Global Medical and Health Communication

Online submission: https://ejournal.unisba.ac.id/index.php/gmhc
DOI: https://doi.org/10.29313/gmhc.v12i3.14073

GMHC. 2024;12(3):218–226
pISSN 2301-9123 | eISSN 2460-5441

RESEARCH ARTICLE

COVID-19 Treatment Patterns in Patients with Acute Respiratory Failure at Dr. Hasan Sadikin General Hospital Bandung in 2021–2022

Enny Rohmawaty,[1] Aklila Qurrota Aini Sumardi,[2] Iceu Dimas Kulsum[3]

[1]Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Sumedang, Indonesia, [2]Faculty of Medicine, Universitas Padjadjaran, Sumedang, Indonesia, [3]Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

Abstract

Acute respiratory failure is the most common complication and cause of death in COVID-19 patients. The COVID-19 medication has yet to be discovered. COVID-19 treatment guidelines are constantly being updated. This study aims to determine the COVID-19 treatment patterns in patients with acute respiratory failure at Dr. Hasan Sadikin General Hospital Bandung in 2021–2022. This retrospective, descriptive study used systematic random sampling to examine medical records of COVID-19 patients with acute respiratory failure at Dr. Hasan Sadikin Central General Hospital between June 2021 and June 2022. Gender, age, length of stay, outcome, comorbidities, and pharmacological and non-pharmacological treatment data were analyzed by SPSS software. This study included 120 COVID-19 patients with acute respiratory failure, with the majority of patients are male (55.83%), 30–60 years old (55.83%), length of stay of 1–3 days (52.5%), and have disease severity at severe condition (43.33%) and one comorbidity (37.5%). Patients mostly received non-rebreathing oxygen mask (54.2%), antiviral remdesivir (83.3%), corticosteroid dexamethasone (76.7%), enoxaparin anticoagulants (61.7%), a combination of vitamin C, vitamin D, and multivitamins (45.8%), and two antibiotics (33.3%). Additional treatments include tocilizumab (0.8%), intravenous immunoglobulin (2.5%), and convalescent plasma (0.8%). Statistical analysis shows that patients who stay at the hospital longer, have less or no comorbidities, and are given oxygen therapy have a significant possibility of recovering. Treatments commonly prescribed to COVID-19 patients with acute respiratory failure are antivirals, corticosteroids, anticoagulants, vitamins, and antibiotics, while the administration of oxygen therapy has a significant probability of recovery.

Keywords: Acute respiratory failure, COVID-19, pattern, treatment

Introduction

Coronavirus disease 2019 (COVID-19) is a worldwide emergency due to its rapid spread and high mortality rate.[1] COVID-19 is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] The World Health Organization (WHO) declared COVID-19 a global pandemic on 11 March 2020.[3]

The primary target of the coronavirus is the human respiratory system. Patients with COVID-19 may exhibit a range of symptoms, from asymptomatic to critical, followed by acute respiratory failure.[4] Acute respiratory failure is the most prevalent complication and a leading cause of death among COVID-19 patients. For COVID-19 patients with acute respiratory failure, the mortality rate reaches 93%.[5] Patients with COVID-19 who develop acute respiratory failure had a lower quality of life compared to those who are not infected.[6]

Existing research on the management of COVID-19 with acute respiratory failure is still limited. The COVID-19 therapy guidelines are still being revised with the most recent scientific findings. Inappropriate drug administration in COVID-19 patients with acute respiratory failure can result in adverse drug reactions, increase mortality, and decrease the cost-effectiveness of treatment.[7] This study aims to identify the COVID-19 treatment patterns in patients with acute respiratory failure at Dr. Hasan Sadikin Central General Hospital Bandung in 2021–2022.

Received: 12 August 2024; Revised: 3 October 2024; Accepted: 12 December 2024; Published: 23 December 2024

Correspondence: Dr. dr. Enny Rohmawaty, M.Kes. Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran. Jln. Raya Bandung–Sumedang km 21, Sumedang 45363, West Java, Indonesia. E-mail: enny.rohmawaty@unpad.ac.id

Methods

This retrospective, descriptive study was conducted on the medical records of COVID-19 patients with acute respiratory failure at Dr. Hasan Sadikin Central General Hospital from October to November 2022, with prior approval from the Research Ethics Committee Universitas Padjadjaran, ethical exemption number 863/UN6.KEP/EC/2022.

The study's sample consisted of the entire population that met the inclusion criteria: patients diagnosed with a critical degree of COVID-19 and acute respiratory failure between June 2021 and June 2022. The total required sample size was 120, and the samples were selected using systematic random sampling (Figure 1). Medical records with insufficient information were excluded.

Data extracted from the medical record included gender, age (the patient's age recorded in the medical record when he was first admitted to the hospital), length of stay (calculated from the date of admission to the date of discharge), outcome (the patient's condition when discharged from the hospital), comorbid diseases, and treatment (pharmacological and non-pharmacological) during at the hospital. The data was analyzed using both Microsoft® Excel 2021 and IBM® SPSS® 26th version.

Results

Two hundred and seventeen of the 337 samples collected did not meet the inclusion criteria and were thus excluded from this study. A total of 120 patients' remaining data were analyzed. Table 1 showed that most patients in this study were male (55.83%) instead of female (44.17%). Most of the patients came from 30–60 years old (55.83%) and with disease severity at severe condition (43.33%). The median length of hospital stay was 2 days (range: 0–33 days), and most patients stayed there for 1–3 days (52.50%).

As shown in Table 1, in all variables, most patients died (90% of total patients of 120). Based on statistical analysis, variable length of stays showed a significant negative correlation with the outcome. It was indicated that patients who stay at the hospital longer have the probability

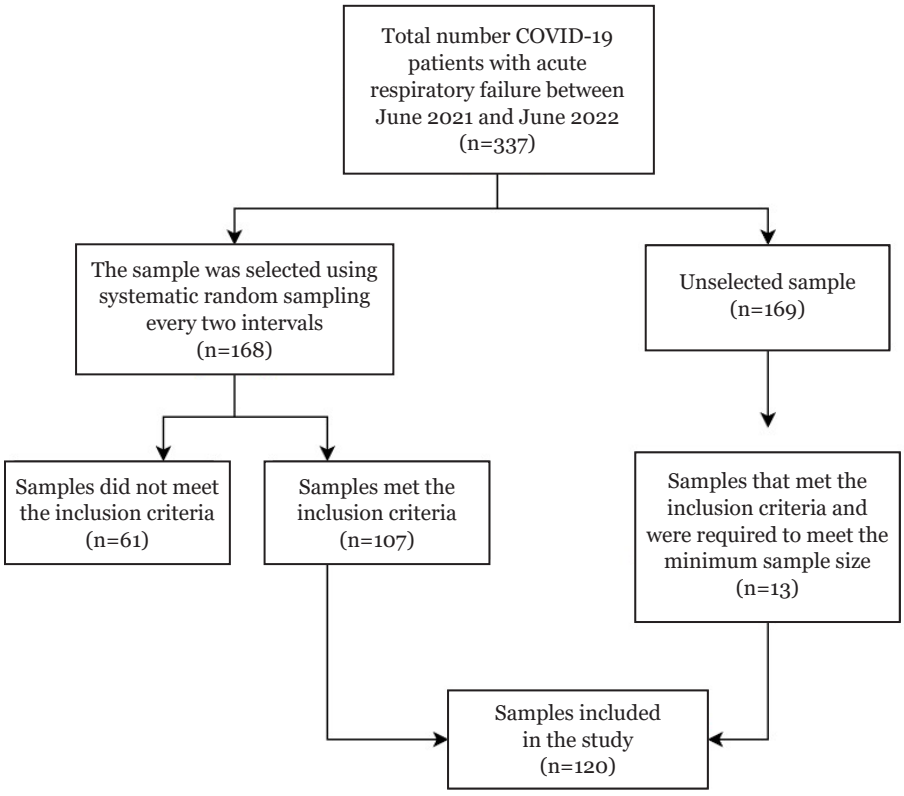

Figure 1 Study Samples Selection

Table 1 Baseline Characteristic of the Study

Variables	Outcome (n=120)		Total n (%)	Spearman Rho Test	
	Death n (%)	Recovered n (%)		Correlation Coefficient	p
Gender				−0.032	0.731
Male	58 (86.57)	6 (11.32)	67 (55.83)		
Female	47 (88.68)	9 (13.43)	53 (44.17)		
Age groups (years)				0.041	0.655
<30	3 (60.00)	2 (40.00)	5 (4.17)		
30–60	60 (89.55)	7 (10.45)	67 (55.83)		
>60	42 (87.50)	6 (12.50)	48 (40.00)		
Length of stay (days)				−0.265	0.003*
<1	13 (92.86)	1 (7.14)	14 (11.67)		
1–3	60 (95.24)	3 (4.76)	63 (52.50)		
>3	32 (74.42)	11 (25.58)	43 (35.83)		
Disease severity				0.082	0.374
Severe	50 (84.75)	9 (15.25)	59 (49.17)		
Critical	55 (90.16)	6 (9.84)	61 (50.83)		

of recovering. A similar condition was shown at variable in gender that has a negative correlation with the outcome but not significantly. On the other hand, disease severity was shown to have a positive correlation but not significantly with the outcome, which means severe disease severity has the probability of recovery.

Most patients (37.5%) had at least one comorbid condition, as shown in Table 2. Some patients had two comorbid diseases (25.8%), three comorbid diseases (4.2%), and more than three comorbid diseases (7.5%). Most of the patients who died in this study had 1 or 3 comorbid diseases. Based on statistical analysis, a number of comorbid diseases have a significant positive correlation with the outcome, which means patients with fewer or no comorbidities have a probability of recovering. The table of comorbid diseases (Figure 2) showed that hypertension (27.7%) and diabetes mellitus (23.3%) are the two most prevalent comorbid diseases among patients in this study.

Table 3 shows the patient's treatment (pharmacological and non-pharmacological). All patients received oxygen therapy with the most frequently employed devices were non-rebreathing oxygen face masks (54.2%) and invasive mechanical ventilation (21.7%). Antivirals were administered to 107 patients (89.2%), with remdesivir (83%) being the most common. Corticosteroids were administered to 105 (87.5%) patients. The most frequently used corticosteroid was dexamethasone (76.7%). Anticoagulants were administered to 108 patients (90%), with enoxaparin, a low molecular weight heparin (61.7%), the most commonly administered type. Only one patient (0.8%) was administered tocilizumab, an anti-IL-6 agent. One

Table 2 History of Comorbidities in COVID-19 Patients with Acute Respiratory Failure

Number of Comorbidities	Outcome (n=120)		Total n (%)	Spearman Rho Test	
	Death n (%)	Recovered n (%)		Correlation Coefficient	p
No comorbidities	28 (23.3)	2 (1.7)	30 (25.0)		
1 comorbidity	43 (35.8)	2 (1.7)	45 (37.5)		
2 comorbidities	28 (23.3)	3 (2.5)	31 (25.8)	0.261	0.004*
3 comorbidities	5 (4.2)	0 (0.0)	5 (4.2)		
>3 comorbidities	4 (3.3)	5 (4.2)	9 (7.5)		

Note: *significant difference at p<0.05

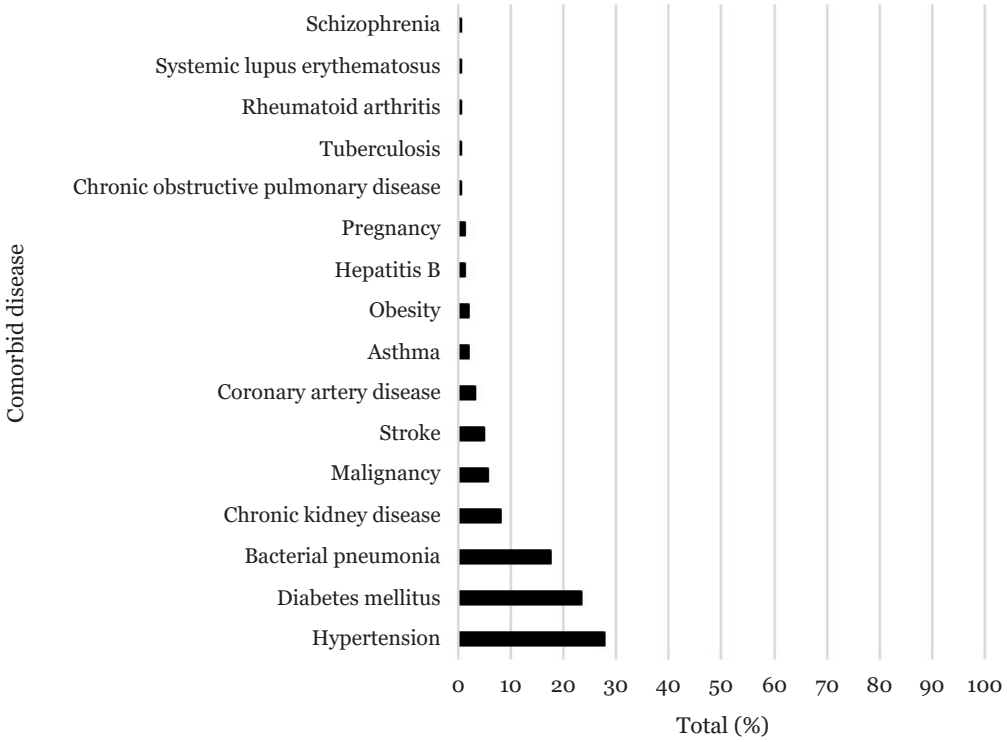

Figure 2 Comorbidities in COVID-19 with Acute Respiratory Failure

hundred and six of 120 patients (88.3%) received vitamins, with vitamin C, D, and multivitamins (45.8%) being the most common combination. Antibiotic therapy was administered to 68 patients (43.3%), and most (33.3%) were given two antibiotics.

Based on statistical analysis of the treatment of COVID-19, it was shown that oxygen therapy has a positive significant correlation with the outcome. It was indicated that the administration of oxygen therapy has the probability of recovery. A positive correlation, but not significant, with the outcome shown when administering antiviral, corticosteroid, and antibiotics to the patients means that administering these drugs has the possibility of recovery. On the other hand, a negative but insignificant correlation was shown with the administration of anticoagulants, anti-IL-6, vitamins, and supplements, which means the treatments didn't show a probability of recovery.

Table 4 shows the additional treatments administered to COVID-19 patients. Intravenous immunoglobulin (2.5%) and convalescent plasma (0.8%) were administered as adjunctive therapies to a total of 4 patients (3.3%). Based on statistical analysis, additional treatments have a negative correlation with the outcome, which means additional treatment didn't show a probability of recovery.

Discussion

Between June 2021 and June 2022, there were 337 patients (10.6%) at Dr. Hasan Sadikin General Hospital Bandung were confirmed to have COVID-19 and acute respiratory failure. COVID-19 primarily targets the respiratory system and is characterized by an immune dysregulation that causes a "cytokine storm" in the body, particularly in the lung tissue.[8]

According to subject characteristics data, the mean age in this study was 54.9±13.6 years, with the majority falling within the 30–60 age group. But it also showed that younger age can recover. Several factors, including a decline in immune function, pre-existing health conditions, and the inflammatory response, significantly impact recovery from COVID-19 across different age groups. This is comparable to a study conducted by Xu et al.[9] in China, which found that the median age of patients was 56.5 years (range: 47.5–67.8),

Table 3 Treatment of COVID-19 Patients with Acute Respiratory Failure

Treatment	Outcome (n=120)		Total n (%)	Spearman Rho Test	
	Death n (%)	Recovered n (%)		Correlation Coefficient	p
Oxygen therapy				0.298	0.001*
NRM	63 (52.5)	2 (1.7)	65 (54.2)		
IMV	23 (19.2)	3 (2.5)	26 (21.7)		
NRM+HFNC	10 (8.3)	2 (1.7)	12 (10.0)		
HFNC	6 (5.0)	2 (1.7)	8 (6.7)		
NRM+IMV	3 (2.5)	3 (2.5)	6 (5.0)		
NRM+HFNC+IMV	3 (2.5)	0 (0.0)	3 (2.5)		
Antiviral				0.130	0.157
Remdesivir	89 (74.2)	11 (9.2)	100 (83.3)		
No antiviral	13 (10.8)	0 (0.0)	13 (10.8)		
Remdesivir+favipiravir	4 (3.3)	0 (0.0)	4 (3.3)		
Favipiravir	2 (1.7)	1 (0.8)	3 (2.5)		
Corticosteroid				0.132	0.149
Dexamethasone	82 (68.3)	10 (8.3)	92 (76.7)		
No corticosteroid	15 (12.5)	0 (0.0)	15 (12.5)		
Dexamethasone+methylprednisolone	9 (7.5)	2 (1.7)	11 (9.2)		
Methylprednisolone	1 (0.8)	0 (0.0)	1 (0.8)		
Methylprednisolone+hydrocortisone	1 (0.8)	0 (0.0)	1 (0.8)		
Anticoagulant				−0.147	0.108
Enoxaparin	70 (58.3)	4 (3.3)	74 (61.7)		
UFH+enoxaparin	19 (15.8)	5 (4.2)	24 (20.0)		
No anticoagulant	11 (9.2)	1 (0.8)	12 (10.0)		
UFH	8 (6.7)	2 (1.7)	10 (8.3)		
Anti-IL-6				−0.035	0.707
No anti-IL-6	107 (89.2)	12 (10.0)	119 (99.2)		
Tocilizumab	1 (0.8)	0 (0.0)	1 (0.8)		
Vit and supplement				−0.013	0.886
Vit C+vit D+multivitamin	47 (39.2)	8 (6.7)	55 (45.8)		
Multivitamin	15 (12.5)	1 (0.8)	16 (13.3)		
Vit D+multivitamin	13 (10.8)	1 (0.8)	14 (11.7)		
No vit	14 (11.7)	0 (0.0)	14 (11.7)		
Vit C+vit D	13 (10.8)	0 (0.0)	13 (10.8)		
Vit C	2 (1.7)	0 (0.0)	2 (1.7)		
Multivitamin+vit K	1 (0.8)	1 (0.8)	2 (1.7)		
Vit C+vit D+vit K+multivitamin	1 (0.8)	1 (0.8)	2 (1.7)		
Vit C+multivitamin	1 (0.8)	0 (0.0)	1 (0.8)		
Vit B+vit C+multivitamin	1 (0.8)	0 (0.0)	1 (0.8)		
Antibiotic				0.074	0.423
No antibiotics	51 (42.5)	1 (0.8)	52 (43.3)		
2 antibiotics	36 (30)	4 (3.3)	40 (33.3)		
3 antibiotics	7 (5.8)	2 (1.7)	9 (7.5)		
4 antibiotics	5 (4.2)	3 (2.5)	8 (6.7)		
1 antibiotic	6 (5.0)	1 (0.8)	7 (5.8)		
>4 antibiotics	3 (2.5)	1 (0.8)	4 (3.3)		

Note: *significant difference at p<0.05, NRM: non-rebreathing oxygen mask, IMV: invasive mechanical ventilation, HFNC: high-flow nasal cannula, UFH: unfractionated heparin, vit: vitamin

and the majority were under 70 years.

On the other hand, based on gender, male patients outnumbered female patients. This finding is consistent with Bhatraju et al.,[10] indicating that COVID-19 with acute respiratory failure is more prevalent in males. Biological

(different immune responses in males and females) and social factors, such as a high-risk lifestyle, may contribute to the high incidence and severity of COVID-19 infection in men.[11]

The median length of stay of patients was 2 days (range: 0–33 days), in contrast to the results of the study by COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators, which showed that the median length of stay of patients was 23 days (range: 13–39 days).[12] Most of the patients in this study died (90%). When this study was conducted in 2021–2022, Indonesia experienced two peaks of COVID-19 due to the Delta and Omicron variants. Compared to previous variants, the Delta was linked with a greater risk of death. A high number of hospitalizations, a shortage of hospital beds, a lack of ICU spaces, and a lack of medical supplies were all factors that could have contributed to this period's high fatality rate and short hospital length of stay.[13]

However, based on statistical analysis, patients who stay longer in hospital have the possibility of recovering. This study is in line with the Faes et al.[14] study, which observed that in elderly patients, the median length of stay for patients who die varies between 5.7 days and 15.7 days, while for patients who recover, it varies between 15.7 days. It may be related to improved clinical experience and treatments throughout the epidemic.

The majority of patients have a comorbid disease. This study is in line with Guan et al.,[15] which states more than half of patients (52.56%) who died due to COVID-19 had more than two comorbidities, and the rest had only one comorbid. Hypertension, diabetes, and bacterial pneumonia are the most prevalent coexisting conditions. Hypertension and diabetes were the most common comorbidities in patients' deaths due to COVID-19. According to Djaharuddin et al.[16] shows that the most comorbidities were hypertension (42.31%) and diabetes (28.21%). Since patients with chronic conditions are more susceptible to COVID-19 infection, they are at increased risk for complications such as deterioration of underlying diseases, pneumonia, failure of other organs, and sepsis; consequently, their chronic diseases may become severe, or the patients may die.[17] Our findings show that comorbidities may be risk factors for mortality in COVID-19-exposed patients.

Oxygen therapy administration has more of a possibility of recovery. Non-rebreathing oxygen mask (NRM) is the most common type of oxygen therapy used by patients. Despite this, NRM users had the highest mortality rate (52.5%) among all other groups. Invasive mechanical ventilation (IMV) has a positive effect on the recovery of many patients. Based on COVID-19 management guidelines in Indonesia, NRM is used as an initial therapy, but patients with acute respiratory failure were advised to be given IMV immediately.[18] In 2021–2022, Indonesia was confronted with two peaks of the Delta and Omicron variants of COVID-19. This period characterized increased hospitalizations and a lack of medical resources, such as oxygen supplies, IMV, and high-flow nasal cannula (HFNC). This led to a greater reliance on NRM in this study.[10] This study, in line with Ospina-Tascón et al.,[19] shows that patients receiving high-flow oxygen therapy showed earlier clinical recovery than conventional low-flow oxygen therapy.

On the other hand, administering antiviral, corticosteroid, and antibiotics to the patients can also recover, but the correlation was not significant. The remdesivir group accounted for the majority of patients who exhibited improvement. This is following management guidelines which recommend using remdesivir as a first-line antiviral for COVID-19.[18] The study conducted by Al-Ardhi et al.[20] revealed that remdesivir has significant advantages over other antivirals when administered to patients with severe to critical degrees. Remdesivir reduces the viral load in the body by inhibiting the RNA-dependent RNA polymerase (RdRp) enzyme, which is involved in the replication process of SARS-CoV-2.[21]

Dexamethasone has a positive effect, as indicated by the many patients who experience improvement. This follows the COVID-19 management guidelines, which recommend dexamethasone as the first-line corticosteroid, methylprednisolone, and hydrocortisone for patients receiving oxygen therapy who are severely ill.[18] According to a study, dexamethasone was the first drug to significantly reduce the risk of death in COVID-19 patients with respiratory failure requiring oxygen therapy.[22]

Besides cephalosporin and quinolone, some antibiotics like aminoglycoside and β-lactam are commonly used, especially in combination with

four antibiotics. These findings are consistent with the Indonesian Ministry of Health guidelines for selecting antibiotics for community pneumonia.[23] According to Risa et al.[24] found that up to 60% of COVID-19 patients with acute respiratory failure had a secondary bacterial infection; therefore, using empirical antibiotics is strongly advised, especially for ventilator-dependent patients.

The other drugs, like anticoagulants, anti-IL-6, vitamins, and additional treatments, didn't show a possibility of recovery. Anticoagulant enoxaparin was administered to 74 patients (61.7%). The majority of patients treated with enoxaparin died. Unfractionated heparin (UFH) and enoxaparin have demonstrated a lower mortality rate and a more significant number of improvements compared to other treatments. This is consistent with the COVID-19 management guidelines, which recommend enoxaparin for critically ill patients and UFH for those with moderate to severe symptoms.[18] Pawlowski et al.[25] discovered that the mortality rate and risk of bleeding in COVID-19 patients who received enoxaparin were significantly lower than in those who received UFH. This may account for the high use of enoxaparin in this study.

Only one patient was administered anti-IL-6 as tocilizumab, and no improvement was observed. Guidelines for managing COVID-19 in Indonesia and The Italian Society of Infectious and Tropical Disease (SIMIT) recommend using tocilizumab in patients with severe COVID-19 or acute respiratory failure.[18]

Most patients were given vitamins in the form of a combination of vitamin C, vitamin D, and multivitamins, and eight patients (6.7%) experienced improvement. It is in line with the management guidelines that recommend a combination of vitamin C, vitamin B1, and vitamin D.[18] Most of the patients in this study obtained vitamin B1 through the ingredients in the multivitamin. In addition to the standard treatment, four patients received intravenous immunoglobulin (2.5%) and convalescent plasma (0.8%). All patients who received adjunctive therapy perished.

The research has a limitation: this study did not assess treatment duration, which may have influenced treatment outcomes. Additional research analyzing the suitability of treatment relative to hospital standard operating procedures and the duration of treatment can confirm this finding.

Conclusions

COVID-19 patients with acute respiratory failure were predominantly male, aged 30–60 years old, and had a hospital stay of 1 to 3 days. The majority presented with severe disease and at least one comorbidity. Pharmacological treatments commonly administered included antivirals, corticosteroids, anticoagulants, vitamins, and antibiotics. In addition to standard therapies, other interventions such as anti-IL-6, intravenous immunoglobulin (IVIG), and convalescent plasma were also employed. Potential therapies that may enhance patient recovery include oxygen therapy, antiviral agents, corticosteroids, and antibiotics.

Conflict of Interest

The authors have declared that no conflict of interest exists.

References

1. Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B, et al. COVID-19: immunopathogenesis and immunotherapeutics. Signal Transduct Target Ther. 2020;5(1):128.
2. Burki T. The origin of SARS-CoV-2. Lancet Infect Dis. 2020;20(9):1018–9.
3. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. Geneva: World Health Organization; 2020 [cited 2024 June 12]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
4. Surendra H, Elyazar IR, Djaafara BA, Ekawati LL, Saraswati K, Adrian V, et al. Clinical characteristics and mortality associated with COVID-19 in Jakarta, Indonesia: a hospital-based retrospective cohort study. Lancet Reg Health West Pac. 2021;9:100108.
5. 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):1054–62.
6. Valent A, Dudoignon E, Ressaire Q, Dépret F, Plaud B. Three-month quality of life in survivors of ARDS due to COVID-19: a preliminary report from a French academic centre. Anaesth Crit Care Pain Med. 2020; 39(6):740–1.
7. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). [Updated 2023 Aug 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [2024 June 16]. Available from: ncbi.nlm.nih.gov/books/NBK554776.
8. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'cytokine storm' in COVID-19. J Infect. 2020;80(6):607–13.
9. Xu W, Sun NN, Gao HN, Chen ZY, Yang Y, Ju B, et al. Risk factors analysis of COVID-19 patients with ARDS and prediction based on machine learning. Sci Rep. 2021;11(1):2933.
10. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. COVID-19 in critically ill patients in the Seattle region—case series. N Engl J Med. 2020;382(21):2012–22.
11. Takahashi T, Ellingson MK, Wong P, Israelow B, Lucas C, Klein J, et al. Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature. 2020;588(7837):315–20.
12. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021;47(1):60–73.
13. Zali A, Khodadoost M, Gholamzadeh S, Janbazi S, Piri H, Taraghikhah N, et al. Mortality among hospitalized COVID-19 patients during surges of SARS-CoV-2 alpha (B.1.1.7) and delta (B.1.617.2) variants. Sci Rep. 2022;12(1):18918.
14. Faes C, Abrams S, Van Beckhoven D, Meyfroidt G, Vlieghe E, Hens N; Belgian Collaborative Group on COVID-19 Hospital Surveillance. Time between symptom onset, hospitalisation and recovery or death: statistical analysis of Belgian COVID-19 patients. Int J Environ Res Public Health. 2020;17(20):7560.
15. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5):200054.
16. Djaharuddin I, Munawwarah S, Nurulita A, Ilyas M, Tabri NA, Lihawa N. Comorbidities and mortality in COVID-19 patients. Gac Sanit. 2021;35(Suppl 2):S530–2.
17. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91–5.
18. Burhan E, Susanto AD, Isbaniah F, Nasution SA, Ginanjar E, Pitoyo CW, et al. Pedoman tatalaksana COVID-19. 4th Edition. Jakarta: PDPI, PERKI, PAPDI, PERDATIN, IDAI; 2022.
19. Ospina-Tascón GA, Calderón-Tapia LE, García AF, Zarama V, Gómez-Álvarez F, Álvarez-Saa T, et al. Effect of high-flow oxygen therapy vs conventional oxygen therapy on invasive mechanical ventilation and clinical recovery in patients with severe COVID-19: a randomized clinical trial. JAMA. 2021;326(21):2161–71.
20. Al-Ardhi FM, Novotny L, Alhunayan A, Al-Tannak NF. Comparison of remdesivir and favipiravir - the anti-COVID-19 agents mimicking purine RNA constituents. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2022;166(1):12–20.
21. Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J Biol Chem. 2020;295(20):6785–97.
22. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med. 202;384(8):693–704.
23. Peraturan Menteri Kesehatan Republik Indonesia Nomor 2406/MENKES/ PER/XII/2011 tentang Pedoman Umum Penggunaan Antibiotik.
24. Risa E, Roach D, Budak JZ, Hebert C, Chan JD, Mani NS, et al. Characterization of secondary bacterial infections and antibiotic use in mechanically ventilated patients

with COVID-19 induced acute respiratory distress syndrome. J Intensive Care Med. 2021;36(10):1167–75.
25. Pawlowski C, Venkatakrishnan AJ, Kirkup C, Berner G, Puranik A, O'Horo JC, et al. Enoxaparin is associated with lower rates of mortality than unfractionated Heparin in hospitalized COVID-19 patients. EClinicalMedicine. 2021;33:100774.