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Determinants of Death among COVID-19 Patients Admitted in Amhara Region COVID-19 Treatment Centers, Ethiopia, 2021, Unmatched Case Control Study

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Abstract

Background: The rapid emergence of the novel corona virus disease 2019 (COVID-19) has resulted in millions of infected patients and deaths in worldwide. Studies conducted till today show that the outcome of COVID-19 varies based on individual characteristics. The purpose of this investigation was to identify the determinants of COVID-19 deaths in Amhara Region. The study aimed to identify the determinants of death among COVID-19 patients admitted in Amhara region COVID-19 treatment centers, Ethiopia, 2021.

Method: Unmatched case control study design was conducted among 675 COVID-19 patients (135 case and 540 control by 1:4 ratio) admitted in 8 COVID-19 treatment centers in Amhara region from march 1, 2020 to march 30, 2021. From study participants cases were all death in COVID-19 treatment centers and controls were selected using simple random sampling technique of lottery method. Data were collected by using Epicollect5 software from 8 COVID-19 treatments centers and analyzed via STATA version 14. Mean, median and interquartile range were computed for cases and control groups and Variables that had (P-value < 0.25) in the Bivariable logistic regression analysis were entered in Multivariable logistic regression model. Finally Adjusted Odds ratio (AOR), 95% CI for AOR, and P-values < 0.05 were used to declare statistical significance and interpretation of results.

Result: Analyses were done on 675 COVID-19 patients comprising 135 cases and 540 controls. Factors such as older age (AOR 1.14, 95% CI 1.11-1.17), male sex (AOR 3.63, 95% CI 1.74-7.55), rural residence (AOR 0.21, 95% CI 0.10-0.42), patients who had fever (AOR 3.65, 95% CI 1.72-7.75), Sign of respiratory distress (AOR 4.04, 95% CI 1.94-8.42), hypertension AOR (2.58, 95% CI 1.06-6.25) and diabetes mellitus (AOR 5.3, 39% CI 1.33-8.64) were found to be independent determinants of Death.

Conclusion: Increment in age, male sex, urban residence, having fever and signs of respiratory distress at admission, comorbidity of diabetic Mellitus, and hypertension were found to be significant determinants of death among COVID-19 patients.

Keyword

Amhara region, Case-control, COVID-19, Death, Determinant

Acronyms

ACE: Angiotensin-Converting Enzyme; AHR: Adjusted Hazard Ratio; ARBs: Angiotensin Receptor Blockers; ARDS: Acute Respiratory Distress Syndrome; BOS: Blood Oxygen Saturation; COPD: Chronic Obstructive Pulmonary Disease; ICU: Intensive Care Unit; IMV: Invasive Mechanical Ventilation; NCIP: National Commission on Indigenous Peoples; NHC: National Health Commission; NGO: Non Governmental Organization; MERS: Middle East Respiratory Syndrome; RT-PCR: Reverse Transcriptase-Polymerase Chain Reaction; SARS: Severe Acute Respiratory Syndrome; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SPSS: Statistical Package for Social Science; SOFA: Sequential Organ Failure Assessment; WHO: World Health Organization

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Background

Coronavirus illness (COVID-19) could be a worldwide catastrophe, with rapid dispersion, that has influenced passing around the world. It may be a breathing disease that can spread from person to the person causing virus in extreme cases and death. It was, to begin with, reported in China and the World Health Organization asserted the event of a widespread [1].

COVID -19 debasements are rumored to spread through breathing large droplets, contact with body fluids, and with contaminated surfaces. The COVID-19 scourge is transmitted person to person through tainted discuss precipitation, individuals making contact with fingers or faces that contain the infection and after that touching their eyes, nose, or mouth with unclean hands [2].

All arrive borders have since been closed as an infection control degree with several restrictions and execution of physical distancing and mask-wearing measures. But the pandemic is rising due to a temperature change (summer season) and the public ignoring Ministry of Health's rules for controlling the COVID-19 pandemic. Even though such measures wear taken in Ethiopia, death the record becomes rise (274,480 cases with 4,257 deaths) since the epidemic began, according to Ethiopia's Ministry of Health June 16, 2021). In addition, Amhara region there are 11,791 positive cases from 290,889 testes and 293 deaths of covid-19 [3].

Internationally, healthcare services delivery is being compromised due to the surge in the number of infected patients during this COVID-19 pandemic. Overwhelming the health-care the system will lead to an unexpected rise in morbidity and mortality of various treatable conditions.

Therefore, it is critical to risk stratify COVID-19 patients based on their predicted outcomes and guide appropriate management and disposition accordingly. The clinical manifestation of COVID-19 is broad and ranges from asymptomatic and mild upper respiratory tract symptoms to severe illnesses with multi-organ failure and death [4].

Furthermore, it is challenging to predict the clinical course or determine patients at risk of deterioration. Previous reports showed that old age and male gender are risk factors for disease severity and mortality other medical comorbidities are associated with poor prognoses such as cardiovascular disease, diabetes mellitus, chronic respiratory disease, and hypertension [5-7].

Even though Ethiopia is among the top four leading African countries with the COVID-19 case, there is only one study conducted on the determinants of death among patients in Millennium COVID-19 Care Center in Ethiopia and it is the only case-control study conducted in Ethiopia on determinants of death among

COVID-19 patients [8], they recommended conducting further research that investigates the determinants of death among COVID-19 patients in a broader social context and larger sample size. This research will try to fill this gap by broadening the study area, relatively increasing the sample size and adding some variables in socio-demographic characteristics like marital status, residence, occupation, and admission symptoms characteristics.

Methods

The state of Amhara consists of 10 administrative zones, one special zone, 105 wored as, and 78 urban centers. In the Amhara region, there are 15 COVID-19 test sites and 8 treatment sites which are Gonder University, Tibebe Ghion hospital, Debre Birhan-Tebasi health center, Borumed a hospital, Debre Markos University, Injibara University, Kobo hospital, and Dessie hospital COVID-19 treatment center. Institution-based unmatched case-control study design was employed from all laboratory-confirmed COVID-19 cases located in COVID-19 treatment centers in Amhara Region from March 1, 2020, to March 30, 2021. The information available in the eligible patients' medical records was observed and then recorded using the epicollect5 data extraction tool prepared by adapting from different studies which consist of socio-demographic factors, co-morbidity factors, admission signs, and vital signs. Then, from COVID-19 patients, diagnosed between from March 1, 2020, to March 30, 2021, using simple random sampling technique by lottery method select controls from medical records and then reviewed baseline records and death certificate supplemented was identified from medical records by their medical record number. Then, the records of the study participants were selected according to the eligibility criteria.

Data processing and analysis

After the data collection, Data were first checked for completeness then the data were downloaded from epicollect5 and exported to STATA™ 14.1 for analysis. The data were checked Based on the nature of variables frequency distribution, summary statistics such as mean, median, and IQR were computed for cases and control groups.

Extent of multicollinearity between independent variables was measured using variance inflation factor (VIF) for contentious data and for a categorical variable using correlation coefficient. Regression model assumptions were checked using a test like the Hosmer & Leme show goodness of fit test to identify and exclude variables that cause poor fit in the model. The bivariable logistic regression model was fitted for each explanatory variable. Accordingly, those variables having a p-value less than 0.25 [9] in the bivariable analysis were taken as candidates for the multivariable logistic regression model. In a multivariable logistic regression AOR with

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Table 1: Socio-demographic characteristics of COVID-19 patients in Amhara region COVID-19 treatment centers (n = 675) in Ethiopia, 2021.

Variable	Control Number (%)	Case Number (%)	Total Number (%)
Sex			
Male	290 (53.7)	99 (73.6)	389 (57.6)
Female	250 (46.3)	36 (26.7)	286 (42.4)
Occupation			
Employed	346 (64.1)	93 (68.9)	439 (65.1)
Un Employed	194 (35.9)	42 (37.1)	236 (34.9)
Marital status			
Married	361 (66.9)	89 (65.9)	450 (66.7)
Not married	179 (32.6)	46 (34.1)	225 (33.3)
Residence			
Urban	307 (56.9)	104 (77.0)	411 (60.9)
Rural	233 (43.1)	31 (22.9)	264 (39.1)

P-value, less than 0.05 with a 95% confidence interval was considered as a statistically significant association. Finally, the result of the study will be presented using text, tables, and graphs.

Patient and public involvement

There was no direct interaction with patients in this study and no direct patient involvement in the design or conduct of this study.

Source of population

All COVID-19 positive patients who were admitted in Amhara region COVID-19 treatment centers.

Study population

Medical records of COVID-19 positive patients in Amhara region COVID-19 treatment centers who were diagnosed and admitted during the defined period.

Inclusion and exclusive criteria

Inclusive criteria:

Case: All COVID-19 positive patients admitted in Amhara region COVID-19 treatment center during the defined period whose treatment outcome was death.

Control: All COVID-19 positive patients admitted in Amhara region COVID-19 treatment center during the defined period and who recovered from the disease and was discharged alive (who did not die).

Exclusion criteria: COVID-19 patients who were on treatment and follow at the Center during the observation period. COVID-19 patients whose outcome status is unknown due to transfer to other hospitals or any other reason that resulted in the discharge of the patient before the observation of the outcome.

Sample size determination and sampling procedure

From All COVID-19 treatment centers, there are 135

dead patents since the Center started admission on March 1, 2020, up to March 30, 2021, and then with a 1:4 ratio of a case to control (135 cases (deaths) and 540 controls (recovered)) a total of 675 patients were included in the study. To select controls, a simple random sampling method was employed to recruit these study participants from all medical records of a confirmed diagnosis of COVID-19 patients registered from March 1, 2020, to March 30, 2021, were assessed.

Ethical approval

Ethical clearance was obtained from the Institutional Review Boards (IRB) of Bahir Dar University, College of Medicine and Health Sciences with protocol number 087/2021. The chief executive officer at Hospitals offered permission to conduct the study. Confidentiality was maintained by omitting the personal identifier of the participant during the data collection procedure and information was used only for research purposes.

Result

Socio-demographic characteristics

Median age of the patients is 42-years-old with an IQR of 56 – 33 = 23. Almost two-thirds (57.6 %) of the patients were male. More than one-third (34.9%) of patients were unemployed. Regarding marital status and residence 450 (66.7%) patients were married and 411 (60.9%) were urban residents (Table 1).

Clinical sign and symptoms characteristics

Almost all 634 (93.9%) of the patients had a history of admission signs and symptoms. The majority had a headache (77%) and followed by cough (68.7%), (Table 2).

Pre-existing comorbidity characteristics

Regarding comorbidity characteristics, 201 (29.8%) of the patients had a history of one or more pre-existing co-morbid illness. When we compare case and control

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Table 2: Symptom of COVID-19 patients at admission time in Amhara region COVID-19 treatment centers (n = 675) in Ethiopia, 2021.

Variables	Control Number (%)	Case Number (%)	Total Number (%)
Headache			
No	120 (22.2)	35 (25.9)	155 (22.9)
Yes	420 (77.8)	100 (74.1)	520 (77.1)
Vomiting			
No	479 (88.1)	117 (86.7)	593 (87.8)
Yes	64 (21.9)	18 (13.3)	82 (12.2)
Coma			
No	523 (96.8)	128 (94.8)	651 (96.4)
Yes	17 (3.2)	7 (5.2)	24 (3.56)
Diarrhea			
No	468 (86.7)	112 (82.9)	580 (85.9)
Yes	72 (23.3)	23 (17.1)	95 (14.1)
Fever			
No	255 (43.2)	31 (22.9)	286 (42.4)
Yes	285 (52.8)	104 (77.0)	389 (57.6)
Chest pain			
No	236 (43.7)	57 (42.2)	293 (31.2)
Yes	304 (56.3)	78 (57.8)	382 (68.8)
Cough			
No	184 (34.1)	27 (20.0)	211 (31.3)
Yes	356 (65.9)	108 (80.0)	464 (68.7)
Throat pain			
No	425 (78.7)	97 (71.9)	522 (77.3)
Yes	115 (21.3)	38 (28.1)	153 (22.7)
Runny nose			
No	480 (88.9)	116 (85.9)	596 (88.3)
Yes	60 (21.1)	19 (14.1)	79 (11.7)
Sign of respiratory distress			
No	461 (85.4)	59 (43.7)	520 (77.1)
Yes	79 (24.6)	76 (56.3)	155 (22.9)

Table 3: Pre-existing co-morbid illness of COVID-19 patients in Amhara region COVID-19 treatment centers (n = 675) in Ethiopia, 2021.

Pre-existing Co-morbidity			
Variable	Control Number (%)	Case Number (%)	Total Number (%)
Hypertension			
No	507 (93.9)	101 (74.8)	608 (90.1)
Yes	33 (6.1)	34 (25.2)	67 (9.9)
Diabetes mellitus			
No	508 (94.1)	97 (71.8)	605 (89.6)
Yes	32 (5.9)	38 (28.2)	70 (10.4)
Asthma			
No	520 (96.3)	120 (88.9)	640 (94.8)
Yes	20 (3.7)	15 (11.1)	35 (5.2)
HIV			
No	507 (93.9)	118 (87.4)	625 (92.6)
Yes	33 (6.1)	17 (12.6)	50 (7.4)

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Tuberculosis			
No	540 (100)	126 (93.3)	666 (98.7)
Yes	0	9 (6.7)	9 (1.3)
Pregnancy			
No	540 (100)	135 (100)	675 (100)
Yes	0	0	0
Other			
No	505 (93.5)	135 (100)	640 (99.7)
Yes	35 (6.5)	0	35 (0.3)

Table 4: The independent t-test of Baseline vital sign between control (alive) Vs. case (dead) group among COVID-19 patients in Amhara region COVID-19 treatment centers (n = 675) in Ethiopia, 2021.

S.No	Vital sign at presentation	Control	Case	Total	P value
		(Mean)	(Mean)	(Mean)	
1.	Temperature (°C)	36.20	37.14	36.39	0.0002*
2.	Heart rate (Beats/min)	91.46	99.20	93.02	0.0003*
3.	Respiratory rate (RR/min)	22.46	33.48	24.67	0.0001*
4.	SBP (mmHg)	117.83	114.44	117.15	0.1261
5.	DBP (mmHg)	79.52	81.78	79.98	0.0651
6.	Spo2 (%)	91.63	82.53	89.81	0.0001*

28% of Diabetic patents are died followed by 25% hypertension patients are died (Table 3).

Baseline vital signs of COVID-19 patients

The independent t-test result shows that comparing those who have discharged alive Vs. died patients who died had a significantly higher mean admission temperature (36.20 °C Vs. 37.14 °C, p-value = 0.0002), heart rate (91.46 Beats/min vs. 99.20 Beats/min, p-value = 0.0003), respiratory rate (22.46 RR min vs. 33.4 RR/min, p-value = 0.0001) and lower mean admission SpO$_2$ (91.63% vs. 82.52%, p-value = 0.0001) (Table 4).

Determinants of death among COVID-19 patients

Based on the result of the binary logistic regression analysis at a 25% level of significance; Age, sex, residence, fever, cough, a sign of respiratory distress, hypertension, diabetes mellitus, asthma and HIV were found to be a candidate for multiple Logistic Regression models. However; only age, sex, residence, fever, the sign of respiratory distress, hypertension, and diabetes mellitus were found to be significantly associated with mortality of COVID-19 patient's multiple Logistic Regression model at 5% level of significance. Accordingly, after adjusting other covariates, as the patient's age increased by one year the odds of death due to COVID-19 increased 1.14 times (AOR = 1.14, 95% CI = 1.11-1.17), the odds of death because of COVID-19 is 3.63 times higher among those male patients compared to female patients (AOR = 3.63, 95% CI = 1.74-7.55). Rural residents are 21% less likely to die as compared to urban residents (AOR = 0.21, 95% CI: 0.10-0.42). From the Admission sign and symptoms, the odds of death due to COVID-19 is 3.67 times higher among those with having symptoms

of fever at baseline/diagnosis compared to those with no symptom of fever at baseline/diagnosis (AOR = 3.65, 95% 1.72-7.75) and the odds of death because of COVID-19 is 4.04 times higher among those with a sign of respiratory distress at baseline/diagnosis compared to those without sign of respiratory distress at baseline/diagnosis (AOR = 4.04, 95% 1.94-8.42). Similarly, on the comorbidity characteristics, the odds of death due to COVID-19 is 3.39 times higher among those with a history of diabetes compared to those with no diabetes (AOR = 3.39, 95% CI = 1.33-8.64) and the odds of dying among those with a history of hypertension were 2.58 times higher compared to those with non-hypertensive (AOR = 2.58, 95% CI = 1.06-6.25) (Table 5).

Discussion

The overall aim of this study was to identify the determinants of death among COVID-19 patients admitted in Amhara region COVID-19 treatment centers. Accordingly, seven factors were found to be significant determinants of death in patients with COVID-19 disease. This study indicated that an increment in age has a significant effect on death due to COVID-19. This finding is supported by studies done in Millennium COVID-19 Care Center [8], Wuhan China [7], Brazil [10], the Democratic Republic of the Congo study [11], Lombardy Italy [12], and on sub-Saharan research [13]. The possible reasons for this could be as Age increases it causes numerous biological changes in the immune system, which are linked to age-related illnesses and susceptibility to infectious diseases, these changes determine not only the susceptibility to infections but also disease progression and clinical outcomes thereafter [14]. On the other hand, the

Table 5: Results for the final multi-variable binary logistic regression model among COVID-19 patients in Amhara region COVID-19 treatment centers (n = 675) in Ethiopia, 2021.

Variable	Category	Outcome		Bi variable	Multi variable analysis
		Control No (%)	Case No (%)	COR (95% CI)	AOR (95% CI)
Socio demographic variables					
Age				1.13 (1.11-1.15)	1.14 (1.11-1.17)*
Sex	Male	290 (53.7)	99 (73.6)	2.37 (1.56-3.59)	3.63 (1.74-7.55)*
	Female	250 (46.3)	36 (26.7)	1	1
Residence	Urban	307 (56.9)	104 (77.0)	1	1
	Rural	233 (43.1)	31 (22.9)	0.39 (0.25-0.60)	0.21 (0.10-0.42)*
Admission sign and symptoms					
Fever	Yes	285 (52.8)	104 (77.1)	3.00 (1.94-4.63)	3.65 (1.72-7.75)*
	No	255 (47.2)	31 (22.9)	1	1
Cough	Yes	356 (65.9)	108 (80.0)	2.02 (1.30-3.26)	1.05 (0.47-2.33)
	No	184 (34.1)	27 (20.0)	1	1
Throat pain	Yes	115 (21.7)	38 (28.2)	1.44 (0.94-2.22)	2.07 (0.90-4.73)
	No	425 (78.3)	97 (71.8)	1	1
Sign of Respiratory distress	Yes	79 (24.6)	76 (56.3)	7.51 (4.96-11.38)	4.04 (1.94-8.42)*
	No	461 (85.4)	59 (43.7)	1	1
Pre-existing comorbidity					
Hypertension	Yes	33 (6.1)	34 (25.2)	5.17 (3.06-8.73)	2.58 (1.06-6.25)*
	No	507 (93.9)	101 (74.8)	1	1
Diabetes mellitus	Yes	32 (5.9)	38 (28.2)	6.21 (3.70-10.43)	3.39 (1.33-8.64)*
	No	508 (94.1)	97 (71.8)	1	1
Asthma	Yes	20 (3.7)	15 (21.1)	3.24 (1.61-6.53)	2.60 (0.88-7.65)
	No	520 (96.3)	120 (88.9)	1	1
HIV	Yes	33 (6.1)	17 (12.6)	2.21 (1.19-4.10)	1.06 (0.35-3.20)
	No	507 (93.9)	118 (87.4)	1	1

response to therapeutics and the immune response is influenced by age-related changes within the immune system. Therefore, a better understanding of the pathophysiology of aging and the immune response will not only help understand age-related diseases but also guide targeted management strategies for deadly infectious diseases like COVID-19 [14]. Furthermore, the study also showed that males had a significantly higher chance of death. This finding is in line with studies done in the Democratic Republic of the Congo study [11], Lombardy Italy [12], and sub-Saharan research [13]. The possible reason for this finding is sex differences in immune responses, hormones, genes, there are also psychological, social, and behavioral components that influence COVID-19 progression. Compared with women, men tend to engage in more high-risk behaviors that generate the potential for contracting COVID-19, Men also tend to have lower rates than women of hand washing, social distancing, wearing masks, and effectively and proactively seeking medical help [15,16]. Unexpectedly, a study revealed that rural residents are 79% less likely to die as compared to urban residents.

This finding contradicts studies conducted in the united states [17] and South Carolina [18]. The possible reason for this could be rural residents are not seeking health centers due to multiple barriers such as lack of health care resources (E.g. transportation, health insurance, 26 providers, and facilities), geographic distance, and lower socioeconomic status and also they are not able to test COVID-19 virus and also Compared with urban residents, urban residents have higher rates of morbidity and mortality from various diseases with their sedentary way of life [19]. The present study also revealed that clinical signs and symptoms, such as fever and signs of respiratory distress were significantly associated with the death. This finding is in line with studies done in Democratic Republic of the Congo study [11], Lombardy Italy [12]. Therefore, Patients with fever and sign of respiratory distress tended to have increased rates of pulmonary embolism and coagulopathy. This is in keeping with the observation of increased prevalence of pulmonary embolism amongst COVID-19 patients seen in Europe [20]. In other way, a compromised immunity due to different causes the immune system unable

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to mount the ordinary reactions to threats like fever which leads the person to have a higher risk of serious infection and Shortness of breathing is a manifestation of decreased lung function and is considered as a sign of a life-threatening condition. Patients with persistent shortness of breath complaint are those with such lower lung reserve, functional or anatomical cause, that makes them vulnerable to a virus like COVID-19 and are unable to cope with the stress leading to a bad prognosis [21].

Being diabetic was found to be an important predictor of disease outcome. The odds of death due to COVID-19 are 3.39 times higher among those with a history of diabetes compared to those with no diabetes. The result also seems to be the case in others' setup as it is reported that having diabetes mellitus is associated with studies conducted in Millennium COVID-19 Care Center [8], Wuhan China [7], Brazil [10], the Democratic Republic of the Congo study [11] and Lombardy Italy [12]. Although the pathophysiology involved in this comorbidity remains unexplained, several hypotheses have been suggested. Blood glucose level is suggested to play an essential role in the pathogenesis of infectious diseases. The immune system of diabetes patients might be altered by the abnormal blood glucose level, resulting in dysregulation and reduced responses of immune components. Consequently, these patients are susceptible to SARS-CoV-2 and various other types of bacteria [21]. Especially if poorly controlled, is known to lead to compromised immunity that decreases the body's ability to fight off any infection including viral infections like COVID-19. Also, the chances of having and/or developing another chronic illness are higher than non-diabetic individuals. This results in any diabetic patient being 27 vulnerable to develop symptomatic infection and complications from any infectious disease that could result in worse disease prognosis [22].

The findings of this study showed that hypertension had a statistically significant association with death due to COVID-19. The result was in line with studies conducted in Wuhan China [7], the Democratic Republic of the Congo study [11], and Lombardy Italy [12]. This might be linked to, hypertension being treated with ACE inhibitors and ARBs, which results in up-regulation of ACE2 and SARS-CoV-2 binds to their target cells through ACE2. Consequently, the increased expression of ACE2 in hypertension patients, receiving ACE inhibitors would facilitate infection with COVID-19 and decrease blood flow to the brain, which results in oxygen deficiency and also, the chances of having and/or developing other chronic illnesses [23]. Thus, chronically hypertensive patients often have target organ damage that increases susceptibility for SARS-CoV-2 and elevates the risk of unfavorable outcomes in COVID-19 patients [20].

Conclusion

Finally, the study revealed that the death of COVID-19 patients was determined by the following socio-demographic factors such as age increments, male sex, having a fever, and a sign of respiratory distress at admission was also significantly affected the outcome of COVID-19 patients. Rural residents are a preventative factor for determinants of death in COVID-19 patients. Furthermore having comorbidity of diabetic Mellitus and hypertension were found to be significant determinants of death in COVID-19 patients. Based on the findings what the study revealed the following recommendations were given to concerned stakeholders. A special care plan for a patient having comorbidity of hypertension and diabetic Mellitus might be formulated and implemented by the Federal ministry of health. In addition, it is advised for health professionals to give more careful follow-up for aged, male, diabetic, and hypertensive COVID-19 patients. Finally, I recommend to researchers to do strong study designs like prospective study designs.

Author Contributions

ZA conceived of the study and oversaw the study. ZA, MB, AB, TN, SF, and AM designed the study. AM, SF, and ZA prepared the data and performed the statistical analysis. ZA conducted a background literature review and drafted the manuscript. ZA, MB, AB, TN, SF, and AM interpreted the results, critically reviewed and edited the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Competing Interest's Statement

The author reports no conflicts of interest in this work.

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