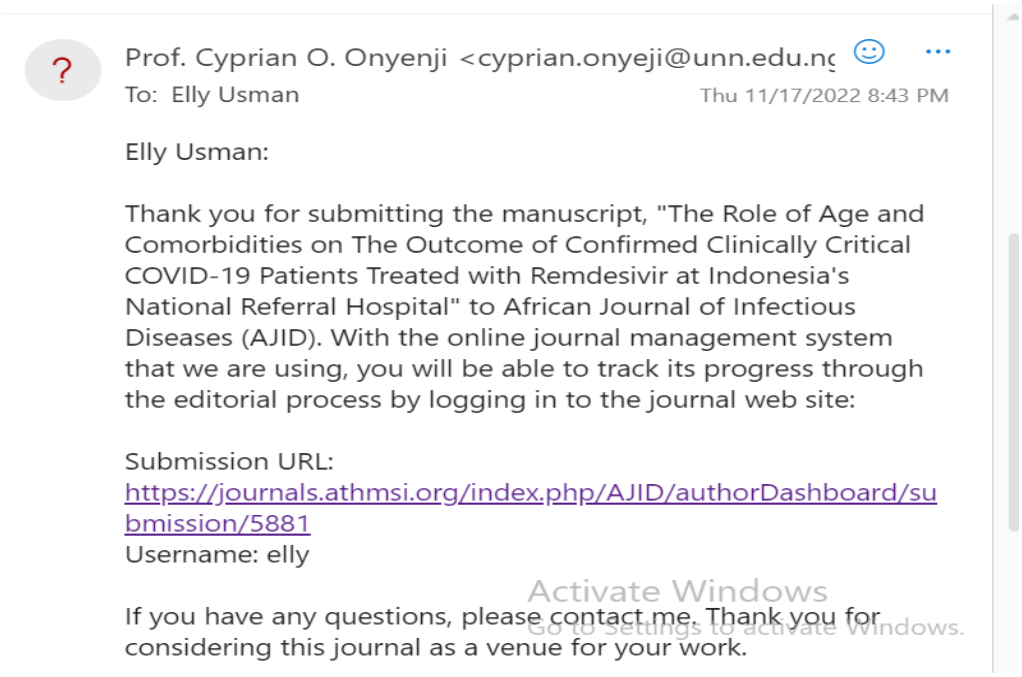
Kronologis Proses Pemasukan (Submission) Artikel hingga Terbit (Published)

Judul artikel	:	The the role of age and comorbidities on the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir at Indonesia's national referral hospital
URL	:	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9885022/
Jurnal	:	African Journal of Infectious Diseases
SJR	:	0,26 (Quartil Q4 sejak 2010 bidang medicine hingga sekarang) https://www.scimagojr.com/journalsearch.php?q=19700175226&tip=sid&clean=0
Submitted	:	17 November 2022
Review report	:	24 November 2022
Revise version	:	28 November 2022
Accepted	:	30 November 2022
Article in press	:	19 Desember 2022
Published	:	22 Desember 2022
Similarity index	:	20% (link hasil pemeriksaan turnitin https://drive.google.com/file/d/1rAxhpS1bMIM7Xe9axQEotm_u6gD6hRio/view?usp=share_link

Kronologis sebagai berikut:

1. **Manuskrip di submit pada tanggal 17 November 2022 dan mendapatkan email pemberitahuan dari editor African Journal of Infectious Diseases bahwa artikel sudah dikirim (submitted) (*Gambar 1*). Original paper terlampir (*Lampiran A*)**



Prof. Cyprian O. Onyenji <cyprian.onyeji@unn.edu.ng

To: Elly Usman

Thu 11/17/2022 8:43 PM

Elly Usman:

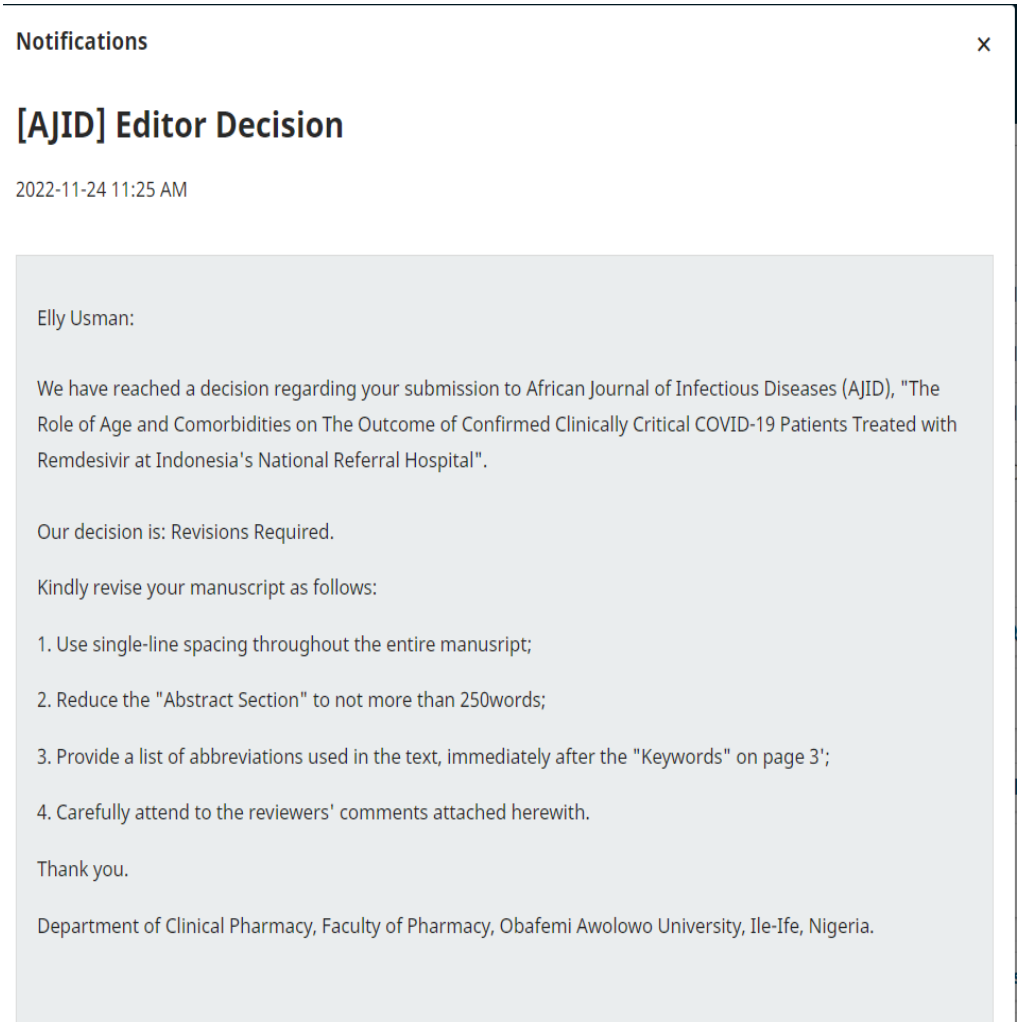
Thank you for submitting the manuscript, "The Role of Age and Comorbidities on The Outcome of Confirmed Clinically Critical COVID-19 Patients Treated with Remdesivir at Indonesia's National Referral Hospital" to African Journal of Infectious Diseases (AJID). With the online journal management system that we are using, you will be able to track its progress through the editorial process by logging in to the journal web site:

Submission URL:
https://journals.athmsi.org/index.php/AJID/authorDashboard/submission/5881
Username: elly

If you have any questions, please contact me. Thank you for considering this journal as a venue for your work.

Gambar 1. Pemberitahuan editor bahwa manuskrip submitted

2. Email pemberitahuan oleh editor terkait hasil review dari 2 orang reviewer pada tanggal 24 November 2022



Notifications ×

[AJID] Editor Decision

2022-11-24 11:25 AM

Elly Usman:

We have reached a decision regarding your submission to African Journal of Infectious Diseases (AJID), "The Role of Age and Comorbidities on The Outcome of Confirmed Clinically Critical COVID-19 Patients Treated with Remdesivir at Indonesia's National Referral Hospital".

Our decision is: Revisions Required.

Kindly revise your manuscript as follows:

1. Use single-line spacing throughout the entire manusript;

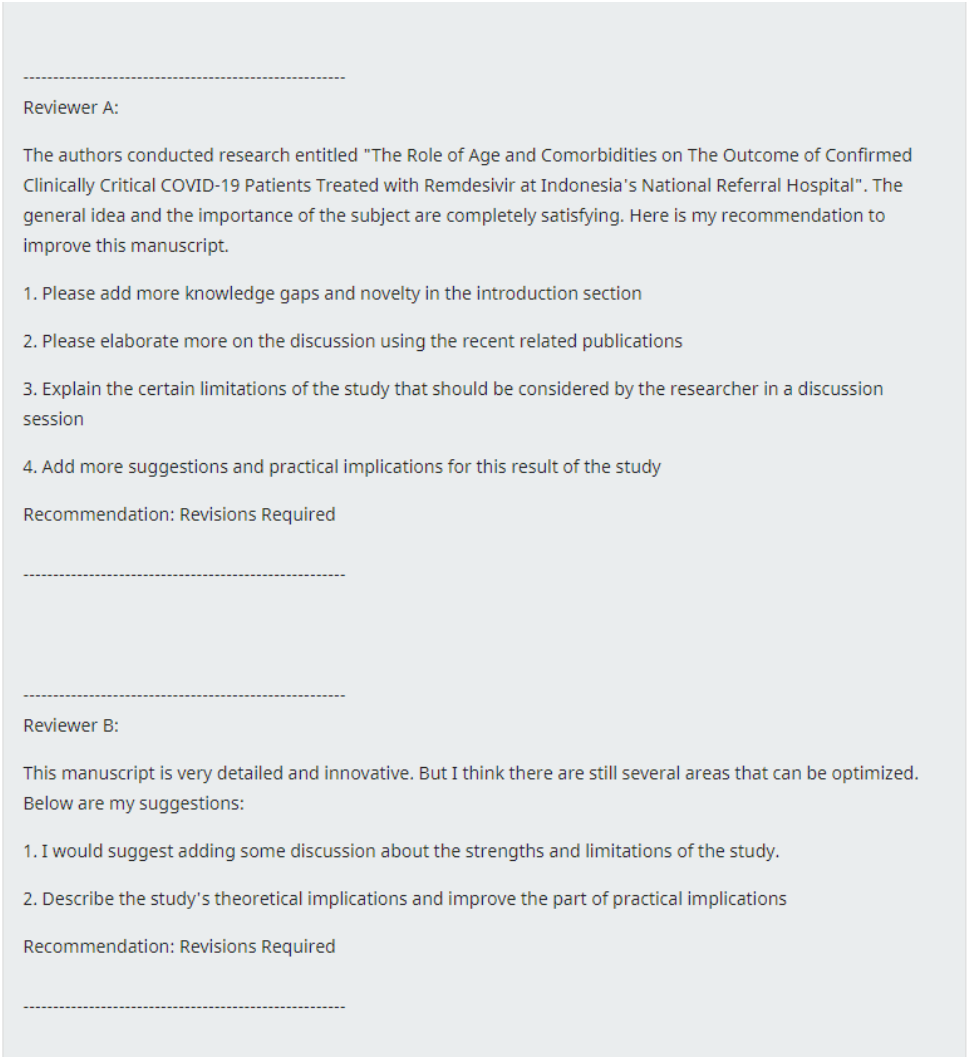
2. Reduce the "Abstract Section" to not more than 250words;

3. Provide a list of abbreviations used in the text, immediately after the "Keywords" on page 3';

4. Carefully attend to the reviewers' comments attached herewith.

Thank you.

Department of Clinical Pharmacy, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria.



Reviewer A:

The authors conducted research entitled "The Role of Age and Comorbidities on The Outcome of Confirmed Clinically Critical COVID-19 Patients Treated with Remdesivir at Indonesia's National Referral Hospital". The general idea and the importance of the subject are completely satisfying. Here is my recommendation to improve this manuscript.

1. Please add more knowledge gaps and novelty in the introduction section

2. Please elaborate more on the discussion using the recent related publications

3. Explain the certain limitations of the study that should be considered by the researcher in a discussion session

4. Add more suggestions and practical implications for this result of the study

Recommendation: Revisions Required

Reviewer B:

This manuscript is very detailed and innovative. But I think there are still several areas that can be optimized. Below are my suggestions:

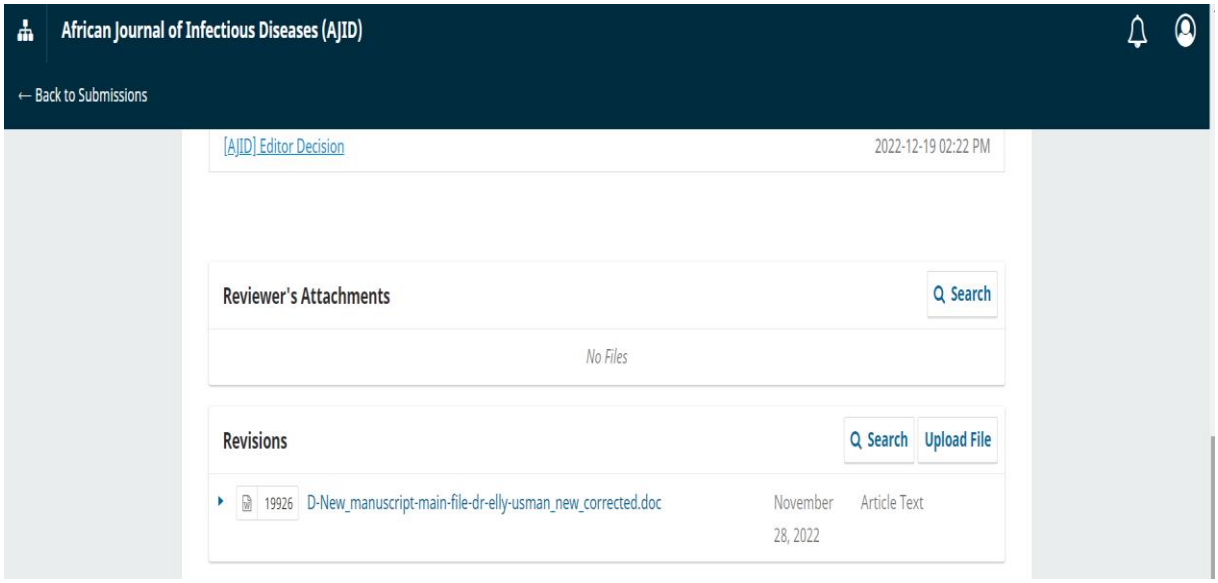
1. I would suggest adding some discussion about the strengths and limitations of the study.

2. Describe the study's theoretical implications and improve the part of practical implications

Recommendation: Revisions Required

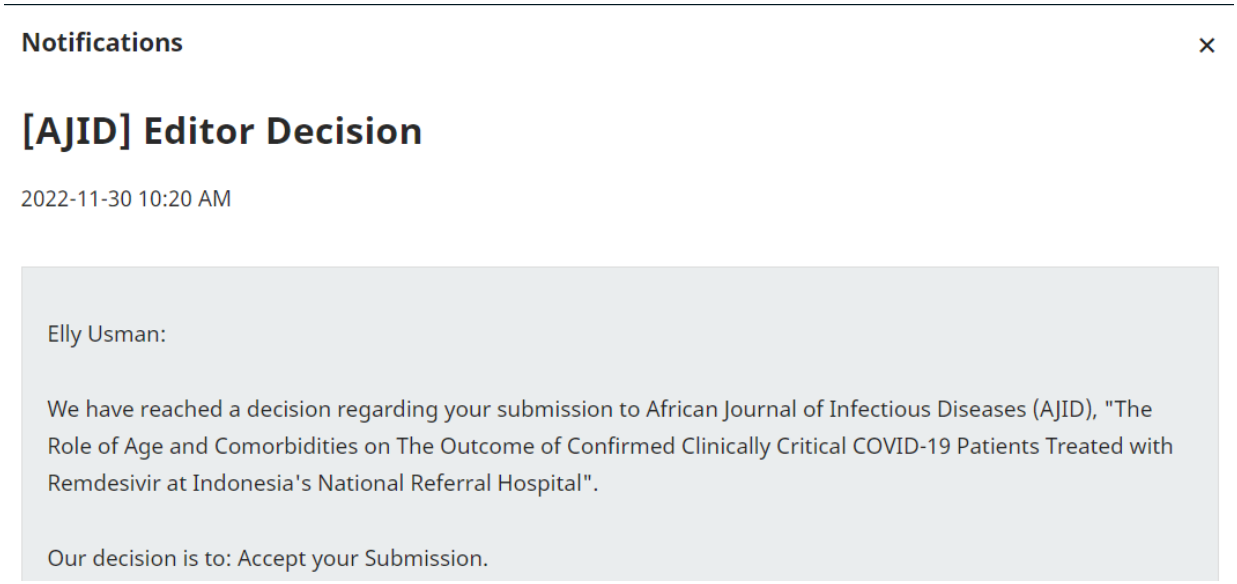
Gambar 2. Pemberitahuan editor terkait hasil review dari 2 orang reviewer

3. **Author mengirimkan perbaikan manuskrip berdasarkan hasil review dari reviewer dan melakukan resubmission ke jurnal system pada tanggal 28 November 2022. Perubahan dan penambahan pada manuskrip penelitian berdasarkan hasil review ditandai dengan tulisan bewarna highlight kuning (*Lampiran B*).**



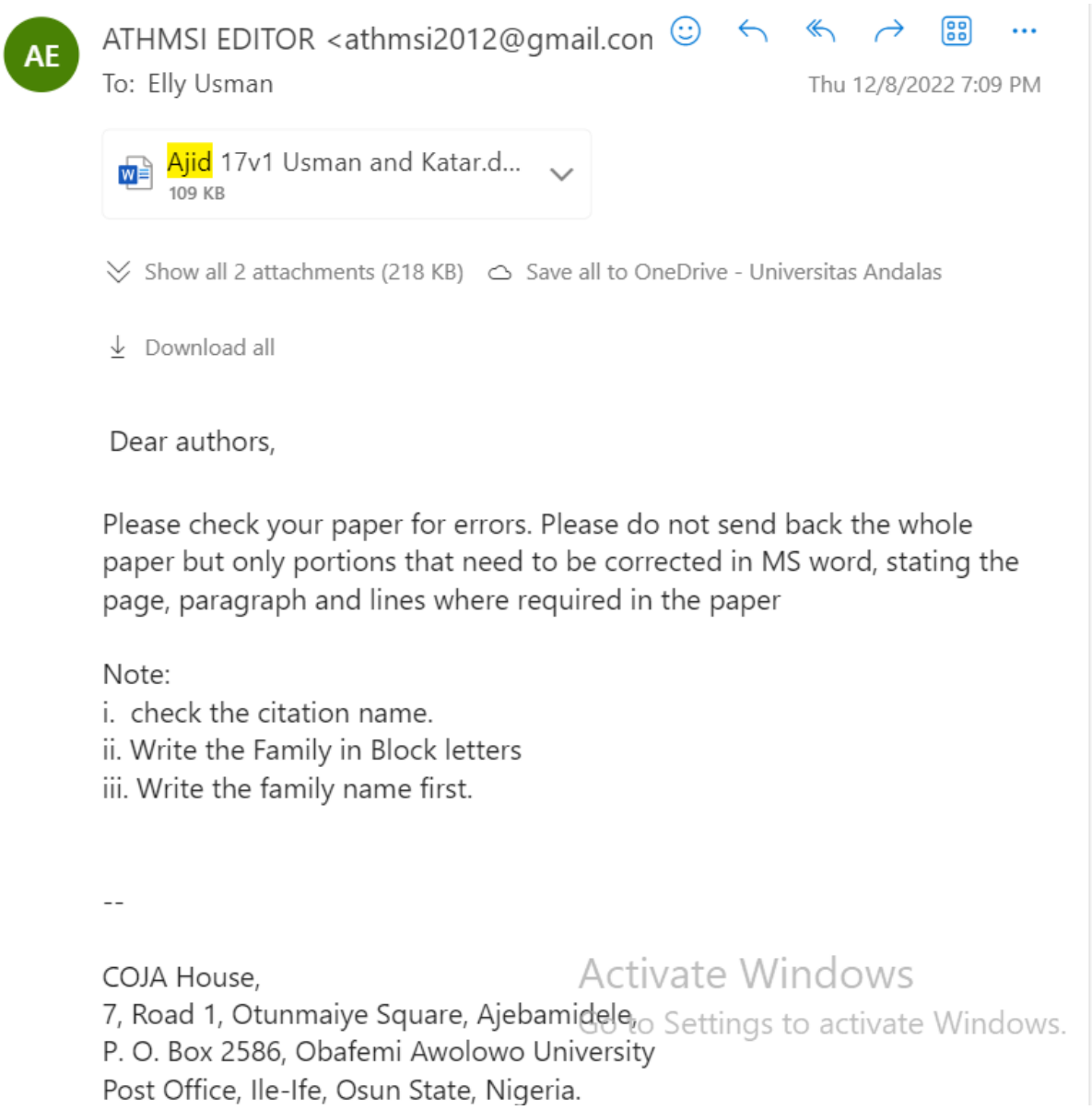
Gambar 3. Penulis mengirimkan hasil revisi berdasarkan review oleh reviewer

4. Pemberitahuan editor bahwa manuskrip diterima setelah dilakukan revisi pada tanggal 30 November 2022



Gambar 4. Pemberitahuan editor bahwa manuskrip diterima setelah dilakukan revisi

5. Pemberitahuan editor Proofreading Request pada tanggal 8 Desember 2022



AE

ATHMSI EDITOR <athmsi2012@gmail.con

To: Elly Usman

Thu 12/8/2022 7:09 PM

Ajid 17v1 Usman and Katar.d...
109 KB

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Dear authors,

Please check your paper for errors. Please do not send back the whole paper but only portions that need to be corrected in MS word, stating the page, paragraph and lines where required in the paper

Note:
i. check the citation name.
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iii. Write the family name first.

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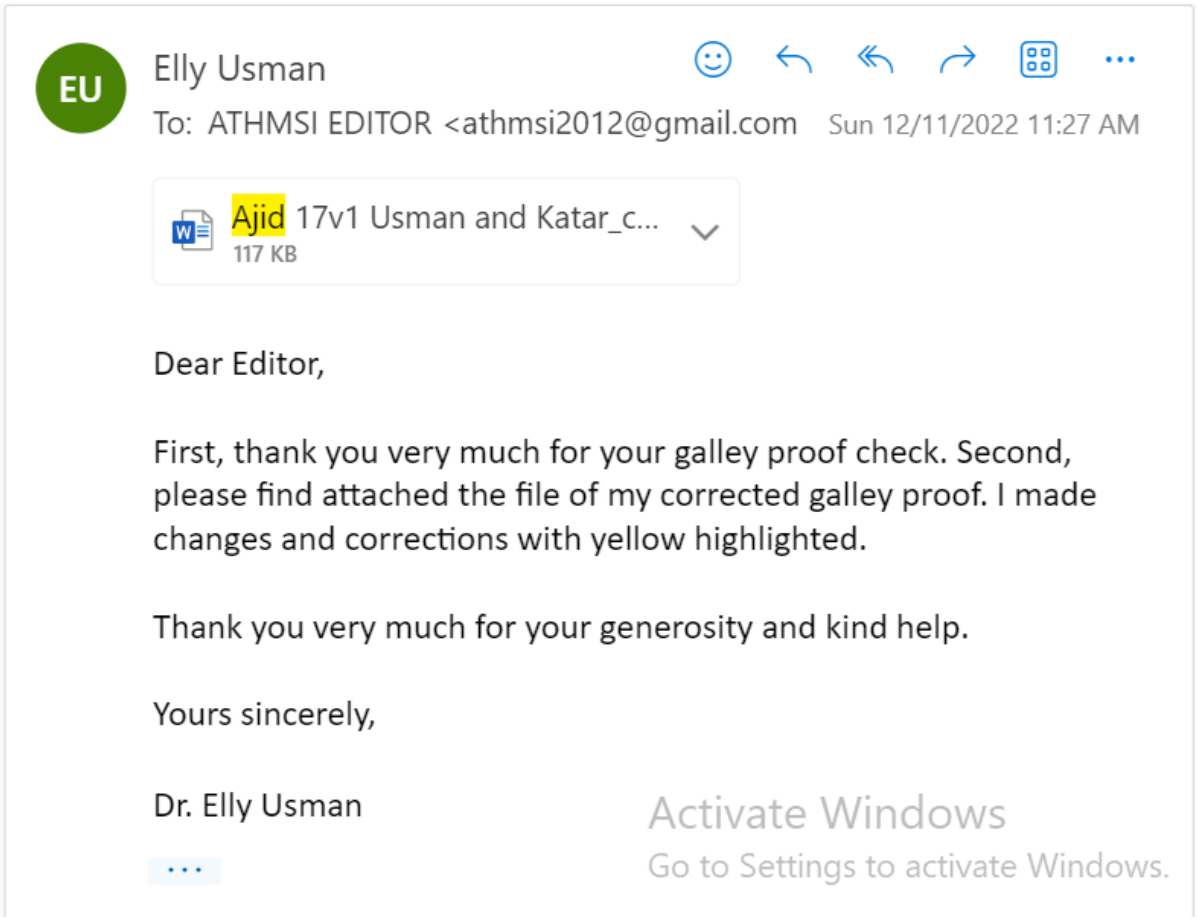
COJA House,
7, Road 1, Otunmaiye Square, Ajebamidele,
P. O. Box 2586, Obafemi Awolowo University
Post Office, Ile-Ife, Osun State, Nigeria.

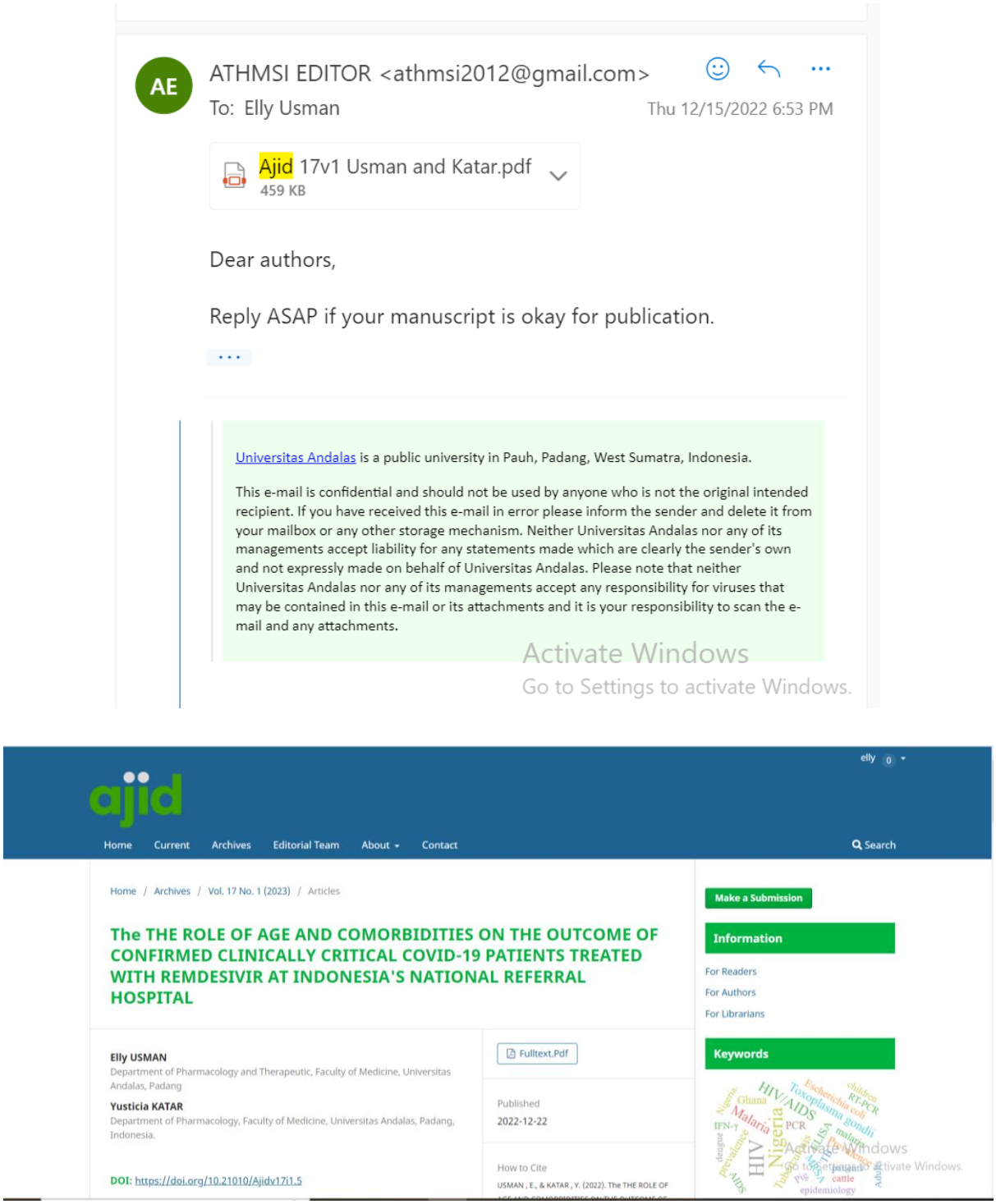
Gambar 5. Pemberitahuan editor proofreading request

6. **Author langsung mengirimkan proofreading ke journal system pada tanggal 11 Desember 2022**



Gambar 6. Author mengirimkan proofreading ke journal system

7. **Pemberitahuan editor bahwa artikel sudah diterbitkan pada jurnal African Journal of Infectious Disease. 2022 Dec 22; 17(1):55-59.**



Gambar 7. Pemberitahuan editor bahwa artikel sudah diterbitkan

LAMPIRAN A

PAPER DENGAN VERSI PERTAMA KALI DIKIRIM (*ORIGINAL VERSION*)

Research article

Manuscript Title:

The Role of Age and Comorbidities on The Outcome of Confirmed Clinically Critical COVID-19 Patients Treated with Remdesivir at Indonesia's National Referral Hospital

Elly Usman[1], Yusticia Katar[1]

Affiliation:

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Running title

The Role of Age and Comorbidities on The Outcome of Confirmed Clinically Critical COVID-19 Patients Treated with Remdesivir

Abstract

Background: There is currently no viable pharmaceutical therapy for COVID-19 illness that has been validated. The use of remdesivir is one of the medications for which there is no consistent evidence of a significant therapeutic benefit or a meaningful effect on survival.

Aim: The aim of this study was to determine the role of age and comorbidities on the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir at Indonesia's National Referral Hospital.

Methods: A retrospective cohort study was used in this study. The subjects in this study were confirmed clinically critical COVID-19 patients who were treated at Dr. M Djamil Hospital Padang, one of Indonesia's national referral hospitals, from January to June 31, 2021. The number of samples in this study was 90 patients. The variables of this study were divided into three independent variables (age, comorbidities, and a number of comorbidities). A dependent variable was the outcome of confirmed clinically critical COVID-19 patients. The Chi-square test was performed in bivariate analysis, and the odds ratio was calculated. SPSS version 17.0 was used to analyze the data.

Results: The results of this study found that there was an association between ages 50-59 years (OR = 10.23, 95% CI 1.89-55.53), 60-69 years (OR = 4.58, 95% CI 1.25-16.76), and > 70 years (OR = 1.91, 95% CI 1.38 -9.59), comorbid diabetes mellitus (OR = 9.78, 95% CI 1.23-77.66), the number of comorbid > 1 (OR = 10.97, 95% CI 2.19-54.96, and the number of comorbid 1 (OR = 5.69, 95% CI 1.59- 20.41) with the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir.

Conclusion: The significance of age and comorbidities on the outcome of COVID-19 patients treated with remdesivir at Indonesia's national referral hospital was confirmed in this study. This study could assist in the management of patient therapy, potentially decreasing morbidity and even patient mortality.

Keywords: Age, Comorbidities, COVID-19, Outcome, Remdesivir

Introduction

Coronavirus disease 2019 (COVID-19) is a contagious illness. This disease has been declared a pandemic by the World Health Organization, which means that the disease's spread is worldwide. There is currently no recognized pharmaceutical therapy for COVID-19 illness, and clinical trials are still ongoing (Li et al., 2020; Lotfi et al., 2020; Babaei et al., 2021).

Previous research found no indication of an effective therapy that reduced morbidity and mortality in COVID-19. COVID-19 treatment focuses on antivirals such as remdesivir, immunosuppressants, and immunomodulators because to the involvement of viral load and inflammatory response in the host (Pascarella et al., 2020; Naik et al., 2021).

Remdesivir is an adenosine nucleotide prodrug that is converted intracellularly to remdesivir triphosphate, which is the active substance (Kichloo et al., 2021). Remdesivir's active form binds to viral RNA-dependent RNA polymerase and inhibits viral replication. Remdesivir has showed in vitro action against SARS-CoV and MERS-CoV, with new in vitro results confirming its effectiveness against SARS-CoV-2 (Chalmers et al., 2021).

Previous research has found no consistent evidence of a significant therapeutic benefit or a meaningful impact on survival with the usage of remdesivir (Liu et al., 2020). Remdesivir was shown to be superior to placebo in terms of reducing recovery time in a randomized controlled experiment. In patients who were on mechanical ventilation, this favorable impact was not observed (Beigel et al., 2020). Another trial indicated that 80% of patients were on mechanical ventilation, demonstrating the drug's promise in critically ill patients (Pasquini et al., 2020).

The aim of this study was to determine the role of age and comorbidities on the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir at Indonesia's National Referral Hospital.

Materials and Methods

Study design and research sample

A retrospective cohort study was used in this study. The subjects in this study were confirmed clinically critical COVID-19 patients who were treated at Dr M Djamil Hospital Padang, one of Indonesia's national referral hospitals, from January to June 31, 2021. The number of samples in this study was 90 patients.

Inclusion and exclusion criteria

COVID-19 patients were included in the study if the findings of an RT PCR/Molecular Rapid Test (TCM) SARS-CoV-2 collected from a nasal/nasopharyngeal swab were clinically critical. Patients with rapidly worsening acute respiratory distress syndrome (ARDS) or respiratory failure, as well as shock, encephalopathy, myocardial damage or heart failure, coagulopathy, acute renal impairment, multiple organ dysfunction, or other sepsis manifestations, are considered clinically critical. Patients above the age of 18 years who are being treated with remdesivir. Exclusion criteria were carried out on incomplete or unreadable patient medical record data.

Operational definition

The variables of this study were divided into three independent variables, that is, age (<50 years, 50-59 years, 60-69 years, ≥ 70 years), comorbidities (hypertension, cardiovascular, diabetes mellitus, chronic lung disease, cerebrovascular, immunodeficiency, obesity, cancer), and number of comorbities (none, 1, ≥ 1). A dependent variable, that is, outcome of of confirmed clinically critical COVID-19 patients (death, life).

Research ethics approval

This study passed the ethical review by the ethics commiittee of Dr M Djamil General Hospital, Padang, Indonesia (No. 27/ KEPK/ 2022).

Data analysis

The results of the univariate analysis are reported as percentages and frequencies. The Chi-square test was performed in bivariate analysis, and the odds ratio was computed. If $p<0.05$, it is declared significant. SPSS version 17.0 was used to analyze the data.

Results

Subject characteristics (Table 1).

Table 1. Subject characteristics

Characteristics	f (%)
Age (years)	
<50	20 (22.2)
50-59	27 (30.0)
60-69	33 (36.7)
≥ 70	10 (11.1)
Sex	
Male	52 (57.8)
Female	38 (42.2)
Comorbidities	
Cerebrovascular	3 (3.3)
Hypertension	30 (33.3)
Cardiovascular	12 (13.3)
Chronic lung disease	3 (3.3)
Cancer	2 (2.2)
Chronic kidney disease	16 (17.8)
Immunodeficiency	1 (1.1)
Diabetes mellitus	26 (28.9)
Obesity	10 (11.1)
Number of comorbidities	
None	29 (32.2)
1 comorbidity	32 (35.6)
>1 comorbidity	29 (32.2)

Table 1 showed most subjects were 60-69 years old (36.7%), followed by 50-59 years (30.0%), <50 years (22.2%) and 70 years (11.1%). More than half of the subjects were male (57.8%). The most comorbidities were hypertension (33.3%), followed by diabetes mellitus (28.9%), chronic kidney disorders (17.8%), cardiovascular (13.3%), obesity (11.1%), cerebrovascular disease (3.3%), chronic lung disease (3.3%), malignancy (2.2%) and immunodeficiency (1.1%). Furthermore, the highest number of comorbids is 1 comorbid (35.6%) and > 1 comorbid (32.2%).

Table 1 that most of the subjects were 60-69 years old (36.7%), followed by 50-59 years (30.0%), <50 years (22.2%), and 70 years old (11.1%). Males made up more than half of the subjects (57.8%). Hypertension was the most common comorbidity (33.3%), followed by diabetes mellitus (28.9%), chronic kidney diseases (17.8%), cardiovascular (13.3%), obesity (11.1%), cerebrovascular disease (3.3%), chronic lung disease (3.3%), cancer (2.2%), and immunodeficiency (1.1%). The highest number of comorbidity was 1 comorbid (35.6%), followed by > 1 comorbidity (32.2%).

The role of age and comorbidities on the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir at Indonesia's national referral hospital (Table 2).

Table 2. The role of age and comorbidities on the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir at Indonesia's national referral hospital

Variables	Outcome		p-value	OR (95% CI)
	Death (f/%) (n=71)	Life (f/%) (n=19)		
Age (years)			**0.011*[a]**	
<50	11 (55.0)	9 (45.0)		Ref
50-59	25 (92.6)	2 (7.4)		**10.23 (1.89-55.33)**
60-69	28 (84.8)	5 (15.2)		**4.58 (1.25-16.76)**
≥ 70	7 (70.0)	3 (30.0)		**1.91 (1.38-9.59)**
Comorbidities				
Cerebrovascular	3 (100.0)	0	n/a	n/a
Hypertension	26 (86.7)	4 (13.3)	0.315	2.17 (0.65-7.22)
Cardiovascular	11 (91.7)	1 (8.3)	0.448	3.30 (0.40-27.32)
Chronic lung disease	3 (100.0)	0	n/a	n/a
Cancer	2 (100.0)	0	n/a	n/a
Chronic kidney disease	14 (87.5)	2 (12.5)	0.507	2.09 (0.43-10.11)
Immunodeficiency	1 (100.0)	0	n/a	n/a
Diabetes mellitus	25 (96.2)	1 (3.8)	**0.023*[a]**	**9.78 (1.23-77.66)**
Obesity	9 (90.0)	1 (10.0)	0.682	2.61 (0.31-22.02)
Number of comorbidities			**0.001*[a]**	
None	16 (55.2)	13 (44.8)		Ref
1 comorbidity	28 (87.5)	4 (12.5)		**5.69 (1.59-20.41)**
>1 comorbidity	27 (93.1)	2 (6.9)		**10.97 (2.19-54.96)**

*p<0.05 considered significant; a, Chi-square test

Table 2 shows comorbid cerebrovascular, hypertension, cardiovascular, chronic lung disease, cancer, chronic kidney disease, immunodeficiency, and obesity had no association on the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir (p>0.05). But, there was an association between age 50-59 years (OR = 10.23, 95% CI 1.89-55.53), 60-69 years (OR = 4.58, 95% CI 1.25-16.76), and > 70 years (OR = 1.91, 95% CI 1.38 -9.59), comorbid diabetes mellitus (OR = 9.78, 95% CI 1.23-77.66), the number of comorbids > 1 (OR = 10.97, 95% CI 2.19-54.96, and the number of comorbid 1 ((OR = 5.69, 95% CI 1.59-20.41) with the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir.

Discussion

The results of this study found that there was an association between age 50-59 years (OR = 10.23, 95% CI 1.89-55.53), 60-69 years (OR = 4.58, 95% CI 1.25-16.76), and > 70 years (OR = 1.91, 95% CI 1.38 -9.59), comorbid diabetes mellitus (OR = 9.78, 95% CI 1.23-77.66), the number of comorbids > 1 (OR = 10.97, 95% CI 2.19-54.96, and the number of comorbid 1 (OR = 5.69, 95% CI 1.59- 20.41) with the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir.

Remdesivir works by inhibiting the viral RNA polymerase that is dependent on viral RNA. Remdesivir has previously been shown to be effective in limiting viral replication and decreasing coronavirus-associated disease in vivo. It's unclear how Remdesivir's direct antiviral activity might be active throughout the immunopathogenic ARDS phase of COVID-

19 disease, implying that off-target consequences could be blamed on the medicine (Nile et al., 2020; Eastman et al., 2020).
Despite severe illness (57% on mechanical ventilation) and severely (8% on extracorporeal membrane oxygenation), another trial in 53 patients from 9 countries getting remdesivir for 1 to 10 days demonstrated clinical improvement in 68 percent of patients, with just 15% exhibiting worsening with COVID-19. Interestingly, improvement was reported in 100% of patients with mild COVID-19 (not getting oxygen support or low-flow oxygen) and 71% of patients with severe COVID-19 (not receiving oxygen support or low-flow oxygen) (receiving high-flow oxygen support) (Singh et al., 2020).
Because comorbidities frequently rise with age, COVID-19 is more severe in the elderly population among COVID-19 patients. The pathophysiological alterations that characterize the respiratory system are associated with worse outcomes as people age. Patients over the age of 80 who have been infected with COVID-19 have a higher chance of death than younger patients, according to existing epidemiological data (Perrotta et al., 2020).
The previous study involved 80 patients with COVID-19 who were treated with remdesivir. Patients were divided into two groups based on their ages: young (under 80 years) and old (above 80 years). Patients who were younger at the time of discharge had a higher rate of clinical improvement than those who were older. The death rate in older patients is higher than in younger patients within 60 days after diagnosis of COVID-19 (Kanai et al., 2021).
Patients infected with SARS-CoV-2 who were admitted to Pesario Hospital's ICU and given remdesivir medication were studied in previous investigations. According to research, comorbidity is a factor that is significantly linked to a higher death rate. Hypertension (54.9%), diabetes mellitus (13.7%), ischemic heart disease (13.7%), chronic kidney failure (7.8%), chronic heart failure (7.8%), and chronic obstructive pulmonary disease (COPD) (7.8%) were the most prevalent comorbidities (5.9%). In this study, it was discovered that remdesivir medication was linked to a higher rate of survival (Pasquini et al., 2020).
The body is under a lot of stress in individuals with comorbid conditions like diabetes and hypertension, and their immunity is usually low. Furthermore, a long-term history of diabetes and hypertension damages blood vessel structure and increases the risk of critical illness. Patients with chronic heart illness are more likely to become infected due to weakened heart function and inadequate immunity, putting them at risk of developing acute cardiovascular events and severe disease if infected with COVID-19. Patients with a history of respiratory disease, such as COPD, have lower viral resistance and are more likely to develop Acute respiratory distress syndrome (ARDS). Diabetes, hypertension, cardiovascular disease, and respiratory disease are all risk factors for disease development (Zheng et al., 2020).

Conclusion

The significance of age and comorbidities on the outcome of COVID-19 patients treated with remdesivir at Indonesia's national referral hospital was confirmed in this study. This study could assist in the management of patient therapy, potentially decreasing morbidity and even patient mortality.

Acknowledgements
The authors would like to thank Universitas Andalas for their grant research and all of the participants in this study.

Conflict of interest statement
There were no potential conflicts of interest stated by the authors.

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mortal COVID-19 cases: A systematic literature review and meta-analysis. *The Journal of Infection*, *81*(2): e16–e25.

LAMPIRAN B

PAPER DENGAN VERSI KEDUA DIKIRIM (*REVISED MANUSCRIPT VERSION*)

Research article

Manuscript Title:
The Role of Age and Comorbidities on The Outcome of Confirmed Clinically Critical COVID-19 Patients Treated with Remdesivir at Indonesia's National Referral Hospital

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Affiliation:

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Running title
The Role of Age and Comorbidities on The Outcome of Confirmed Clinically Critical COVID-19 Patients Treated with Remdesivir

Abstract
Background: There is currently no viable pharmaceutical therapy for COVID-19 that has been validated. The use of remdesivir is one of the medications for which there is no consistent evidence of a significant therapeutic benefit or a meaningful effect on survival.
Aim: The aim of this study was to determine the role of age and comorbidities on the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir.
Methods: A retrospective cohort study was used in this study. The subjects in this study were confirmed clinically critical COVID-19 patients who were treated at Dr. M Djamil Hospital Padang, one of Indonesia's national referral hospitals, from January to June 31, 2021. The number of samples in this study was 90 patients. The Chi-square test was performed in bivariate analysis, and the odds ratio was calculated.
Results: The results of this study found that there was an association between ages 50-59 years (OR = 10.23, 1.89-55.53), 60-69 years (OR = 4.58, 1.25-16.76), and > 70 years (OR = 1.91, 1.38 -9.59), diabetes mellitus (OR = 9.78, 1.23-77.66), the number of comorbid > 1 (OR = 10.97, 2.19-54.96, and one comorbid (OR = 5.69, 1.59- 20.41) with the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir.
Conclusion: The significance of age and comorbidities on the outcome of COVID-19 patients treated with remdesivir was confirmed in this study. This study could assist in the management of patient therapy, potentially decreasing morbidity and even patient mortality.

Keywords: Age, Comorbidities, COVID-19, Outcome, Remdesivir

List of Abbreviations

ARDS: Acute respiratory distress syndrome
CI: Confidence interval
COPD: Chronic obstructive pulmonary disease
COVID-19: Coronavirus disease 2019
ICU: Intensive care unit
MERS-CoV: Middle East respiratory syndrome coronavirus
OR: Odds ratio
RNA: Ribonucleic acid
RT-PCR: Real time polymerase chain reaction
***SARS-CoV*:** Severe acute respiratory syndrome coronavirus

Introduction

Coronavirus disease 2019 (COVID-19) is a contagious illness. This disease has been declared a pandemic by the World Health Organization, which means that the disease's spread is worldwide. There is currently no recognized pharmaceutical therapy for COVID-19 illness, and clinical trials are still ongoing (Li et al., 2020; Lotfi et al., 2020; Babaei et al., 2021).
Previous research found no indication of an effective therapy that reduced morbidity and mortality in COVID-19. COVID-19 treatment focuses on antivirals such as remdesivir, immunosuppressants, and immunomodulators because to the involvement of viral load and inflammatory response in the host (Pascarella et al., 2020; Naik et al., 2021).
Remdesivir is an adenosine nucleotide prodrug that is converted intracellularly to remdesivir triphosphate, which is the active substance (Kichloo et al., 2021). Remdesivir's active form binds to viral ribonucleic acid (RNA) dependent RNA polymerase and inhibits viral replication. Remdesivir has showed in vitro action against severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), with new in vitro results confirming its effectiveness against SARS-CoV-2 (Chalmers et al., 2021).
Previous research has found no consistent evidence of a significant therapeutic benefit or a meaningful impact on survival with the usage of remdesivir (Liu et al., 2020). Remdesivir was shown to be superior to placebo in terms of reducing recovery time in a randomized controlled experiment. In patients who were on mechanical ventilation, this favorable impact was not observed (Beigel et al., 2020). Another trial indicated that 80% of patients were on mechanical ventilation, demonstrating the drug's promise in critically ill patients (Pasquini et al., 2020).
Due to conflicting research results at the time this study was being written regarding the effect of remdesivir administration in clinically critically confirmed COVID-19 patients and a lack of research discussing the role of age and comorbidities in patient outcomes, the authors felt the need to identify the role of age and comorbidities on the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir at Indonesia's National Referral Hospital.

Materials and Methods

Study design and research sample

A retrospective cohort study was used in this study. The subjects in this study were confirmed clinically critical COVID-19 patients who were treated at Dr M Djamil Hospital

Padang, one of Indonesia's national referral hospitals, from January to June 31, 2021. The number of samples in this study was 90 patients.

Inclusion and exclusion criteria

COVID-19 patients were included in the study if the findings of a real time polymerase chain reaction (RT-PCR) SARS-CoV-2 collected from a nasal/nasopharyngeal swab were clinically critical. Patients with rapidly worsening acute respiratory distress syndrome (ARDS) or respiratory failure, as well as shock, encephalopathy, myocardial damage or heart failure, coagulopathy, acute renal impairment, multiple organ dysfunction, or other sepsis manifestations, are considered clinically critical. Patients above the age of 18 years who are being treated with remdesivir. Exclusion criteria were carried out on incomplete or unreadable patient medical record data.

Operational definition

The variables of this study were divided into three independent variables, that is, age (<50 years, 50-59 years, 60-69 years, ≥ 70 years), comorbidities (hypertension, cardiovascular, diabetes mellitus, chronic lung disease, cerebrovascular, immunodeficiency, obesity, cancer), and number of comorbities (none, 1, ≥ 1). A dependent variable, that is, outcome of of confirmed clinically critical COVID-19 patients (death, life).

Research ethics approval

This study passed the ethical review by the ethics commiittee of Dr M Djamil General Hospital, Padang, Indonesia (No. 27/ KEPK/ 2022).

Data analysis

The results of the univariate analysis are reported as percentages and frequencies. The Chi-square test was performed in bivariate analysis, and the odds ratio was computed. If $p<0.05$, it is declared significant. SPSS version 17.0 was used to analyze the data.

Results

Subject characteristics (Table 1).

Table 1. Subject characteristics

Characteristics	f (%)
Age (years)	
<50	20 (22.2)
50-59	27 (30.0)
60-69	33 (36.7)
≥ 70	10 (11.1)
Sex	
Male	52 (57.8)
Female	38 (42.2)
Comorbidities	
Cerebrovascular	3 (3.3)
Hypertension	30 (33.3)
Cardiovascular	12 (13.3)
Chronic lung disease	3 (3.3)
Cancer	2 (2.2)
Chronic kidney disease	16 (17.8)
Immunodeficiency	1 (1.1)
Diabetes mellitus	26 (28.9)
Obesity	10 (11.1)
Number of comorbidities	

None	29 (32.2)
1 comorbidity	32 (35.6)
>1 comorbidity	29 (32.2)

Table 1 showed most subjects were 60-69 years old (36.7%), followed by 50-59 years (30.0%), <50 years (22.2%) and 70 years (11.1%). More than half of the subjects were male (57.8%). The most comorbidities were hypertension (33.3%), followed by diabetes mellitus (28.9%), chronic kidney disorders (17.8%), cardiovascular (13.3%), obesity (11.1%), cerebrovascular disease (3.3%), chronic lung disease (3.3%), malignancy (2.2%) and immunodeficiency (1.1%). Furthermore, the highest number of comorbids is 1 comorbid (35.6%) and > 1 comorbid (32.2%).

Table 1 that most of the subjects were 60-69 years old (36.7%), followed by 50-59 years (30.0%), <50 years (22.2%), and 70 years old (11.1%). Males made up more than half of the subjects (57.8%). Hypertension was the most common comorbidity (33.3%), followed by diabetes mellitus (28.9%), chronic kidney diseases (17.8%), cardiovascular (13.3%), obesity (11.1%), cerebrovascular disease (3.3%), chronic lung disease (3.3%), cancer (2.2%), and immunodeficiency (1.1%). The highest number of comorbidity was 1 comorbid (35.6%), followed by > 1 comorbidity (32.2%).

The role of age and comorbidities on the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir at Indonesia's national referral hospital (Table 2).

Table 2. The role of age and comorbidities on the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir at Indonesia's national referral hospital

Variables	**Outcome**		**p-value**	**OR (95% CI)**
	Death (f/%) (n=71)	**Life (f/%) (n=19)**		
Age (years)			**0.011*[a]**	
<50	11 (55.0)	9 (45.0)		Ref
50-59	25 (92.6)	2 (7.4)		**10.23 (1.89-55.33)**
60-69	28 (84.8)	5 (15.2)		**4.58 (1.25-16.76)**
≥ 70	7 (70.0)	3 (30.0)		**1.91 (1.38-9.59)**
Comorbidities				
Cerebrovascular	3 (100.0)	0	n/a	n/a
Hypertension	26 (86.7)	4 (13.3)	0.315	2.17 (0.65-7.22)
Cardiovascular	11 (91.7)	1 (8.3)	0.448	3.30 (0.40-27.32)
Chronic lung disease	3 (100.0)	0	n/a	n/a
Cancer	2 (100.0)	0	n/a	n/a
Chronic kidney disease	14 (87.5)	2 (12.5)	0.507	2.09 (0.43-10.11)
Immunodeficiency	1 (100.0)	0	n/a	n/a
Diabetes mellitus	25 (96.2)	1 (3.8)	**0.023*[a]**	**9.78 (1.23-77.66)**
Obesity	9 (90.0)	1 (10.0)	0.682	2.61 (0.31-22.02)
Number of comorbidities			**0.001*[a]**	
None	16 (55.2)	13 (44.8)		Ref
1 comorbidity	28 (87.5)	4 (12.5)		**5.69 (1.59-20.41)**
>1 comorbidity	27 (93.1)	2 (6.9)		**10.97 (2.19-54.96)**

*p<0.05 considered significant; a, Chi-square test

Table 2 shows comorbid cerebrovascular, hypertension, cardiovascular, chronic lung disease, cancer, chronic kidney disease, immunodeficiency, and obesity had no association on the

outcome of confirmed clinically critical COVID-19 patients treated with remdesivir (p>0.05). But, there was an association between age 50-59 years (OR = 10.23, 95% CI 1.89-55.53), 60-69 years (OR = 4.58, 95% CI 1.25-16.76), and > 70 years (OR = 1.91, 95% CI 1.38 -9.59), comorbid diabetes mellitus (OR = 9.78, 95% CI 1.23-77.66), the number of comorbids > 1 (OR = 10.97, 95% CI 2.19-54.96, and the number of comorbid 1 ((OR = 5.69, 95% CI 1.59-20.41) with the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir.

Discussion

The results of this study found that there was an association between age 50-59 years (OR = 10.23, 95% CI 1.89-55.53), 60-69 years (OR = 4.58, 95% CI 1.25-16.76), and > 70 years (OR = 1.91, 95% CI 1.38 -9.59), comorbid diabetes mellitus (OR = 9.78, 95% CI 1.23-77.66), the number of comorbids > 1 (OR = 10.97, 95% CI 2.19-54.96, and the number of comorbid 1 (OR = 5.69, 95% CI 1.59- 20.41) with the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir.

Remdesivir works by inhibiting the viral RNA polymerase that is dependent on viral RNA. Remdesivir has previously been shown to be effective in limiting viral replication and decreasing coronavirus-associated disease in vivo. It's unclear how Remdesivir's direct antiviral activity might be active throughout the immunopathogenic ARDS phase of COVID-19 disease, implying that off-target consequences could be blamed on the medicine (Nile et al., 2020; Eastman et al., 2020).

Despite severe illness (57% on mechanical ventilation) and severely (8% on extracorporeal membrane oxygenation), another trial in 53 patients from 9 countries getting remdesivir for 1 to 10 days demonstrated clinical improvement in 68 percent of patients, with just 15% exhibiting worsening with COVID-19. Interestingly, improvement was reported in 100% of patients with mild COVID-19 (not getting oxygen support or low-flow oxygen) and 71% of patients with severe COVID-19 (not receiving oxygen support or low-flow oxygen) (receiving high-flow oxygen support) (Singh et al., 2020).

Because comorbidities frequently rise with age, COVID-19 is more severe in the elderly population among COVID-19 patients. The pathophysiological alterations that characterize the respiratory system are associated with worse outcomes as people age. Patients over the age of 80 who have been infected with COVID-19 have a higher chance of death than younger patients, according to existing epidemiological data (Perrotta et al., 2020; Nindrea et al., 2022).

The previous study involved 80 patients with COVID-19 who were treated with remdesivir. Patients were divided into two groups based on their ages: young (under 80 years) and old (above 80 years). Patients who were younger at the time of discharge had a higher rate of clinical improvement than those who were older. The death rate in older patients is higher than in younger patients within 60 days after diagnosis of COVID-19 (Kanai et al., 2021). As expected, older patients had a greater mortality risk for COVID-19 within 60 days after their diagnosis (Onder et al., 2020; Kanai et al., 2021). In this study, elderly patients typically had problems that necessitated hospitalization, as we previously document.

Patients infected with SARS-CoV-2 who were admitted to Pesario Hospital's ICU and given remdesivir medication were studied in previous investigations. According to research, comorbidity is a factor that is significantly linked to a higher death rate. Hypertension (54.9%), diabetes mellitus (13.7%), ischemic heart disease (13.7%), chronic kidney failure (7.8%), chronic heart failure (7.8%), and chronic obstructive pulmonary disease (COPD) (7.8%) were the most prevalent comorbidities (5.9%). In this study, it was discovered that remdesivir medication was linked to a higher rate of survival (Pasquini et al., 2020).

The body is under a lot of stress in individuals with comorbid conditions like diabetes and hypertension, and their immunity is usually low. Furthermore, a long-term history of diabetes and hypertension damages blood vessel structure and increases the risk of critical illness. Patients with chronic heart illness are more likely to become infected due to weakened heart function and inadequate immunity, putting them at risk of developing acute cardiovascular events and severe disease if infected with COVID-19. Patients with a history of respiratory disease, such as COPD, have lower viral resistance and are more likely to develop ARDS. Diabetes, hypertension, cardiovascular disease, and respiratory disease are all risk factors for COVID-19 development (Zheng et al., 2020; Nindrea et al., 2022).

This study's main strength was being the first study to the role of age and comorbidities on the outcome of confirmed clinically critical COVID-19 patients treated with remdesivir at one of Indonesia's national referral hospitals. Furthermore, our analysis contained several limitations. Because the data used in this analysis were retrospective, it was not possible to compare the findings to those of the comparison group. Data were gathered at a specific moment in time. However, our analysis contributes to the clinical data on the use of remdesivir in COVID-19 by presenting results of a cohort of COVID-19 patients treated with the drug in actual clinical settings in Indonesia.

The implications of the results of this study suggest that clinical research and trials involving a wider population are needed to determine the effectiveness of remdesivir. Remdesivir's function in upfront remdesivir use in the general population based on age and comorbidities, as well as its effectiveness against other versions, are clinical questions that have not yet been resolved. This research may help with patient therapy management, perhaps lowering morbidity and even patient mortality.

Conclusion

The significance of age and comorbidities on the outcome of COVID-19 patients treated with remdesivir at Indonesia's national referral hospital was confirmed in this study. This study could assist in the management of patient therapy, potentially decreasing morbidity and even patient mortality.

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Conflict of interest statement

There were no potential conflicts of interest stated by the authors.

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