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Analysis of Risk Factors for Death in COVID-19 Patients at Bahteramas Regional General Hospital, Southeast Sulawesi Province

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ABSTRACT
Background: Coronavirus disease 2019, or COVID-19, is an infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). COVID-19 has been classified as a pandemic since 2020.
Purpose: The purpose of this study was to determine the risk factors for death due to COVID-19 at the Bahteramas Public Hospital, Southeast Sulawesi Province.
Method: This research is a retrospective analytic study with a cross sectional approach. The number of samples is 85 samples. The sampling technique was purposive sampling. The data were processed using the Chi-Square test and Odds Ratio.
Results: This study shows that 47 people died at the Bahteramas Hospital in Southeast Sulawesi Province from March to November 2020, the variable age (p value = 0.001 and OR value 5.216), gender (p value = 0.078 and OR value = 2.180), hypertension variable (p value = 0.071 and OR value = 2.510), and diabetes mellitus variable (p value = 0.013 and OR value = 3.300).
Conclusion: Age, sex, hypertension, and diabetes mellitus are risk factors for death due to COVID-19 at Bahteramas Public Hospital, Southeast Sulawesi Province.

KEYWORDS: Age, Sex, Hypertension, Diabetes Mellitus, COVID-19, Mortality.

INTRODUCTION

Coronavirus disease 2019, or COVID-19, is an infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). COVID-19 has been classified as a pandemic since 2020 [1]. The SARS-CoV-2 virus belongs to the coronavirus family, along with the Severe Acute Respiratory Distress Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [2].

The first case of pneumonia due to COVID-19 occurred in Wuhan, Hubei Province, China in December 2019 [3]. Shortly after its discovery, COVID-19 had infected more than 200 people, with 3 fatalities in Wuhan. Since then, COVID-19 cases have continued to rise and spread worldwide [4]. Thailand was the first country to report COVID-19 cases after China on January 8, 2020 [5]. In Indonesia, the first case of COVID-19 was identified on March 6, 2020, in a woman suspected of being exposed to a Japanese citizen who visited Indonesia [6].

Signs and symptoms of COVID-19 patients vary greatly depending on the severity of the disease, but the main symptoms include fever, cough, myalgia, tightness, headache, diarrhea, nausea, and abdominal pain [7]. In Indonesia, COVID-19 cases are classified into three categories: suspect (people with clinical symptoms consistent with COVID-19, or those in contact with probable/confirmed cases, or with positive Rapid Diagnostic Test Antigen (RDT-Ag) results); probable (suspected cases who died with a convincing clinical picture of COVID-19 but were not tested for Nucleic Acid Amplification Test (NAAT) or RDT-Ag, or the test results did not confirm or exclude COVID-19); and confirmed cases (people with positive NAAT or positive RDT-Ag results in an area meeting specific criteria) [8].

According to the World Health Organization (WHO), as of February 16, 2024, there were 774 million confirmed cases of COVID-19, with a mortality rate of 7 million cases [9]. Meanwhile, in Indonesia, as of March 2, 2024, the total number of COVID-19 cases reached 61,252,294, with 808,379 deaths [10].

A systematic review conducted by P. Du et al found that the mortality rate among men was 2.5 times higher than that among women. Additionally, the presence of comorbidities and advanced age are supplementary factors contributing to mortality

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among COVID-19 patients. Comorbid factors associated with increased mortality include chronic lung disease, diabetes mellitus (DM), hypertension, renal failure, and heart disease [11].

Another systematic review conducted by Hashim et al revealed Alzheimer's disease as a surprising risk factor for COVID-19 mortality. The relationship between the two conditions remains unexplained. Additionally, other risk factors include advanced age, DM, chronic lung disease, and hypertension [12].

Bahteramas Regional General Hospital in Southeast Sulawesi Province is one of the COVID-19 referral hospitals in Kendari City. Data on confirmed positive patients from March to November 2020 totaled 587, with 47 deaths.

RESEARCH METHODS

The research method used was retrospective analytic research with a cross-sectional approach. The research was conducted in December 2020 at Bahtermas Hospital, Southeast Sulawesi Province. Data were obtained from medical records. The population in this study was 587, and the number of samples studied was 85 samples. The data collection technique used the purposive sampling method..

Data analysis was performed using the Chi-square statistical test and continued using the Odds Ratio (OR). This study has obtained Ethical Clearance from the Health Research Ethics Commission of the Faculty of Medicine, Halu Oleo University with number: 026/UN29.17.1.3/ETIK/2020

RESULTS

After the data was collected, the sample characteristics were obtained as listed in Table 1. Based on age, the highest number was found in the age range of 46-55 years, as many as 22 people (25.9%). Followed by the age range 36-45 years with 21 people (24.7%), the age range 56-65 years with 20 people (23.5%), the age > 65 years with 12 people (14.1%), and the age range 26-35 years with 10 people (11.8%). The most common gender was male, with a total of 47 people (53.3%), while 38 people (44.7%) were female. Patients with a history of comorbid hypertension were found in 24 samples (28.2%), while the remaining 61 samples (71.8%) had no history of hypertension. Patients with a history of comorbid DM were found in 30 samples (35.3%), while the remaining 55 samples (64.7%) did not have a history of DM.

Table 1. Sample Characteristics Based on Age, Gender, Hypertension, and DM.

Sample Characteristics	Number (n)	Percentage (%)
Age		
26-35 Years	10	11,8
36-45 Years	21	24,7
46-55 Years	22	25,9
56-65 Years	20	23,5
> 65 Years	12	14,1
Gender		
Male	47	53,3
Female	38	44,7
Hypertension		
Hypertension	24	28,2
No Hypertension	61	71,8
Diabetes Mellitus		
DM	30	35,3
No DM	55	64,7
Total	**85**	**100**

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The results of the *chi-square* statistical test (see Table 2) to analyze whether age is a risk factor for death in COVID-19 patients obtained a p value of 0.001 (p value ≤ 0.1). This indicates an association between age and death in COVID-19 patients. The *odds ratio* (OR) results show statistical significance (90% *confidence interval (*CI)) with an OR value of 5.216 (OR value > 1). The OR value lies in the interval 2.437-5.008.

Table 2. Analysis of Age Risk Factors with Death from COVID-19

Age	Deaths Due to COVID-19						*p value*	OR (90% CI)
	Died		Not Deceased		Total			
	n	%	n	%	n	%		
> 45 Years	38	44,7	17	20,0	47	64,7	0,001	5,216 (2,437 - 15,008)
≤ 45 Years	9	10,6	21	24,7	38	35,3		
Total	**47**	**55,3**	**38**	**44,7**	**85**	**100**		

The results of the *chi-square* statistical test (see Table 3) to analyze whether male gender is a risk factor for death in COVID-19 patients obtained a p value of 0.078 (p value ≤ 0.1). This indicates an association between male gender and death in COVID-19 patients. The OR results show statistical significance (90% CI) with an OR value of 2.180 (OR value > 1). The OR value lies in the interval 1.050 - 4.532.

Table 3. Analysis of Risk Factors of Gender with Death from COVID-19

Gender	Deaths Due to COVID-19						*p value*	OR (90% CI)
	Died		Not Died		Total			
	n	%	n	%	n	%		
Male	30	35,3	17	20,0	47	55,3	0,078	2,180 (1,050 - 4,532)
Female	17	20,0	21	24,7	38	44,7		
Total	**47**	**55,3**	**38**	**44,7**	**85**	**100**		

The results of the *chi-square* statistical test (see Table 4) to analyze whether hypertension is a risk factor for death in COVID-19 patients obtained a p value of 0.071 (p value ≤ 0.1). This indicates an association between hypertension and death in COVID-19 patients. The OR results show statistical significance (90% CI) with an OR value of 2.510 (OR value > 1). The OR value lies in the interval 1.103 to 6.795.

Table 4. Analysis of Hypertension Risk Factors with Death from COVID-19

Hypertension	Deaths Due to COVID-19						*p value*	OR (90% CI)
	Died		Not Deceased		Total			
	n	%	n	%	n	%		
Hypertension	17	20,0	7	8,2	24	28,2	0,071	2,510 (1,103 - 6,795)
No Hypertension	30	35,3	31	36,5	61	71,8		
Total	**47**	**55,3**	**38**	**44,7**	**85**	**100**		

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The results of the *chi-square* statistical test (see Table 5) to analyze whether DM is a risk factor for death in COVID-19 patients obtained a p value of 0.013 (p value ≤ 0.1). This indicates an association between DM and death in COVID-19 patients. The OR results show statistical significance (90% CI) with an OR value of 3.300 (OR value > 1). The OR value lies in the interval 1.103 to 6.795.

Table 5. Analysis of DM Risk Factors with Death from COVID-19

Diabetes Mellitus	Deaths Due to COVID-19						*p value*	OR (90% CI)
	Died		Not Died		Total			
	n	%	n	%	n	%		
DM	22	25,9	8	9,4	30	35,3	0,071	3,300 (1,103 - 6,795)
No DM	25	29,4	30	35,3	58	64,7		
Total	**47**	**55,3**	**38**	**44,7**	**85**	**100**		

DISCUSSION

SARS-CoV-2, which causes COVID-19, belongs to the *coronavirus* family. SARS-CoV-2 is a positive-sense single-chain RNA virus with a capsid-like structure and no segments. The *coronavirus* family has four main proteins: protein N (nucleocapsid), glycoprotein M (membrane), protein S (spike), and protein E (envelope) [13,14]. Protein N plays a role in protecting and maintaining the integrity of the viral RNA genome, while glycoprotein M plays a role in the formation of the viral membrane. S proteins interact with cellular receptors to facilitate virus penetration into host cells. Meanwhile, E proteins are involved in the process of virus formation and release from host cells. These four proteins have important roles in the life cycle and pathogenesis of coronaviruses [13].

The SARS-CoV-2 infection process begins when the S protein binds to *Angiotensin-Converting Enzyme* 2 *receptors (*ACE2 *receptors*) which are widely expressed on epithelial cells of the airway, lungs, heart, kidneys, intestines, ovaries and testes, followed by viral penetration into the cell [15]. SARS-CoV-2 then releases its RNA into the cell. The process of translation involves the conversion of genome RNA into viral replicase polyproteins pp1a and 1ab, which are subsequently cleaved into smaller products by viral proteinases. Discontinuous transcription is employed by the polymerase to generate a sequence of subgenomic mRNAs, which are subsequently translated into viral proteins that are pertinent to the process. The assembly of viral proteins and genomic RNA occurs in the endoplasmic reticulum (ER) and Golgi apparatus, followed by their transportation through vesicles and subsequent release from the cell [14].

The direct impact of COVID-19 infection on lung tissue damage is through the mediation of a cytokine storm in the lungs, caused by overactivation of the immune system. The cytokine storm causes extensive inflammation, followed by the accumulation of exudates in the lungs that inhibit gas exchange. Continued accumulation of exudates eventually results in the occurrence of acute respiratory distress syndrome (ARDS) and respiratory failure [11].

In general, COVID-19 infection causes mild or even asymptomatic symptoms [16]. COVID-19 cases that result in severe symptoms and death are typically attributed to complications such as ARDS, septic shock, metabolic acidosis, coagulopathy, and multiple organ failure [11]. The factors associated with the emergence of these conditions are diverse [17].

Based on the results of the analysis, several factors were found to increase the risk of death in COVID-19 patients. These factors include advanced age, male gender, and the presence of comorbid diseases such as diabetes mellitus (DM) and hypertension. The presence of these factors significantly contributes to the increased risk of death in individuals infected with the SARS-CoV-2 virus.

The results of the analysis indicate that age is the strongest factor associated with increased mortality in COVID-19 patients, with a p-value of 0.001 (p-value ≤ 0.1 and OR 5.216) (Table 2). Research conducted at the onset of the COVID-19 outbreak in China, focusing on hospitalized patients, revealed that mortality rates rose with age among elderly patients. Among patients under 40 years old, the mortality rate was 0.4%; for those aged 40-50, it was 1.3%; for 50-60 years old, it was 3.6%; for 60-70 years old, it was 8%; and for those over 70 years old, it was 14.8% [18].

Older age is a significant determinant for the development of severe symptoms and death in individuals with COVID-19 [17]. In a recent study conducted by Du et al, a comprehensive review and meta-analysis of 17 publications published in 2020

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revealed that older age emerged as a noteworthy risk factor for the occurrence of severe symptoms (OR 5.67, 95% CI) and death (OR 3.72, 95% CI) due to COVID-19 [11]. This study aligns with the results of a systematic review conducted by Kang and Jung that included research papers from multiple countries. The review demonstrated a strong association between advanced age and death from COVID-19 [19]. Similarly, the study conducted by Sasson (2021) found that age is a significant risk factor associated with death (OR 3.2; 90% CI) from COVID-19 [20].

As individuals progress into the later stages of life, there is a noticeable deterioration in various physical and physiological processes, including the immune system [21,22]. The deterioration of immune system function in elderly individuals renders them more vulnerable to infections, cancers, and autoimmune illnesses [21]. The term "immunosenescence" is commonly used to describe the decline in immune system function associated with aging [23,24]. Immunosenescence is characterized by the simultaneous dysfunction of both the innate and adaptive immune systems [21,25].

The occurrence of immunosenescence in geriatric individuals who are infected with COVID-19 renders them susceptible to experiencing severe clinical symptoms and potentially fatal outcomes. Immunosenescence was observed to be characterized by an elevation in the synthesis of pro-inflammatory cytokines, such as IL-6. The dysregulation is attributed to the activation of senescent memory T cells and macrophages as a response to combat the SARS-CoV-2 infection. Nevertheless, the overabundance of pro-inflammatory cytokines leads to an unregulated immune response, resulting in the widespread release of cytokines and the occurrence of a cytokine storm. The aforementioned scenario is further enhanced by the existence of comorbidities commonly observed in geriatric individuals [19,24]. The dysregulation of the immune system is further aggravated by the occurrence of *inflammaging* in the geriatric population. This condition can initiate and exacerbate the immune system dysregulation that occurs [16]. Inflammaging is a persistent low level systemic inflammatory state that arises as a result of the natural aging process in the absence of any infectious agents [26].

Another factor associated with increased mortality rates in COVID-19 patients is male gender. The results of this study show that COVID-19 patients who died were more men (63.8%) than women (36.2%). The results of the *chi-square* test, obtained a *p value of* 0.078 (*p* value $\leq$ 0.1 and OR 2.180), indicate that male gender is one of the significant risk factors causing death in COVID-19 patients (table 3).

The results of this study align with a meta-analysis conducted by Du et al, which revealed that a significant proportion of the literature examined indicated a higher vulnerability of men to infection compared to women. Furthermore, the study revealed that male gender was associated with an increased risk of COVID-19 symptom severity (OR 1.49; 95% CI) and death (OR 1.54; 95% CI) of COVID-19 [11]. A separate investigation carried out by Ramírez-Soto et al that analyzed data on COVID-19 cases in 73 countries from 2020 to 2021. The study revealed that the mortality rate among males was greater (3.17%) compared to females (2.26%) [27]. In a study conducted by Albitar et al that examined COVID-19 open access data from many countries, encompassing a sample size of 828 individuals. The findings revealed a higher incidence of infection among males (59.1%) compared to females (40.9%). The findings of their analysis indicated that the male gender was a significant contributing factor to the increased mortality rate (OR 1.607; 95% CI: 1.002-2.576) among the COVID-19 patients included in their study [28].

Based on global statistics, more than 70% of deaths caused by COVID-19 occur in male individuals. While the exact cause is not fully known, there are several scientific theories that may explain the phenomenon. Some of these theories include differences in the number of ACE2 receptors, variations in the immune system, the influence of sexual hormones, and habits and lifestyle [11,29–32].

SARS-CoV-2 employs S (spike) proteins to establish a binding interaction with ACE2 receptors, facilitating cellular entry and initiating the infection mechanism. The presence of ACE2 receptors has been observed in various anatomical regions, including the airway, lungs, heart, kidneys, intestines, ovaries, and testes. Studies indicate that males have a greater quantity of ACE2 receptors compared to females, which is believed to expedite and exacerbate infection in males [11,31,32].. The immunological response in female is often more efficient compared to male, due to the presence of two X chromosomes, whereas males possess just one X chromosome. The genes responsible for regulating the immune system are located on the X chromosome [29–31]. Another significant issue to consider is the influence of sexual hormones. Testosterone in males has been found to have immunosuppressive effects, while estrogen in females has been observed to have immunological response-promoting effects [31]. Lifestyle factors also play an important role; males tend to consume alcohol and smoke more than females. Smoking can make the lungs more susceptible

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to COVID-19 infection. Males are also less likely than femlaes to adhere the health protocols such as social distancing, handwashing and getting vaccinations [29–32].

Hypertension has been identified as a significant factor exhibiting a strong association with higher rates of death in patients diagnosed with COVID-19. *The* results of the *chi-square* test obtained a *p* value of 0.071 (*p* value ≤ 0.1 and OR 2.51) (table 4). This result aligns with the findings of systematic reviews, meta-analyses, and meta-regression studies conducted by Pranata et al. These studies revealed that hypertension is associated with higher rates of death (RR 2.21 (1.74, 2.81), p < 0.001; I2, 66%), the occurrence of ARDS (RR 1.64 (1.11, 2.43)), the requirement for intensive care unit (ICU) care (RR 2.11 (1.34, 3.33), p = 0.001; I2 18%, p = 0.30) [33]. In their recent study, Du et al conducted a comprehensive review and meta-analysis, demonstrating that hypertension is a noteworthy risk factor for severe symptoms (OR: 1.82; 95% CI: 1.19-2.77; P < 0.005) and death (OR: 2.17; 95% CI: 1.67-2.82; P < 0.001) among patients diagnosed with COVID-19 [34]. A comprehensive review conducted by De Almeida-Pititto et al found that hypertension (OR 2.88, CI: 2.22-3.74), along with diabetes mellitus and cardiovascular disease, exhibited a substantial association with death in individuals diagnosed with COVID-19 [35].

The concept that COVID-19 exacerbates pre-existing hypertension conditions provides an explanation for the observed association between hypertension and heightened mortality rates among COVID-19 patients. The infection caused by SARS-CoV-2 involves the utilization of the ACE2 receptor to invade cells, hence causing disturbances in the normal function of the renin-angiotensin system (RAS). Reduced ACE2 activity can hinder the transformation of angiotensin II into angiotensin (1–7). The vasoconstrictive impact of angiotensin II has been observed to contribute to persistently raised blood pressure and exacerbate the condition of individuals diagnosed with COVID-19 [34,36]..

COVID-19 patients with diabetes mellitus (DM) have a higher risk of death. Based on the results of the chi-square test, a p value of 0.071 was obtained (p value ≤ 0.1 and OR 3.300). This study provides further evidence supporting the results obtained from a systematic review conducted by Huang et al, which suggests a significant association between DM and death (RR 2.12 [1.44, 3.11], p < 0.001; I2: 72%), the presence of severe symptoms (RR 2.45 [1.79, 3.35], p < 0.001; I2: 45%), ARDS (RR 4.64 [1.86, 11.58], p = 0.001; I2: 9%), and rapid deterioration (RR 3.31 [1.08, 10.14], p = 0.04; I2: 0%) among COVID-19 patients [37]. A study conducted by Barron et al in England found that individuals with type 1 DM (OR 3.51; 95% CI) and type 2 DM (OR 2.03; 95% CI) had a higher likelihood of death among COVID-19 patients [38]. Another study conducted by Varikasuvu et al found that having a previous history of DM raised the severity of symptoms (OR = 2.20, 95% CI = 1.69-2.86, *p* < 0.00001) and increased the risk of death (OR = 2.52, 95% CI = 1.93-3.30, *p* = < 0.00001) in COVID-19 patients [39].

Individuals diagnosed with COVID-19 who have a prior medical history of diabetes DM are at an elevated risk of death due to the potential of hyperglycemia and insulin resistance to induce persistent inflammation, elevate oxidative stress levels, and compromise the immune system's ability to combat infections [40]. Furthermore, individuals with a prior occurrence of DM exhibit elevated levels of ACE2 receptor expression, particularly in the lungs, liver, and pancreas. The entrance point for SARS-CoV-2 virus infection into cells is facilitated by ACE2 receptors [38]. Individuals who have a medical background of diabetes mellitus (DM) are prone to experiencing comorbidities as a result of chronic macrovascular and microvascular problems, which might impede the body's capacity to adapt to stress [41].

CONCLUSIONS

Based on the research that has been conducted, it can be concluded that age, male gender, and comorbid hypertension and DM are risk factors that increase deaths from COVID-19 at Bahteramas Hospital, Southeast Sulawesi Province.

ADVICE

This research is expected to be a guide for policymaking to protect groups vulnerable to COVID-19 infection and can also be a reference for further research.

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