
43. Petrakis D, Margină D, Tsarouhas K, Kouretas D, Spandidos DA, Tsatsakis A. Obesity - a risk factor for increased COVID - 19 prevalence , severity and lethality (Review). 2020;9–19.