FACTORS ASSOCIATED WITH COVID-19 DISEASE SEVERITY AND TREATMENT OUTCOMES IN JIMMA MEDICAL CENTER, SOUTH WEST ETHIOPIA. RETROSPECTIVE STUDY

BY: BIKILA YAECOB (B. PHARM)

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Factors associated with COVID-19 disease severity and treatment outcomes in Jimma Medical Center, South West Ethiopia

By: Bikila Yaecob (B. Pharm)

Advisors

Mrs. Mestawet Getachew (MSc), (Ass/associate prof. Pharmacy, Jimma University)

Prof. Esayas Kebede (MD, DTMH, PhD prof. Medicine Jimma University)

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JIMMA, ETHIOPIA

Assurance of principal investigator

The undersign certify that he/she has read and here by recommend for acceptance by school of pharmacy, institute of health, Jimma University a research Thesis entitled; **"Factors associated with COVI-19 disease severity and treatment outcomes in Jimma Medical Center, South West Ethiopia"** In partial fulfillments of requirements for the Degree of Master of Science (MSc) in clinical pharmacy.

Name of the student: **Bikila Yaecob (B.pharm.)** **ID: RM 3393/12**

Signature _____ Date _____

Approval of the Advisors

Name of the advisors: Mrs. Mestawet Getachew and Prof. Esayas Kebede (MD, Internist)

Signature _____ Date _____

Signature _____ Date _____

Approval of examiner

Name of the examiner _____

Signature _____ Date _____

Approval of school/department head

Name of school/department head _____

Signature _____ Date _____

ABSTRACT

Background: COVID-19 is a disease caused by a virus known as severe acute respiratory syndrome (SARS-Cov-2) and it is suggested as beta coronavirus by genetic sequencing. Although cardiovascular disease is a major comorbidity of corona virus disease 2019 (COVID-19), its impact on Covid-19 disease severity and treatment outcome is not clear.

Objective: To assess the severity, treatment outcome and associated factors among hospitalized COVID-19 patients at Jimma Medical Center

Methods: Retrospective study was conducted at COVID-19 treatment center of Jimma Medical Center. Data were collected from January 3 to March 4 2022 by reviewing patient's medical charts and from database using data abstraction checklist prepared for this research. Logistic regression models were used to determine the degree of association between factors like age, sex, residence, medications used for cardiovascular management, treatments used for COVID-19 and pre-existing cardiovascular disease on COVID-19 disease severity and treatment outcomes. A variable having a p-value of ≤0.25 in the binary analysis was subjected to multivariable analysis.

Results: A total of 275 patient cards were included in this study, of which 66.5% were males. Hypertension was the most prevalent and associated with high risk of death from the spectrum of cardiovascular diseases. From all cardiovascular disease hypertension was the most prevalent. The risk of developing critical COVID-19 in patients with comorbid cardiovascular disease was higher compared to patients without comorbid cardiovascular disease [AOR, 5.794; 95% CI, 2.516- 13.343]. Patients with comorbid cardiovascular disease and prescribed antibiotics has high risk of death [AOR 2.137; CI 95% 1.02-4.476] and [AOR 2.692; CI 95% 1.132-6.404] compared to patients without comorbid cardiovascular disease and not prescribed antibiotics respectively.

Conclusion and Recommendations: In general the presence of pre-existing cardiovascular disease was associated with higher risk of severe COVID-19 and death. Thus priority should be given to the prevention of the infection.

Key words: critical; mortality; predictors; SARS-COV-2; survival

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Abbreviation /acronym

ACEI- Angiotensin converting enzyme inhibitors

AOR- Adjusted odd ratio

ARB- Angiotensin receptor blocker

COPD- Chronic obstructive pulmonary disease

COVID-19 – Corona virus disease-2019

CVD- Cardiovascular disease

ICU- Intensive care unit

LDH- Lactate dehydrogenase

PCT- Procalcitonin

RT-PCR – Reverse transcriptase polymerase chain reaction

SARS-COV – Severe acute respiratory syndrome

SOB- Shortness of breath

SpO2- oxygen saturation

1. Introduction

1.1. Background

Corona virus disease-2019 (COVID-19) is a disease caused by a virus known as severe acute respiratory syndrome (SARS-Cov-2) and it is suggested as beta coronavirus by genetic sequencing (1). Later when it is investigated in detail it is found to be Ribonucleic acid virus and is made up of 30,000 nucleotides. The virus cannot be able to reproduce out of the body but may stay alive on inanimate things even though the duration of survival on these things differ(2). It is initially thought that the virus have originated from bat and other unknown reservoir hosts(3).

The first cases of COVID-19 have been reported on December 2019 in Wuhan City of China and it was declared as global pandemic on 11 March 2020 (4). In Ethiopia the first confirmed disease was reported on 13 March 2020(5).

The appearance of the sign and symptoms after acquiring the virus (i.e incubation period) was estimated to be in the range of 2 to 14 days. The chest x-ray finding varies, but bilateral multifocal opacities are common (6). The manifestation of COVID-19 may range from asymptomatic infection, mild upper respiratory illness to severe viral pneumonia with respiratory failure and even death (7).

Early during the outbreak, there was an assumption that the virus did not transmit from human to human. However, as the outbreak propagated, human to human transmission was confirmed (8). World health organization ascertains clinically patients with COVID-19 may present by either the combination of acute fever and cough, combination of 3 or more of fever, cough, general weakness, headache, myalgia, sore throat, coryza, anorexia, nausea and vomiting (9). Like other respiratory tract virus they are transmitted when a positive individual cough and sneezes. The distance of less than 6 feet (1.8 meter) between the individuals increase the chance of transmission. The survival of the virus on objects and surfaces differ: plastic material, stainless steel, cardboard, copper are 2 to 3 days, 2 to 3 days, 1 day and 4 hours respectively (10).

The severity of Covid-19 complication is highly associated with sex and age. The rate of hospitalization and death in children is low, while it is high in males, elders and immune-

compromised persons. Following COVID-19 infection some patients may develop severe complications like coagulation disorder (deep venous thrombosis and disseminated intravascular coagulation), laryngeal edema and laryngitis in critically ill patients, superimposed necrotizing pneumonia, cardiovascular complications like acute myocardial injury, acute pericarditis, left ventricular dysfunction, arrhythmia and heart failure, respiratory failure and multi organ failure (11). There is insufficient data on clinical consequences following recovery and long term sequelae from COVID-19. However, emerging data show persistence of respiratory dysfunction like diffusion impairment, reduction in total lung capacity and lung fibrosis(12).

Cardiovascular disease (CVD) was the most prevalent comorbidity in COVID-19 positive patients. It is also most prevalent in patients died and developed critical COVID-19. Even though the most frequently observed manifestation of COVID-19 was viral pneumonia it can also case cardiovascular complications like myocardial injury, arrhythmia, acute coronary syndrome and thromboembolism. In some individuals without typical symptoms like fever and cough they may initially present with cardiac symptoms. COVID-19 infection may directly damage cardiovascular system and pre-existing CVD may predispose to COVID-19 infection (13,14).

Since this viral infection is expanding rapidly, it is necessary to identify the populations at high risk of morbidities and mortalities. From these risk factors those with pre-existing comorbidities have high chance to develop severe disease and poor treatment outcomes (15). As to one systematic review and meta-analysis done by Jain and his colleagues pre-existing CVD, cardiovascular risk factors and other comorbid disease are highly associated with admission to Intensive care unit (ICU) and severe disease(16). The angiotensin converting enzyme inhibitors/ angiotensin receptor blockers (ACEI/ARB) do neither increase nor decrease the disease severity and mortality secondary to COVID-19. Moreover, they have no effect on the duration of hospital stay (17–19).

1.2. Statement of the problem

In COVID-19 positive patients' disease severity and mortality was high in elders (i.e. > 60 years) and those with comorbid illnesses like cancer, chronic respiratory disease and CVD. As of 20 February 2020 in China, from confirmed cases there is high rate of mortality in those populations with comorbid diseases and from these comorbid conditions cardiovascular disease was the most prevalent (20).

According to one retrospective study conducted in China the presence of comorbidities were associated with high risk of severe COVID-19 and mortality. From these comorbidities pre-existing CVD conferred highest risk of developing severe COVID-19 compared to mild disease. Again pre-existing cardiovascular disease was associated high risk of mortality. Another study done in Italy show highest case fatality rate in COVID-19 positive patients with pre-existing CVD (21,22).

According to one single center study conducted in China investigating hospitalized patients with pneumonia secondary to COVID-19: already 40% had cardiovascular disease specifically coronary artery disease and cerebrovascular disease(7). Again according to one study done in China on hospitalized patients there was high COVID-19 mortality rate in elders and with cardiovascular comorbidities. The percentage of death in patients with comorbid CVD compared to without comorbid CVD was 8.4% versus 1% respectively (20).

Systematic review on the prevalence and risk factors for death and severe disease show the overall rate of death was 20% and severe disease accounts 28%. Associated factors with death were age > 60 years, CVD, diabetes, chronic kidney disease (CKD), smoking history, COPD (chronic obstructive pulmonary disease) and chronic liver disease (CLD) (23).

According to meta-analysis done by Espinosa and his colleagues the prevalence of comorbid condition was 42% from the total positive patients. While it accounted for 61% in patients admitted to ICU and 77% in recorded death. From the total population studied the most common comorbid diseases were CVD, diabetes and COPD. In patients admitted to ICU and developed fatal cases the most common comorbid diseases were diabetes and heart diseases (24).

In Lagos, south west Nigeria from COVID-19 positive individuals 22.5% of them had at least one comorbid condition. These comorbid diseases were CVD, diabetes, renal disease and asthma. While from these comorbid diseases CVD was associated with highest risk of death. While these individuals developed severe to critical disease. Most of the patients with comorbid conditions aged greater than 50 years (25).

CVD is responsible for 17.9 million deaths annually throughout the globe. COVID-19 itself is responsible for acute cardiac injury in 7 to 28% of infected patients and from this 10.5% died due to underlying CVD. From CVDs hypertension accounts 30% and is responsible for 6% of death. Generally CVD is most prevalent in patients who developed severe disease (26).

As one study done in Ethiopia from COVID-19 infected patients 75% of them have at least one comorbidity and CVD was one of the commonest from these comorbidities. In China also CVD was the most prevalent comorbidity which is associated with severe illness and increased mortality. From all CVD hypertension was the most prevalent (27,28).

As we can see from the above most of COVID-19 positive patients have at least one comorbidity . These comorbid diseases were associated with severe disease and poor treatment outcomes. From this comorbid disease CVD is one of the most prevalent comorbid condition which was associated with severe disease and high mortality. In Africa particularly in Ethiopia there was no sufficient data on the effect of underlying CVD among COVID-19 infected patients. Thus the aim of this study was to evaluate the specific prevalence of cardiovascular disease and risk of cardiovascular disease on disease severity and treatment outcome.

1.3. Significance of the study

Despite pre-existing CVD has significant impact on COVID-19 disease severity and treatment outcome, there been insufficient data in Ethiopia. Most available literatures were from developed countries which do not consider our knowledge and resources for COVID-19 management. By considering this the information generated in this study tries to address the gap.

The information generated by this study used as an input by clinicians to specially focus on the prevention of COVID-19.

2. Literature Review

Globally COVID-19 is still now posing great problem. World Health Organization (WHO) reported as of 7 August 2022, 581.8 million confirmed cases and 6.4 million deaths have been reported globally (29). COVID-19 places double burden on patients with chronic disease which includes the additive adverse effect of COVID-19 and chronic disease and the disruption of cares given (30).

The first reports of COVID-19 in Wuhan China show that the disease was highly prevalent in those with comorbid conditions like diabetes and cardiovascular disease. Also fatal outcomes was high in these group of patients (31).

COVID-19 is responsible for acute cardiac complication like left ventricular dysfunction, heart failure, arrhythmias and acute coronary syndrome. The fatality rate in patients with comorbid cardiovascular disease was estimated to be five to ten folds. (32). Cohort study conducted in Florida and observational study conducted in Italy indicates the risk of death in patients with comorbid hypertension and heart failure was 4 times and 1.24 times higher respectively (33,34).

A retrospective cross sectional study done on all African countries indicates 3.1% of patients have at least one chronic disease. Mortality rate is estimated to be 5.6% and the most common risk factors associated with mortality were older age, presence of chronic disease, travel history and viral load (35).

A retrospective study done in China on hypertensive individuals, comparing patients taking ACEI/ARB versus other antihypertensive medications show there was no statistically significant difference in hospital mortality, intensive care unit (ICU) admission and mechanical ventilation utilization. Also length of hospital stay and duration of viral shedding was not affected by the prescription of these antihypertensive medications (36).

A meta-analysis done in china indicates CVD were highly associated with severe outcomes in individuals co-infected with COVID-19. In patients with comorbid CVD the likely to develop severe COVID-19 was 4 times higher compared to patients without comorbid CVD (37).

The existence of underlying cardiovascular disease and cardiovascular disease risk factors like arterial hypertension, coronary heart disease and diabetes mellitus were highly associated with acute myocardial injury in hospitalized patients for COVID-19 compared to patients without

comorbid cardiac disease and risk factors. In patients with pre-existing CVD there was hyper-expression of angiotensin converting enzyme 2 (ACE2) which increase susceptibility risk and facilitates easy colonization of cardiovascular system by Covid-19 (8).

According to meta-analysis done by yang and his colleagues on COVID-19 positive patients comparing severe disease with non-severe, the presence of respiratory disease and cardiovascular disease are responsible for severe disease. Even though presence of comorbidities have significant effect on the COVID-19 severity the degree of the effect was not the same (38).

COVID-19 positive patients with underlying diabetes, CVD, COPD, CKD and cancer were associated with high risk of severe disease and again CVD, COPD, CKD, cerebrovascular disease and cancer are responsible for high probability of mortality. According to this study 9.7% of patients with severe disease have underlying CVD and also associated with high risk of mortality. In general the presence of underlying CVD and COPD were associated with development of severe disease and mortality of two fold (39).

Among death recorded in Wuhan cohort, 40% of COVID-19 deaths were due to the myocardial damage and heart failure, either alone or in associated with respiratory failure(40). Those patients with elevated biomarkers of cardiac injury were at highest risk of death. Mortality risk associated with elevated cardiac biomarkers was more significant than mortality associated with age, diabetes mellitus, chronic pulmonary disease and pre-existing cardiovascular disease. Overall cardiovascular system involvement was prevalent and again its involvement was used for prediction of prognosis in COVID-19. The elevation of cardiac markers reflect systemic illness in critically ill patients with COVID-19 (41).

According to one case control study conducted in Ethiopia at the Millennium COVID-19 Care Center (MCCC) the presence of fever on admission was associated with having good outcome of being discharged alive. On the other hand the presence of shortness of breath (SOB) was associated with worse outcome like death. Those patients with history of SOB on presentation had 4 times chance to die compared to patients recovered (42).

The median time for viral clearance once one person becomes positive was 19 days, but the range was very wide (i.e 2 to 71 days). The median time by which one person tests negative by PCR for SARS-CoV-2 was not affected by sex, BMI, blood type and symptom status. Comorbid

diseases prolong the duration of viral clearance (43). Other study conducted in China shows the presence comorbid CVD has no effect on time to test negative of the virus (44).

2.1. Conceptual framework

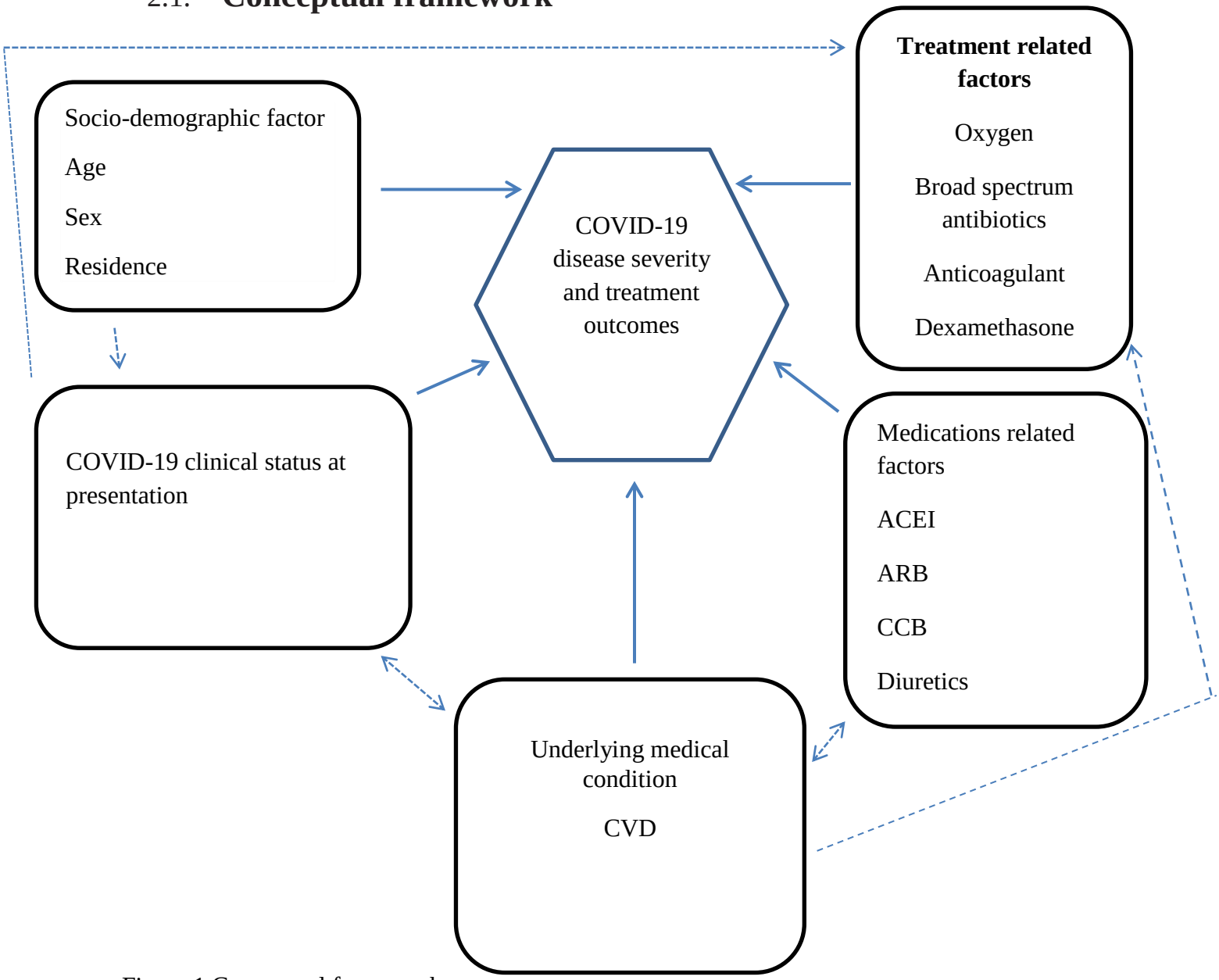

Figure 1 Conceptual framework

This conceptual framework was developed after reviewing literatures from number (8,35–41,43)

3. Objectives

3.1. General objective

To assess the severity, treatment outcome and associated factors among hospitalized COVID-19 patients at Jimma Medical Center in Ethiopia

3.2. Specific objectives

- To assess the prevalence of each cardiovascular diseases among hospitalized COVID-19 patients at JMC
- To identify factors associated with COVID-19 disease severity at JMC
- To identify factors associated with COVID-19 related death at JMC

4. Methods and participants

4.1. Study area and period

The study was conducted at Jimma Medical Center, and a teaching hospital located in Jimma Zone in south West Ethiopia. Geographically, it is located the city of Jimma, 352 kilometer southwest of Addis Ababa. Currently it is the only teaching and referral hospital in southwestern part of the country, providing services for approximately 16000 inpatient, 220000 outpatient attendants, 12000 emergency cases and 4500 deliveries in a year coming to the hospital from the catchment population of about 15 million people (45). The study was conducted from 3 January to 4 March 2022.

Study design

Retrospective cross-sectional study was conducted

4.2. Study participant

4.2.1. Source population

All confirmed or suspected COVID-19 patients who were admitted to JMC COVID-19 treatment center.

4.2.2. Study population

All confirmed COVID-19 patients with pre-existing CVD admitted to JMC COVID-19 treatment center

Eligibility criteria

4.2.3. Inclusion criteria

RT-PCR confirmed COVID-19 and Admitted to JMC COVID-19 treatment center starting from 16 May 2020 to 4 March 2022

Age ≥18 years

4.2.4. Exclusion criteria

- COVID-19 patients with comorbidity except CVD
- Pregnancy

- Incomplete patient medical chart

4.3. Sample size and sampling strategies

All adult patients with RT-PCR confirmed COVID-19 admitted to JMC COVID-19 treatment center that fulfills the inclusion criteria.

Study variables

4.3.1. Independent variables

Patient related factor

- ✓ Age
- ✓ Residence
- ✓ Sex

Disease related factor

- ✓ Pre-existing cardiovascular disease
- ✓ Sign and symptoms of the patient on admission

Supportive treatment related factors

- ✓ Oxygen
- ✓ Broad spectrum antibiotics
- ✓ Anticoagulant
- ✓ Dexamethasone

Medications related factors

- ✓ ACEI
- ✓ ARB
- ✓ CCB
- ✓ Diuretics

4.3.2. Dependent variables

Primary outcome

Death

Secondary outcome

Disease severity

4.5 Definition of terms

The severity of Covid-19 is classified as below based on sign and symptoms of the patient:

Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, or abnormal chest imaging. Additionally Asymptomatic or Pre-symptomatic Infection can be considered as mild since initially they feel fine while the virus is their bodies later begin to experience symptoms (46).

Moderate illness: Individuals with the evidence of lower respiratory tract infection by clinical assessment or by imaging but oxygen saturation (SpO2) >94%. (47)

Severe illness:

Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%(48).

Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunctions. (48)

Cardiovascular disease: they are a group of disorders of the heart and blood vessels and they include:

- ✓ Coronary heart disease – disease of the blood vessels supplying the heart muscle
- ✓ Cerebrovascular disease – disease of the blood vessels supplying the brain
- ✓ Peripheral arterial disease – disease of blood vessels supplying the arms and legs
- ✓ Rheumatic heart disease – damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria
- ✓ Congenital heart disease – malformations of heart structure existing at birth
- ✓ Deep vein thrombosis and pulmonary embolism – blood clots in the leg veins, which can dislodge and move to the heart and lungs
- ✓ Hypertension - high blood pressure (49).

Length of Hospital stay: it is the number of days between admission to treatment center after being positive by RT-PCR until two consecutive negative results of the virus by the RT-PCR in 24 hours or clinical recovery (43).

Confirmed case: If the individual tested by reverse transcriptase polymerase chain reaction and becomes positive for SARS-CoV-2 (50).

Death: COVID-19 deaths include people who have had a positive molecular (PCR) or antigen test for COVID-19, who died without fully recovering from COVID-19, and who had no alternative cause of death identified (51).

Comorbidity refers to the presence of known medical conditions specifically cardiovascular disease among the COVID-19 confirmed cases (43).

4.6 Data collection instrument and procedure

Patient information was collected from both medical chart and computer database available in this clinic. The data abstraction checklist was prepared by reviewing previously published literatures through adaptation method (25,27,28,38,43) and it has three parts which includes socio-demographics and patient identification, clinical characteristics of the disease and COVID-19 disease severity and treatment outcome. Then using prepared data abstraction checklist the necessary information was collected and coded.

4.7 Data analysis and procedures

The collected data was checked for completeness and coded. Then entered to Epi Data version 4.6.0.6 and then exported to Statistical Package for Social Sciences (SPSS) version 23 for analysis. Descriptive statistics such as frequencies, means, percentage and charts were used. Multiple logistic regression model was used to determine the degree of association between sign and symptoms, age, sex, residence, presence or absence cardiovascular disease, medications used for CVD and COVID-19 management with COVID-19 treatment outcomes. Variables having a p value of ≤ 0.25 in the Univariate model were subjected to multivariable analysis and P-value of <0.05 considered as statistically significant. Ordinal logistic regression model was used to analyze factors associated with COVID-19 severity.

4.8 Data Quality assurance

Data quality was ensured through strict follow up, data abstraction checklist was thoroughly checked for completeness and consistency by the supervisor. To ensure quality of data collection

tool prior to carrying out the study pretest was conducted on 20 patients at JMC COVID-19 treatment center. After analyzing pretest result, necessary modification and correction was made accordingly.

Every day the collected data was checked for clarity, consistency and completeness by the supervisor. Consequently, amendments and corrections were made before the start of the next day's work. Training was given to the data collectors by the principal investigator on how to use the data abstraction checklist, objectives of the study and how to review contents of cards. The data was collected by two Pharmacists and one professional Nurse.

4.9 Ethical consideration

Ethical clearance was obtained from Jimma University Institutional Review Board. Supportive letter was written to Jimma university medical center. Data collection has been carried out after permissions were obtained from hospital managers/medical directors. Strict confidentiality was assured through anonymous recording and coding of questionnaires and placed in safe place.

4.10 Dissemination plan

The research result will be presented during thesis defense and submitted to Jimma university school of pharmacy. A result of the study will be compiled in the form of thesis, and will be communicated to all concerned bodies and attempts will be made to present findings on scientific journal. The result of this thesis will be presented for partial fulfillment of the requirement of masters of Science degree in clinical pharmacy.

5. RESULTS

5.1 Study participants Enrollment information

A total of 406 Covid-19 positive patients were treated in this center. But only 374 patient medical charts were obtained. From these 119 patients have been excluded because they have comorbid medical conditions and used for pre-test study. Finally 275 patients were included for the analysis (figure 2))

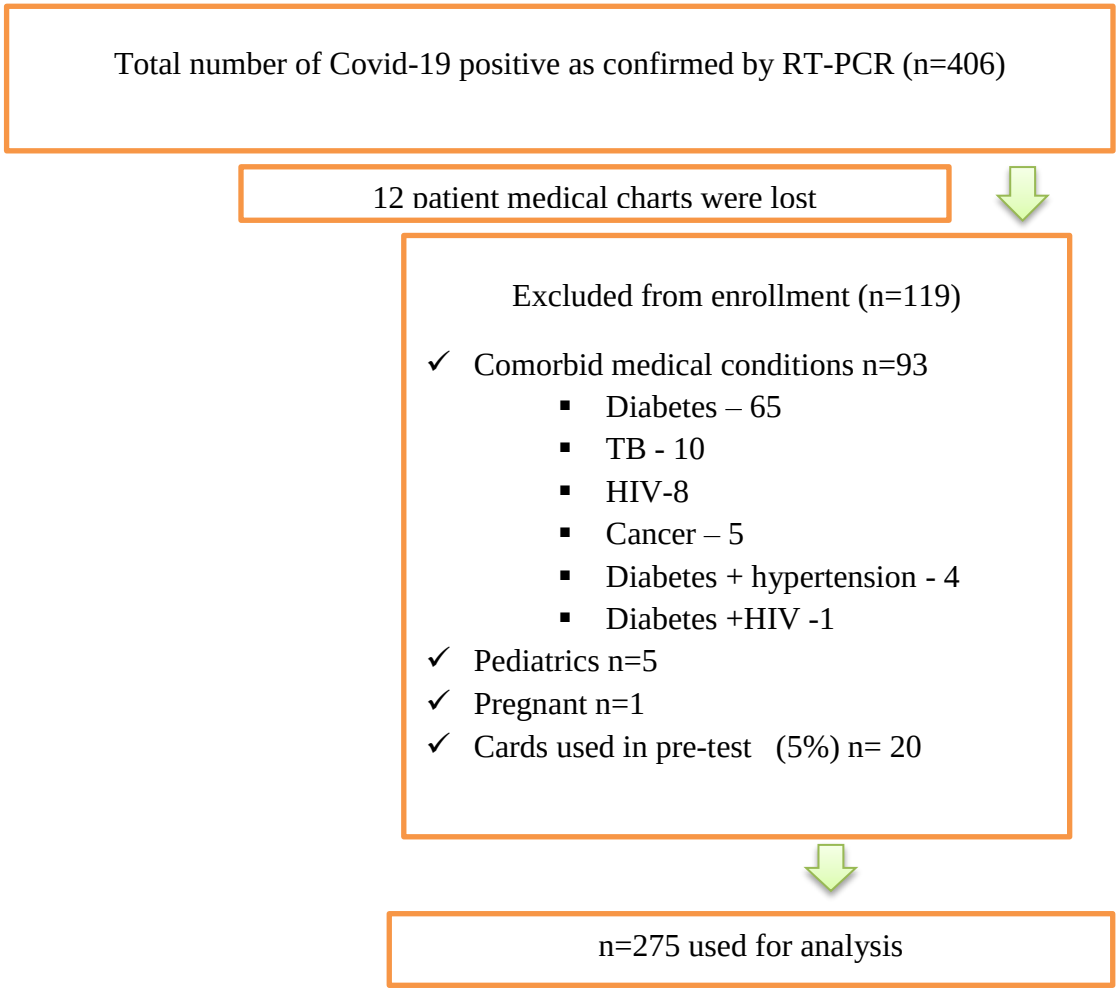

Figure 2 Study participant recruitment flow diagram

5.2 Socio-demographic characteristics and pattern Covid-19 disease severity distribution

From those patients eligible for the study 66.5% of them were males and the mean age of patients died was 60.01±15.797 versus 50.82 ± 17.461 years compared improved. Majority 55.3% of the patients studied were from urban population. (Table 1)

Table 1 Socio-demographic characteristics COVID-19 positive in Jimma Medical center from January 3 to March 4, 2022

Variable	Category	COVID-19 treatment outcomes		
		Improved and discharged (%)	Death (%)	Total
Sex	Male	115(65.0)	68 (69.4)	183(66.5)
	Female	62 (35)	30 (30.6)	92(33.5)
Residence	Urban	99 (55.9)	53 (54.1)	152 (55.3)
	Rural	78 (44.1)	45 (45.9)	123 (44.8)
Age	Age (mean ± standard deviation)	50.82 ± 17.461	60.01±15.797	

5.3 Clinical characteristics of the participants

The prevalence of each comorbid CVD differs in Covid-19 positive patients. Among these cardiovascular diseases hypertension was the most prevalent 27.6% and also associated with high percentage of death. Overall, only hypertension and heart failure have significant association with COVID-19 treatment outcomes. Dry cough, shortness of breath and fatigue were the most common symptoms present at admission in both patients improved and died. (Table 4)

Table 2 Clinical characteristics of the participants in Jimma medical center from January 3 to March 4, 2022

Cardiovascular diseases	COVID-19 treatment outcomes		
	Improved and discharged- N(%)	Death - N(%)	Total (%)
Hypertension	34 (19.2)	42(42.9)	76 (27.6)
Heart failure	12 (6.8)	15 (15.3)	27 (9.8)
Arrytthmia	3 (1.7)	5 (5.1)	8 (2.3)
Acute coronary syndrome	3 (1.7)	6 (6.1)	9 (3.3)
Venous thrombosis	2 (1.1)	3 (3.1)	5 (1.8)
Valvular heart disease	9 (5.1)	8 (8.2)	17 (6.2)
Fever	51 (28.8)	39 (39.8)	90 (32.7)
Dry cough	136 (76.8)	89 (90.8)	225 (81.8)
Head ache	21 (11.9)	12 (12.2)	33 (12)
Nausea	30 (16.9)	25 (25.5)	55 (20)
Muscle ache	34 (19.2)	23 (23.5)	57 (20.7)
Vomiting	5 (2.8)	4 (4.1)	9 (3.3)
Loss of appetite	59 (33.3)	38 (38.8)	97 (35.3)
Anosmia	32 (18.1)	17 (17.3)	49 (17.8)
Sore throat	10 (5.6)	5 (5.1)	15 (5.5)
Shortness of breath	116 (65.5)	83 (84.7)	199 (72.4)
Fatigue	81 (45.8)	54 (55.1)	135 (49.1)

5.4 Prevalence of COVID-19 disease severities and Duration of hospital stay

The mean duration of hospital stay was 11.26 ±7.5 days. Severe COVID-19 was most prevalent in patients with pre-existing CVD. (Table 3)

Table 3 The Prevalence of COVID-19 disease severities and Duration of hospital stay in patients with COVID-19 patients at JMC in January 3 to March 4, 2022

Variable		**N (%)**
Duration of hospital stay (in days)	Mean ± SD	11.26 ±7.5
COVID-19 disease severities	Mild	56 (20.4)
	Moderate	56 (20.4)
	Severe	124(45.1)
	Critical	39 (14.2)

5.5 Factors associated with inpatient mortality in COVID-19 positive patients

The risk of death in patients with comorbid CVD was (AOR 2.137; CI 95% 1.020-4.476) compared to patients without comorbid CVD. Patient groups prescribed antibiotics has high odds of death (AOR 2.692; CI 95% 1.132-6.404) compared to patients groups who did not took antibiotics. While the administration of dexamethasone, anticoagulants and oxygen has no significant effect on reducing Covid-19 related death. The medications taken for comorbid CVD management like ACEI, CCB, beta blockers, loop diuretics and others had no significant association with Covid-19 related death. (Table 7)

Table 4 Factors associated with in patient mortality in Jimma Medical Center from January 3 to March 4, 2022

Variable	Bivariate logistic regression				Multiple logistic regression			
		CI				CI		
	COR	Lower	Upper	p-value	AOR	Lower	Upper	p-value
Cardiovascular disease	3.037	1.820	5.069	<0.001	2.137	1.020	4.476	0.044
Antibiotics	4.817	2.400	9.671	<0.001	2.692	1.132	6.404	0.025
Dexamethasone	3.129	1.747	5.602	<0.001	1.295	0.592	2.832	0.518
Oxygen	3.265	1.867	5.708	<0.001	1.505	0.760	2.981	0.241
Fever	1.633	0.972	2.744	.064	1.434	0.809	2.542	0.217
Dry cough	2.981	1.381	6.435	0.005	0.938	0.345	2.549	0.901
Shortness of breath	2.910	1.548	5.470	0.001	1.291	0.599	2.779	0.514
Fatigue	1.455	0.886	2.388	0.139	0.967	0.554	1.689	0.907
Anticoagulants	3.757	1.862	7.580	0.001	0.977	0.355	2.692	0.965
ACEI	1.724	.835	3.556	0.141	0.842	0.341	2.075	0.708

COR/AOR- crude/adjusted odd ratio CI- confidence interval

5.6 Factors associated with COVID-19 disease severity

The likelihood that patients with comorbid cardiovascular disease to develop critical Covid-19 was [AOR, 5.794; 95% CI, 2.516- 13.343] compared to patients without comorbid cardiovascular disease. Patients prescribed beta-blockers for CVD had 0.697 times lower risk of developing critical Covid-19. However the prescription of ACEI, CCB, ARB, thiazides and statins as well as being in the age group of 30 to 60 years has no significant association with Covid-19 disease severities. (Table 7)

Table 5 Factors associated with COVID-19 disease severity at Jimma Medical center Covid-19 treatment center from January 3 to March 4, 2022

Variable		COR	AOR	Confidence interval		p-value
				Lower	Upper	
Cardiovascular disease	Yes	1.757	5.794	2.516	13.343	<0.001
	No	-1.757	0.158	1		
ACEI	Yes	-0.022	0.978	.418	2.290	0.960
	No	0.022	1.055	1		
CCB	Yes	-0.578	0.561	.236	1.333	0.190
	No	0.578	1.801	1		
ARB	Yes	1.109	3.032	.060	153.830	0.580
	No	-1.109	0.291	1		
Thiazides	Yes	-0.229	0.796	.290	2.182	0.657
	No	0.229	1.258	1		
Beta-blockers	Yes	-1.193	0.303	.104	.882	0.028
	No	1.193	3.46	1		
Statins	Yes	-0.419	0.658	.071	6.076	0.712
	No	0.419	1.426	1		
Age classification	18-30	-1.818	0.162	.073	.363	<0.001
	30-60	-0.472	0.624	.375	1.038	0.069
	>61	2.29	9.535	1		

ACE- angiotensin converting enzyme inhibitors, CCB- calcium channel blockers, ARB- angiotensin receptor blockers, COR/AOR- crude/adjusted odd ratio

6. DISCUSSION

In this study the presence of pre-existing CVD and patients prescribed antibiotics had higher risk of mortality. Being male or female and the residence of the patient had no impact on COVID-19 related mortality. On the other hand, pre-existing CVD was associated with higher risk of developing severe disease. Despite beta-blockers were used for CVD management they were associated with lower risk of developing severe disease in COVID-19 positive patients.

COVID-19 causes mainly lower respiratory tract infection (52) and its manifestation ranges from no symptom to critical illness. In this study the most common sign and symptoms present on presentation were dry cough, shortness of breath, fatigue, loss of appetite and fever. They had no statistically significant association with COVID-19 death. A cross sectional study done in China shows the common symptoms were fever (84.3%), cough (56.9%) and fatigue (27.5%) (53). On the other hand, the study conducted in Qatar show fever and cough were the most frequently reported symptoms (54). This difference may be due to geographical locations, participants included and sample size.

In this study the prevalence of CVD was 40%. From these spectrums of CVD hypertension and heart failure were the most common comorbidities. The study done eastern part of Ethiopia shows the prevalence CVD (37%) and from this hypertension accounts 19.9% (55). This result is in line with the review done in china (26). Again another study done in Italy show hypertension was the most prevalent followed by coronary artery disease and atrial fibrillation (33). The similarity in the prevalence of hypertension may be due to high epidemiological prevalence of hypertension as compared to other CVD. In this study the second most common CVD was heart failure and also related with high proportion of death following hypertension. This may be due to synergistic adverse effect of pre-existing heart failure and Covid-19 complications. This result is in line with cohort study done in Florida (34).

The prevalence of COVID-19 disease severities was severe, moderate, mild and critical in their descending order respectively. This result is in line with study done in Bangladesh which shows severe, moderate, and mild as 66.7%, 18.7% and 14.6% respectively (56). While another study done in Lebanese show COVID-19 disease severity mild, severe/critical, and moderate as 86.3%, 7.5% and 6.2% respectively (57). This difference may be due to participants included and sample size.

The presence of pre-existing CVD and other factors affect the type of Covid-19 severity developed. In this study the pre-existence of CVD was associated with high odds of developing severe and critical Covid-19 compared to patients without comorbid cardiovascular disease. The study done in Ethiopia and meta-analysis conducted in South Korea indicates the presence of pre-existing CVD was related with development of severe Covid-19 compared to patients without comorbid CVD (58,59). Following the infection by Covid-19 virus there is activation of monocytes and macrophages. The ensuing inflammatory response causes blood vessel dilation and increase endothelial leakage and the presence of pre-existing CVD further aggravates the pathway which is responsible for the development of severe and critical Covid-19 (58). In this study patients prescribed with beta-blockers for the management of CVD has low odds of developing severe and critical Covid-19. The retrospective study done on hospitalized Covid-19 patients in Poland indicates beta-blockers were associated with low risk of developing severe and critical Covid-19. This effect may be mediated by the reduction of catecholamine dependent inflammatory over response by beta-blockers (60). The odds of developing critical Covid-19 was 1.784 times higher in patients greater than 61 years compared to patients in the age group 18 to 30 years. The meta-analysis done by Matsushita with his colleagues and case control done in Ethiopia show that severe Covid-19 was more developed by elder populations than adolescents (61,62). This may be related with increased number of chronic diseases and decreased immunity in elderly patients.

In the current study the pre-existing cardiovascular disease and antibiotic prescription were independent predictors for Covid-19 related death. From these CVD hypertension has been related with high risk of death. This result was in line with the meta-analysis done in Unites states of America (63). Other meta-analysis done in Brazil also shows that the pre-existing CVD has been associated with high risk of death and the prescription of ACEI/ARB for the management of CVD had no significant association with Covid-19 related death (64). The retrospective study conducted in Russia indicates the usage of ACEI, statins and antiplatelet drugs for CVD management has no significant effect on COVID-19 treatment outcome (65). From the supportive treatments used for Covid-19 antibiotic prescription was associated with high risk of death as compared to patients with no antibiotic prescription. The study done in Romania and France indicates risk of mortality were high in patient groups a prescribed

antibiotics (66,67). Overall most studies indicate pre-existing CVD was associated with high risk of death compared to patients without comorbid CVD (23,63).

Strength and limitation of the study

This study presents that pre-existing CVD has significant association with COVID-19 severity and mortality. By considering this it enables concerned bodies to take preventive measures.

This study has limitations since it was retrospective in nature and also some patient information was not available. In most of the patients medical chart laboratory investigation was not done because of this some variables which have significant effect on the outcome in literatures were not included. The investigator cannot control over the quality and completeness of the data since it was for patient care not for research purpose.

7. Conclusions and Recommendations

Conclusions

In general the presence of pre-existing CVD was associated with high risk of severe COVID-19 and high risk of death. From these CVD hypertension was the most prevalent and frequently associated with severe disease and death. Antibiotic prescription was associated with higher risk of death.

Recommendations

The current study show that the prevalence of comorbid CVD was significant as well associated with high risk of death in COVID-19 positive patients. Since this disease has still now has no curative treatment our primary focus should be on the prevention of the infection. Priority should be given for patient with comorbid CVD to be vaccinated and awareness should be created about life style modifications which help as for the prevention of the disease.

The following recommendations are forwarded to:

1. For Jimma Medical center
- To educate patients and create awareness on the ways of disease prevention specially life style modification
- To carry out study on the rational utilization of antibiotics used as a supportive therapy
2. For researchers
- To carryout nationwide study to assess the significance of comorbid diseases on Covid-19 disease severity and treatment outcome
3. For ministry of health
- To create nationwide awareness on life style modification for prevention of COVID-19

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Annex I Data abstraction checklist

Jimma University

Institute of Health

School of pharmacy

Department of clinical pharmacy

Title: To assess the severity, treatment outcome and associated factors among hospitalized COVID-19 patients at Jimma Medical Center in Ethiopia

Sponsor: Jimma University

Part I: Socio demographic Characteristics

1. Name of the patient (the initials): …..
2. Card number : ……
3. Sex : M ◯ F ◯
4. Age of the patient : …….
5. Residence of the patient: rural ◯ urban ◯

Part II - Clinical characteristics of the disease

6. Baseline clinical features of the patient on admission (thick in front)
   - Fever
   - Cough
   - Dyspnea
   - Head ache
   - Muscle ache
   - Sore throat
   - Loss of appetite
   - Anosmia
   - Diarrhea
   - Nausea
   - Vomiting
   - Rash
7. Does the patient have comorbid cardiovascular disease?

   Yes ◯ No ◯

8. If yes to the above question, which type of cardiovascular disease?

- Hypertension
- Heart failure
- Arrhythmia
- Acute coronary syndrome
- Venous thrombosis
- Valvular heart disease
- Cardiomyopathies
- Others …….

9. How many comorbid cardiovascular diseases do they have? …….
10. What are the medications and their dosage the patient is taking for the management of cardiovascular disease?

- ✓ ACEI
- ✓ ARB
- ✓ CCB
- ✓ Thiazides
- ✓ Statins
- ✓ Morphine
- ✓ Loop diuretics
- ✓ Aspirin
- ✓ Others ……

Part III- Covid-19 disease severity and treatment outcome

11. Based on the following subjective and objective data what is the severity class of COVID-19 severity?

- ➢ Mild
- ➢ Moderate
- ➢ Severe
- ➢ Critical

12. What are the interventions done for the management of Covid-19?

- ✓ Oxygen
- ✓ Broad spectrum antibiotics
- ✓ Anticoagulants
- ✓ Dexamethasone
- ✓ Other (specify)

13. After how many days the patient has been discharged either improved or died? …….

14. What are the outcomes of the intervention?

- ➢ Discharged (improved)
- ➢ Death