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Effect of Secondary Infections and Risk Factors on the Outcome of Covid-19 Patients in the Intensive Care Unit

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ABSTRACT

Introduction: Coronavirus Disease 2019 (Covid-19) is an infection caused by a virus with a high virulence level, which has progressively become a pandemic. Several studies have shown that risk factors and comorbidities associated with the disease can lead to severe and critical pneumonia requiring ICU treatment. This indicates that a proper understanding is needed in selecting the right therapy and determining patient prognosis. Therefore, this study aims to analyze the risk factors affecting the outcome of Covid-19 patients in the ICU of Regional General Hospital Dr. Moewardi Surakarta.

Methods: This was a retrospective cross-sectional study with a total sampling technique. The risk factors analyzed included old age, hypertension, cardiovascular disease, diabetes mellitus, Invasive Mechanical Ventilators (IMV) use, and secondary infections. Data collection was carried out by reading medical records, as well as blood and/or sputum culture results of Covid-19 patients at the study location from March-October 2020. The data obtained were then analyzed using the chi-square statistical analysis and logistic regression ($\alpha = 0.05$) with SPSS software version 21.

Results: Based on the chi-square test, ventilator type ($p<0.001$), and secondary infection ($p=0.004$) were statistically associated with the outcome of Covid-19 patients. Meanwhile, age ($p=0.739$), hypertension ($p=0.202$), cardiovascular disease ($p=0.073$), and diabetes mellitus ($p=0.124$) had no statistical relationship. The logistic regression test results showed that IMV was a risk factor for Covid-19 death and secondary infection was associated with mortality.

Conclusion: The ventilator type and secondary infection had a significant relationship with the outcome of Covid-19 patients. Furthermore, IMV use was a risk factor for mortality among infected people.

Keywords: covid-19, risk factors, outcome, ICU

INTRODUCTION

At present, the world is affected by a health disaster caused by the SARS-CoV-2 virus, commonly known as Coronavirus disease-19 (Covid-19). The disease was first detected in Hubei Province, China, in late 2019, and quickly spread across the world. On January 29, 2020, the World Health Organization (WHO) reported 6065 confirmed cases of Covid-19 worldwide, with 5997 occurring in China[1]. A day later, on January 30, 2020, it was declared a pandemic and a world health emergency by WHO[2]. The occurrence of this virus has been reported to significantly impact the health management system, economy, and socio-cultural aspects of human life, leading to changes in social behavior[3].

The SARS-CoV-2 virus is primarily transmitted through respiratory droplets, which can enter the body via the eyes, nose, or mouth while talking, coughing, or sneezing[4]. It attacks the lower respiratory tract with symptoms, such as cough, fever, and easy fatigue, as well as death in severe/critical clinical manifestations[5]. Several studies have shown that SARS-CoV-2 can cause secondary infections and

damage various organs of the body[6]. For example, a meta-analysis study by Langford et al, reported that a total of 14.3% of Covid-19 patients experienced bacterial infections[7]. A retrospective study was also carried out by Zhou et al, where 15% of affected people had secondary infections, 59% had sepsis, and 26% required ICU admission[8]. Huang et al reported that on January 2 2020, 41 Covid-19 patients suffered from pneumonia, and 29% had complications from Acute Respiratory Distress Syndrome (ARDS). Furthermore, 10% had secondary infections, 32% were treated in the ICU, and 15% died. The results also showed that the average age of affected people was 49 years, and the virus was predominantly found in males, with no report of infection in children or adolescents. A total of thirteen patients had comorbidities, such as diabetes, hypertension, and cardiovascular disease, and 38% required treatment in the ICU[9].

Antibiotic treatment is still commonly prescribed as a therapy for Covid-19, although there are limited information on its effectiveness. Some guidelines even recommend the use of empiric antibiotics as a treatment for the disease[7]. This has led to an increase in its usage in several studies, such as Zhou et al, which reported that 95% of Covid-19 patients were given the therapy[8]. However, the high use of antibiotics has raised concerns due to the potential risk of developing bacterial resistance to the drugs. This indicates that a proper understanding of the causative pathogens, risk factors, pathogenesis, and co-morbidities is very important for Covid-19 therapy. It can also help in selecting the right antibiotics to minimize the negative effects of excessive usage[7].

In Indonesia, there has been a limited number of studies on secondary infection in Covid-19, making it difficult to provide effective treatment for infected patients. The analysis of risk factors associated with morbidity and mortality for Covid-19 is also inadequate. This has raised several concerns since comorbidities, such as diabetes mellitus, hypertension, and cardiovascular disease are often found in patients.

Therefore, this study aims to analyze the types of secondary infections and risk factors associated with clinical outcomes in Covid-19 patients in the ICU of Regional General Hospital Dr. Moewardi Surakarta.

METHOD

This is a retrospective cross-sectional study from medical record data of confirmed Covid-19 patients aged 18 years, who were treated at the ICU Regional General Hospital Dr. Moewardi Surakarta from March-October 2020. Incomplete medical record data were then excluded from this study.

This study was ethically approved by the Health Research Ethics Commission at Regional General Hospital Dr. Moewardi Surakarta with reference number 629/V/HREC/2021.

Data collection was carried out using the total sampling method, where all patients who met the inclusion criteria were included. The independent variables in this study consisted of age, hypertension, cardiovascular disease, diabetes, type of ventilator, and secondary infection, while the patient's clinical outcome was the dependent variable.

Age was classified into three categories, namely younger (18-35 years), middle-aged (36-55 years), and older (> 55 years) adults. Furthermore, hypertension was characterized by systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. This variable was then classified into yes (hypertensive sufferers) and no (non-hypertensive sufferers).

Cardiovascular disease is a condition caused by impaired heart or blood vessel function, and it was classified into the yes (suffers/has a history of cardiovascular disease) and no (does not suffer/has a history of cardiovascular disease) categories.

Diabetes was due to high blood sugar levels characterized by GDP ≥ 126 mg/dL or GDS ≥ 200 mg/dl or TTG ≥ 200 mg/dL or A1C ≥ 6.5%, and it was classified into yes (diabetics) and no (non-diabetics).

This study used two types of ventilators, namely Non-Invasive Ventilators (NIV) and Invasive Mechanical Ventilators (IMV).

Secondary infections were co-infections often caused by non-virulent pathogens, particularly bacteria. In this study, bacterial infections were categorized based on the resistance to antibiotics from blood or sputum culture results. The categories included no secondary, Non-Multidrug resistance organism (MDRO), and MDRO infections. Furthermore, MDRO or multidrug-resistant organisms were bacteria that were resistant to at least one type of antibiotic from ≥ 3 classes of antibiotics[11].

Patient clinical outcomes were the impact of certain interventions in the form of negative conversions or death.

The independent and dependent variables were then analyzed using bivariate and multivariate analyzes. Bivariate analysis was performed using the chi-square test to determine the relationship of each independent variable to the dependent variable, while the multivariate was carried out using the logistic regression test technique. The p-values < 0.05 on the chi-square were considered statistically significant. The logistic regression test was performed on variables with a p-value <0.25. and was considered significant if a p-value <0.05 was obtained.

RESULT

Study Result Data

Table 1. Characteristics of Sample Data

Characteristics	n	%
Age		
Younger adult	9	6.5
Middle-aged adult	70	50.3
Older adult	60	43.2
Hypertension		
No	84	60.4
Yes	55	39.6
Cardiovascular Disease		
No	69	49.6
Yes	70	50.4
Diabetes		
No	79	56.8
Yes	60	43.2
Type of ventilator		
NIV	86	61.9
IMV	53	38.1
Secondary Infection		
No	119	85.6
Non-MDRO	3	2.2
MDRO	17	12.2

Based on Table 1, a total of 139 patients met the inclusion and exclusion criteria, of which 70 were aged 36-55 years (50.3%). Furthermore, the majority of them did not experience hypertension (60.4%), diabetes (56.8%), and secondary infection by antibiotic-resistant bacteria (85.6%). The results also showed that there was no significant difference between patients with and without a history of cardiovascular disease, namely 70 and 69, respectively. The most used type of ventilator was NIV by 86 participants, accounting for 61.9% of the total population.

Analysis Result Data

Bivariate analysis was carried out on the data obtained from the chi-square test to determine the relationship between each independent variable and the patient's clinical outcome, as shown in Table 2.

Table 2 shows that the type of ventilator and secondary infection have a statistically significant relationship with the clinical outcomes of Covid-19 patients. The type of ventilator variable had a p-value <0.001 with an OR (CI) of 22.174 (5.073-96.922), indicating that it had a significant relationship with the dependent variable. Furthermore, the use of IMV increased the risk of death among people with the disease.

Table 2. Results of Chi-square Bivariate Analysis

	Outcome		p-*value*	Des.	OR (CI)
	Healed n(%)	Die n(%)			
Age					
Younger adult	2 (1.5)	7 (5)	0.739	Not significant	-
Middle-aged adult	23 (16.5)	47 (33.8)			
Older adult	17 (12.2)	43 (31)			
Total	42 (30.2)	97 (69.8)			
Hypertension					
No	22 (15.8)	62 (44.6)	0.202	Not significant	-
Yes	20 (14.4)	35 (25.2)			
Total	42 (30.2)	97 (69.8)			
Cardiovascular Disease					
No	16 (11.5)	53 (38.1)	0.073	Not significant	-
Ya	26 (18.7)	44 (31.7)			
Total	42 (30.2)	97 (69.8)			
Diabetes					
No	28 (20.1)	51 (36.7)	0.124	Not significant	-
Yes	14 (10.1)	46 (33.1)			
Total	42 (30.2)	97 (69.8)			
Ventilator Type					
NIV	40 (28.8)	46 (33.1)	<0.001	Significant	22.174 (5.073-96.922)
IMV	2 (1.4)	51 (36.7)			
Total	42 (30.2)	97 (69.8)			
Secondary Infection	30 (21.6)		0.004	Significant	0.256 (0.098-0.667)
Nothing	2 (1.4)	88 (63.3)			
Non-MDRO	10 (7.2)	1 (0.8)			
MDRO	42 (30.2)	8 (5.7)			
Total		97 (69.8)			

The secondary infection had a p-value of 0.004 with an OR (CI) of 0.256 (0.098-0.667), indicating the presence of a significant association. The results of blood culture or sputum samples are presented in Table 3.

The age, hypertension, cardiovascular disease, and diabetes variables were not significantly related to the outcome of Covid-19 patients with p-values of 0.739, 0.202, 0.073, and 0.124, respectively. Subsequently, a multivariate analysis was carried out on variables with a p-value <0.25, namely hypertension, cardiovascular disease, diabetes, type of ventilator, and secondary infections

Based on Table 4, the type of ventilator and secondary infection had a significant association with the outcomes of Covid-19 patients with p-values of <0.001 and 0.003, respectively.

Table 3. Distribution of Bacterial Types that Cause Secondary Infections

Antibiotics	Resistance (%)	Not Resistance (%)
Macrolides		
Erythromisin	0	2 (100)
Clindamisin	0	2 (100)
Penicillin		
Amoxicillin	0	2 (100)
Ampisilin	2 (100)	0
Penisilin-G	0	2 (100)
β lactam and β-*lactamase inhibitor*		
Ampisilin-sulbactam	0	2 (100)
Amoxiclav	0	2 (100)
Carbapenem		
Meropenem	0	2 (100)
Doripenem	0	2 (100)
Cephalosporins		
Cefazolin	0	2 (100)
Cefuroxime	0	2 (100)
Ceftriaxone	1 (50)	1 (50)
Cefixime	0	2 (100)
Cefepime	0	2 (100)
Ceftazidime	0	2 (100)
Aminoglycosides		
Gentamisin	1 (50)	1 (50)
Amikasin	0	2 (100)
Quinolones		
Ciprofloxacin	1 (50)	1 (50)
Levofloxacin	0	2 (100)
Tetracycline	0	2 (100)
Cotrimoxazole	1 (50)	1 (50)

Table 4. Results of Logistic Regression Multivariate Analysis

	Coefficient	p-*value*	OR (CI)
Hypertension	-0,353	0,489	0,702 (0,258-1,913)
Cardiovascular Disease	-0,700	0,159	0,496 (0,187-1,317)
Diabetes	0,722	0,131	2,058 (0,806-5,254)
Ventilator Type	3,518	<0,001	33,726 (6,508-174,784)
Secondary Infection	-2,140	0,003	0,118 (0,029-0,483)
Constant	0,641	0,092	1,899

DISCUSSION

The analysis results of the relationship between age and outcome showed that the majority of patients died in the categories of young, middle-aged, and old adults. This finding indicated that there was no significant relationship between age and clinical outcome in Covid-19 patients. The results of this study are consistent with Ramatillah and Isnaini (2021), who obtained similar results. Several studies also reported that age as an independent variable was not a risk factor for outcomes among infected people[12].

However, the risk of mortality for Covid-19 patients increased with the presence of comorbidities [12]. The older adult category was not a risk factor for mortality in this study because the majority of sufferers in Indonesia were middle-aged adults with an age range of 31-45 years (31.4%), as of 6th August 2020[12]. This was because an average Indonesian was in the middle-aged adult category characterized by high mobility, thereby increasing the potential for infection[13].

Based on the analysis of the association between hypertension and outcome in Covid-19 patients, the majority of infected individuals died, including those with and without the comorbidity. This finding showed that hypertension has no significant relationship with outcomes. In this study, a total of 57.1% of patients who died with the comorbidity were aged >55 years, while 82.9% had cardiovascular disease. These results are in line with Zhong et al (2021) that hypertension did not affect the outcomes in Covid-19 patients. However, all hypertensive individuals who died were accompanied by at least one other risk factor[14]. Sun et al (2021) also stated that hypertension alone was not a risk factor, although ARDS or respiratory failure had occurred[15]. Hypertension was reported to have a significant association with outcomes in Covid-19 patients when accompanied by other factors[15]. In this study, the patients treated in the ICU had severe or critical conditions that can develop into ARDS. A previous study revealed that the occurrence of ARDS/comorbid respiratory failure, such as hypertension does not increase mortality[15]

The chi-square test results showed that there was no significant relationship between cardiovascular disease and the outcomes of Covid-19 sufferers. This finding is inconsistent with Harrison, et al (2021) that the association between both variables was a risk factor with twice the risk of death compared to those without cardiovascular disease[16]. Furthermore, these results are in line with Sabatino, et al (2020), who obtained similar findings. In this study, the mechanism of death of cardiovascular disease patients as an independent variable was unknown, hence, further studies are still needed.

The results of the relationship analysis between diabetes and outcomes in Covid-19 patients showed that the majority of patients died with or without the comorbidity. This indicated that there was no statistically significant relationship between both variables. The results of this study are consistent with Gupta et al (2020), who reported similar findings[18]. Tadic et al (2021) also stated that diabetes was not related to mortality in Covid-19 patients[19]. Some factors that were rarely considered, but can affect outcomes in diabetic patients included the duration of diabetes, diabetes-related complications, therapy, and blood sugar control during infection[20]. Patients admitted to the ICU in this study had severe or critical conditions that can develop into ARDS. A previous study reported that the presence of ARDS/comorbid respiratory failure, such as diabetes mellitus does not increase mortality[15].

Based on the analysis results of the type of ventilator and outcome, the majority of patients died using both IMV and NIV. However, the results of the chi-square test with a p-value <0.001 and OR (CI) of 22.174 (5.073-96.922) showed that there was a significant relationship between both variables. The use of the IMV increased the risk of death among people infected. The results of this study are consistent with Chang et al (2021) that the usage of IMV was associated with mortality in the ICU. Some of the potentials that can increase mortality due to this type of ventilator included the use of too fast or late intubation, staff who are less trained or exhausted, as well as complications, such as secondary infections and Ventilator-associated Pneumoniae (VAP) [21,22]. The incidence of secondary infection in IMV patients who had poor outcomes only occurred in seven out of 97 (7.2%) sufferers who died. In the "Covid-19 Handling Guidelines Edition 3," it was stated that intubation was carried out only if there was a worsening or lack of improvement after the usage of the NIV, indicating late IMV installation. This was believed to be the cause of increased mortality among Covid-19 patients in the ICU Regional General Hospital Dr. Moewardi Surakarta.

The results of the study of the relationship between secondary infection and outcome found that the majority of patients who died were not accompanied by secondary infections. These results occurred

due to uneven distribution of data with the majority of patients (85.6%) not being infected, hence, equalization of data was needed for further studies. Furthermore, the results of the chi-square test showed that there was a significant relationship between secondary infection and outcome in Covid-19 patients. An odds ratio of 0.256 was also obtained with a confidence interval of 0.098-0.667, indicating that this variable was not a risk factor for death at the study location. These findings are inconsistent with Zhang et al (2020) that Covid-19 patients with secondary infection had a higher mortality rate compared to others[23]. The results also showed that secondary infections occurred in 22 of 38 (57.9%) patients. These variations in results were caused by the asymmetric distribution of data and the small number of secondary infections, leading to a biased assessment. Therefore, it is necessary to conduct further studies on the relationship between this variable and outcomes in Covid-19 patients. Based on the results, the antibiotics that can be given to affected people in the ICU Regional General Hospital Dr. Moewardi Surakarta included ampicillin, cefazolin, cefixime, and amikacin, as shown in Tables 4-12.

The multivariate analysis results showed that ventilator type and secondary infection had a significant relationship with the outcome of Covid-19 patients in the ICU Regional General Hospital Dr. Moewardi Surakarta.

In this study, there were several limitations, namely the use of different therapies between patients and uncontrolled bias, which can affect the results. Further studies are advised to focus on each independent variable, using a case-control or cohort design, and bias control.

CONCLUSION

Based on the results, the type of ventilator and secondary infection had a significant relationship with the outcome of Covid-19 patients in the ICU of Regional General Hospital Dr. Moewardi Surakarta. Furthermore, the use of IMV-type ventilators was a risk factor for mortality due to late installation.

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CONFLICT OF INTEREST

The authors reported no competing interests.

REFERENCES

1. WHO. Novel Corona Virus Update Background. 2020;(January).
2. Velavan TP, Meyer CG. The COVID-19 epidemic. Vol. 25, Tropical Medicine and International Health. 2020.
3. Khaedir Y. Perspektif Sains Pandemi Covid-19: Pendekatan Aspek Virologi Dan Epidemiologi Klinik. MAARIF. 2020;15(1).
4. Zhou J, Ghose B, Wang R, Wu R, Li Z, Huang R, et al. The health perceptions and misconceptions regarding COVID-19: spreading mechanism and elimination strategy in China. J Med Internet Res. 2020;

5. Ganji A, Mosayebi G, Khaki M, Ghazavi A. A Review of the 2019 Novel Coronavirus (Covid-19): Immunopathogenesis, Molecular Biology and Clinical Aspects. J Arak Univ Med Sci. 2020;

6. Hendaus MA, Jomha FA. Covid-19 induced superimposed bacterial infection. Journal of Biomolecular Structure and Dynamics. 2020.

7. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Vol. 26, Clinical Microbiology and Infection. 2020.

8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229).

9. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223).

10. Masturoh I, Anggita N. Metodologi Penenlitian Kesehatan. 2018

11. Estiningsih D, Puspitasari I, Nuryastuti T. Identifikasi Infeksi Multidrug-Resistant Organisms pada Pasien yang dirawat di Bangsal Neonatal Intensive Care Unit (NICU) RSUP DR. Soeradji Tirtonegoro Klaten. J Manaj dan Pelayanan Farm. 2016;6(3):243–8.

12. Ramatillah DL, Isnaini S. Treatment profiles and clinical outcomes of COVID-19 patients at private hospital in Jakarta. PLoS One [Internet]. 2021;16(4 April):1–11. Available from: http://dx.doi.org/10.1371/journal.pone.0250147

13. Maiti, Bidinger. The younger age prolife of COVID-19 deaths in developing countries. J Chem Inf Model. 2020;53(9):1689–99.

14. Zhong L, Wu Y, Gao J, Zhang J, Xie Q, He H, et al. Effects of hypertension on the outcomes of COVID-19: a multicentre retrospective cohort study. Ann Med [Internet]. 2021;53(1):770–6. Available from: https://doi.org/10.1080/07853890.2021.1931957

15. Sun Y, Guan X, Jia L, Xing N, Cheng L, Liu B, et al. Independent and combined effects of hypertension and diabetes on clinical outcomes in patients with COVID-19: A retrospective cohort study of Huoshen Mountain Hospital and Guanggu Fangcang Shelter Hospital. J Clin Hypertens. 2021;23(2):218–31.

16. Harrison SL, Buckley BJR, Rivera-Caravaca JM, Zhang J, Lip GYH. Cardiovascular risk factors, cardiovascular disease, and COVID-19: An umbrella review of systematic reviews. Eur Hear J - Qual Care Clin Outcomes. 2021;7(4):330–9.

17. Sabatino J, de Rosa S, Di Salvo G, Indolfi C. Impact of cardiovascular risk profile on COVID-19 outcome. A meta-analysis. PLoS One [Internet]. 2020;15(8):1–12. Available from: http://dx.doi.org/10.1371/journal.pone.0237131

18. Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, et al. Factors Associated with Death in Critically Ill Patients with Coronavirus Disease 2019 in the US. JAMA Intern Med. 2020;180(11):1436–47.

19. Tadic M, Saeed S, Grassi G, Taddei S, Mancia G, Cuspidi C. Hypertension and COVID-19: Ongoing Controversies. Front Cardiovasc Med. 2021;8(February):6–11.

20. Leoni MLG, Lombardelli L, Colombi D, Bignami EG, Pergolotti B, Repetti F, et al. Prediction of 28-day mortality in critically ill patients with COVID-19: Development and internal validation of a clinical prediction model. PLoS One [Internet]. 2021;16(7 July):1–13. Available from: http://dx.doi.org/10.1371/journal.pone.0254550

21. Chang R, Elhusseiny KM, Yeh YC, Sun WZ. COVID-19 ICU and mechanical ventilation patient characteristics and outcomes—A systematic review and meta-analysis. PLoS One [Internet]. 2021;16(2 February):1□16. Available from: http://dx.doi.org/10.1371/journal.pone.0246318

22. Roedl K, Jarczak D, Weber CF. Mechanical ventilation and mortality among 223 critically ill patients with coronavirus disease 2019 : A multicentric study in Germany. 2020;(January).

23. Zhang H, Zhang Y, Wu J, Li Y, Zhou X, Li X, et al. Risks and features of secondary infections in severe and critical ill COVID-19 patients. Emerg Microbes Infect. 2020;9(1).

24. Burhan, E. *et al*. (2020) *Pedoman Tatalaksana Covid-19* Edisi ke-3. Jakarta, pp: 3-22.