EFFECT OF CHRONIC KIDNEY DISEASE ON MORTALITY RATE OF SEPSIS PATIENTS

Muhamad Ibnu Aziz[1], Evi Nurhayatun[2], Ratih Tri Kusuma Dewi[2], Agung Susanto[3]

Affiliation:
1. Bachelor of Medicine Study Program, Sebelas Maret University, Surakarta
2. Internal Medicine Department , Faculty of Medicine, Sebelas Maret University, Surakarta
3. Internal Medicine Department, Dr Moewardi Hospital, Surakarta

Correspondence: Muhamad Ibnu Aziz, mibnu63@student.uns.ac.id, Bachelor of Medicine Study Program, Sebelas Maret University, Surakarta, Kentingan, Jebres, Surakarta, 57126

Received: 3/2/2022
Accepted: 27/06/2023
Published:1/07/2023

ABSTRACT

Introduction: Sepsis is a deathly disease caused by a dysregulation of the body's response to infection. The mortality rate of sepsis has been discovered to be almost equivalent to 20% of the global mortality rate. Comorbidity is one of the non-modifiable risk factors of sepsis. Chronic kidney disease is a comorbid risk factor for sepsis development. Decreasing GFR and albuminuria in chronic kidney disease is strongly associated with an increased mortality rate due to infection. Sepsis with chronic kidney disease shows a higher SOFA score than sepsis without chronic kidney disease. This study aims to determine the effect of chronic kidney disease on the mortality rate of patients with sepsis.

Methods: This study is an observational analytic study with a cross-sectional approach. The data retrieval used purposive sampling, and the sample comprised 90 respondents. Data were taken from medical records of the patients with sepsis hospitalized in Dr Moewardi Hospital from January 2016 to May 2021. Data were analyzed using the Chi-Square test.

Results: Chronic kidney disease significantly affected the sepsis mortality rate with p-value = 0.033 ($p < 0.05$). The prevalence ratio was 2.531 (95%CI, 1.07 – 5.97).

Conclusion: Chronic kidney disease significantly affects the increasing mortality rate of sepsis patients.

Keywords: Chronic kidney disease; Mortality; Sepsis,.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction resulting from dysregulation of the body's response to an infection. Sepsis can be known from the clinical criteria, including an acute increase in SOFA score of 2 points or more1. The mortality rate caused by sepsis is almost equivalent to 20% of the global mortality rate [2].

In general, sepsis risk factors can be grouped into modifiable and non-modifiable. Interventions during critical patient care and surgery are modifiable risk factors. At the same time, age, sex, and comorbidities are non- modifiable risk factors [3]. Some groups of people are more at risk for sepsis. One is people with chronic diseases, such as diabetes, lung disease, cancer, and kidney disease [4]. This study took one of the comorbidities of sepsis, namely chronic kidney disease.

Chronic Kidney Disease (CKD) is an abnormality found in the structure or function of the kidneys that has lasted for more than three months that can affect a person's health [5]. The early stages of CKD do not cause clinical manifestations but only appear when CKD has reached stage 4 or 5. Some common symptoms and signs in CKD patients include nausea, vomiting, sleep disturbances, swelling of the feet and ankles, persistent pruritus, hypertension that is difficult to control and oliguria [6].

In CKD patients, a decrease in GFR (glomerular filtration rate) and albuminuria values can be found. GFR is one component of excretory function that can represent the overall index of kidney function and decreases along with decreased kidney function. While albumin is one of the normal types of plasma protein found in urine, it significantly increases in patients with kidney disease [5]. Research conducted by Wang et al. concluded that a decrease in GFR and albuminuria values was strongly associated with an increased risk of death of patients due to infection [7].

Research conducted by Mansur et al. revealed that sepsis patients with CKD have the highest risk of death compared to sepsis patients without CKD or other chronic diseases. Patients with CKD showed higher SOFA scores than patients without CKD. These results indicate higher cardiovascular, kidney, and coagulation organ dysfunction [8]. Based on the above, researchers are interested in researching the effect of chronic kidney disease on sepsis mortality rates.

METHOD

This study is an analytical observational study with a cross-sectional design. The location used in the study was the Medical Records Installation of Dr Moewardi Hospital, with the research subject of sepsis patients treated at Dr Moewardi Hospital from 2016-2021. The sampling technique used is purposive sampling, where samples are taken by selecting subjects based on specific characteristics per the research objectives, the inclusion criteria include: 1) Patients diagnosed with sepsis, 2) Stage V CKD patients on hemodialysis, and 3) Age >18 years, while the exclusion criteria include: 1) Incomplete medical record data, 2) Immunodeficiency diseases, 3) Patients diagnosed with postoperative sepsis, 4) Confirmed positive for covid-19.

The sample size of this study was 90 people. The samples were grouped into groups with CKD risk factors and groups without CKD risk factors, with each group of 45 people. The variable tied to this study was Sepsis Mortality (death of patients in organ dysfunction conditions caused by dysregulation of the body's response to an infection). At the same time, the independent variable is CKD (abnormalities of kidney structure and function that have lasted for more than three months.). Other confounding variables in this study were age, sex, and malignant disease. Data analysis was performed univariately to describe sample characteristics and bivariate using the Chi- Square, Fisher, and Mann-Whitney tests. The research has received Ethical Feasibility by the Health Research Ethics Commission of Dr Moewardi Hospital with 530/IV/HREC/2021 and Research Permit number: 045/5.143/2021.

RESULT

This is an analytical observational study with research samples taken based on medical records of sepsis patients treated at Dr Moewardi Hospital from 2016-2021. The research samples were taken from June 22, 2021, to August 28, 2021, at the Medical Records Installation of Dr. Moewardi Hospital. The number of samples in this study was 90 people selected using *purposive sampling techniques*.

Table 1. Distribution of Sample Frequency Based on Sepsis Mortality, CKD, Sex, Age, and Malignant Disease

Characteristic	Frequency (n=90)	Percentage
CKD		
Yes	45	50%
Do not	45	50%
Sepsis Mortality		
Already	52	57,8%
Do not	38	42,2%
Gender		
Male	50	55,6%
Woman	40	44,4%
Age		
18 – 24	2	2,2%
25 – 44	17	18,9%
45 – 59	30	33,3%
≥60	41	45,6%
Diseases of Violence		
Already	11	12,2%
Do not	79	87,8%

In CKD, data frequency was obtained with a ratio of 1: 1 between patients with comorbid CKD and patients without comorbid CKD. This follows the study design, which divides the sample into groups with risk factors and without risk factors. Based on sepsis mortality and sex, the sampling frequency was almost the same. Namely, as many as 57.8% of sepsis patients died, 42.2% of sepsis patients did not die, and 55.6% were male and 44.4% were female. Meanwhile, based on the history of malignant diseases, there was an uneven frequency distribution, with 12.2% of patients suffering from malignant diseases and 87.9% not suffering from malignant diseases. Based on the age of patients, the frequency distribution increased with the increase in age groups, namely 2.2% in the age group 18 – 24 years, 18.9% in the age group 25 – 44 years, 33.3% in the age group 45 – 59, and 45.6% in the age group ≥60.

In this study, bivariate analysis with the *Chi-Square* test was conducted to determine the effect of CKD variables on sepsis mortality variables and obtained the following results:

Table 2. Results of Chi-Square *Test Analysis* of the Effect of CKD on Sepsis Mortality

Variable	Sepsis Mortality		Total N (%)	P *Value*
	Already N (%)	Do not N (%)		
PGK				
Already	31 (68,9)	14 (31,1)	45 (100)	0,033
Do not	21 (46,7)	24 (53,3)	45 (100)	

Based on the Chi-Square test results, a P value of 0.033 (p<0.05) was obtained. These results show the effect of CKD on sepsis mortality significantly. In addition, a Prevalence Ratio (PR) value of 2.531 (95% CI, 1.07 – 5.97) was obtained, which showed that sepsis patients with CKD increased the risk of death by 2.531 times compared to sepsis patients without CKD.

Furthermore, confounding variable analysis is carried out to determine the influence of the independent variable on the dependent variable by considering the confounding variable. The data will be analyzed by multivariate analysis to determine the influence of confounding variables. However, before confounding variables are included in the multivariate analysis model, selection will be carried out first using bivariate analysis. Variables that have a value of P<0.25 will be included in the multivariate analysis.

Table 3. Results of *Chi-Square Test* Analysis of Sex Relationship with Sepsis Mortality

Variable	Sepsis Mortality		Total N (%)	P *Value*
	Already N (%)	Do not N (%)		
Gender				
Man	31 (62)	19 (38)	50 (100)	0,365
Woman	21 (52,5)	19 (47,5)	40 (100)	

Based on the Chi-Square test results between sex and sepsis mortality (table 3), a P value of 0.365 was obtained. These results showed no association between sex and sepsis mortality significantly.

Table 4. Results of Chi-Square *Test Analysis of* Age Relationship with Sepsis Mortality

Variable	Sepsis Mortality		Total N (%)	P *Value*
	Already N (%)	Do not N (%)		
Age				
18 – 24	2 (100)	0	2 (100)	0,979
25 – 44	8 (47,1)	9 (52,9)	17 (100)	
45 – 59	19 (63,3)	11 (36,7)	30 (100)	
≥60	23 (56,1)	18 (43,9)	41 (100)	

The *Chi-Square test* was initially conducted to analyze the relationship between age variables and sepsis mortality. However, the *Chi-Square* test requirement is not met in the form of 2 cells with *an expected count* of <5. Because the age variable scales ordinal categorical data, the Mann-Whitney test is used alternatively. Based on the *Mann-Whitney test* (table 4), a P value of 0.979 was obtained. These results showed no significant association between age and sepsis mortality.

Table 5. Fisher Test Analysis Results of Malignancy Disease Relationship with Sepsis Mortality

Variable	Sepsis Mortality		Total N (%)	P *Value*
	Already	Do not		

	N (%)	N (%)		
Diseases of Violence				
Already	7 (63,6)	4 (36,4)	11 (100)	0,468
Do not	45 (57)	34 (43)	79 (100)	

The relationship between malignancy and sepsis mortality was initially analyzed using the *Chi-Square* test. However, the Fisher test is carried out as an alternative because the Chi-Square test requirements are not met in the form of 1 cell with an expected count of <5. Based on the results *of the Fisher* test (table 5), a P value of 0.468 was obtained. This showed that there was no association between malignancy and sepsis mortality significantly.

Based on the bivariate analysis results of the three confounding variables, none of the confounding variables had a value of P<0.25. Thus, multivariate analysis cannot be carried out between age, sex, malignancy, and CKD variables on sepsis mortality.

DISCUSSION

The Effect of CKD on Sepsis Mortality

CKD is one of the chronic diseases that can be a risk factor for sepsis. Based on the research of Wang et al., it is known that CKD and chronic lung disease show the strongest association with the incidence of sepsis compared to other comorbid disease risk factors [7]. Meanwhile, a study conducted by Chang et al. in CKD patients with advanced stages found that sepsis is one of the most common types of infection that occurs in CKD [9]. This may be related to chronic inflammation that occurs with CKD, which increases the risk of sepsis when exposed to pathogens [7].

In CKD, abnormalities can occur in the immune system resulting in persistent systemic inflammation and immunosuppression. This immunosuppression condition results in infectious complications in CKD patients, affecting patient mortality and morbidity [10]. This can occur due to decreased GFR and tubular dysfunction in CKD and ESRD, which can trigger uremia. Uremia causes an increase in the number of bacteria in the intestine that can eventually penetrate the barrier and trigger a systemic inflammatory response. Systemic inflammatory conditions, oxidative stress, and dysfunction are the main mechanisms that can cause immune system dysfunction in CKD. As a result, CKD patients with infectious complications and cardiovascular disease have high mortality [11].

This study aims to determine the effect of CKD on sepsis mortality rates. Based on the Chi-Square test results, it was found that CKD significantly affected the sepsis mortality rate with a Prevalence Ratio (PR) of 2.531 (95% CI, 1.07 – 5.97). These results showed that sepsis patients with pre-existing comorbid CKD had a 2,531 times greater risk of death than sepsis patients without comorbid CKD.

In this study, the CKD sample selected based on inclusion and exclusion criteria was stage 5 CKD with hemodialysis. This study's results align with research conducted by Chang et al. on advanced CKD patients and the impact caused after dialysis. The study was conducted on end-stage CKD patients who switched to dialysis. The results found that exposure to infection in advanced CKD risked worse outcomes after dialysis. Exposure to infection independently increases the risk of death in the first year of dialysis (HR, 1.34; 95% CI, 1.27–1.42) as well as in the entire dialysis period (HR, 1.19; 95% CI, 1.16–1.22) [7].

The results of this study follow research conducted by Mansur et al., which states that CKD has the highest risk of sepsis death in 90 days compared to patients without CKD or with other chronic diseases. Multivariate analysis with a Cox regression model has been carried out and found that CKD has the highest risk of death (HR,

2.25; 95% CI, 1.46-3.46), followed by diabetes mellitus (HR, 1.65; 95% CI, 0.96-2.83) and history of cancer (HR, 1.63; 95% CI, 1.09-2.34). Patients with CKD showed three higher SOFA scores compared to patients without CKD. These results indicate the presence of more severe organ dysfunction in the cardiovascular organ system, kidneys, and coagulation [8].

In this study, there are three confounding variables (gender, age, and malignancy) which will be discussed individually. Male patients have a higher risk of sepsis mortality than women [12]. This is because estrogen can contribute to restoring organ function after shock and sepsis to minimize sepsis mortality in women [13]. The results of the analysis of sex variables with sepsis mortality in this study showed that there was no significant relationship between the two variables.

This analysis's results align with research conducted by Madsen et al., which showed no difference between male and female sex with sepsis bundle management or sepsis mortality [14]. However, another study conducted by Pietropaoli et al. showed that significantly the mortality of sepsis in women was higher than in men [15].

The insignificance of the relationship between sex and sepsis mortality is due to the relationship between estrogen levels and mortality. Estrogen concentrations can be higher in older women compared to critically ill young women. At the same time, in men, estrogen can increase when in critical condition16.

Elderly patients have an increased risk of sepsis morbidity and mortality [17]. The results of the analysis of age-confounding variables in this study showed that there was no significant relationship between age and sepsis mortality. This study's results follow research conducted by Chen et al. in 2014. The study concluded that age was not a significant predictor of death in ICU patients with sepsis. Multivariate analysis showed significant results in females, patients with active cancer, septic shock, ARDS, hematologic disorders, APACHE II scores > 25, and inadequate management of the source of infection. This suggests many other factors contributing to sepsis mortality [18].

Patients with malignant diseases have a high risk of infection. Cancer patients with chemotherapy treatment are susceptible to neutropenia conditions [19]. Meanwhile, sepsis and septic shock are the leading causes of ICU care and death in patients with malignancies undergoing chemotherapy [20].

The results of the analysis of confounding variables of malignant diseases in this study showed that there was no significant relationship between malignant diseases and sepsis mortality. These results are in contrast to research conducted by Liu et al., which showed that sepsis patients with cancer significantly increased the risk of death [21]. Meanwhile, another study conducted by Cooper et al. showed that the death of sepsis patients with cancer reduced mortality significantly. This is due to advances in cancer management and better sepsis care, especially in patients with cancer [22].

The insignificance of the relationship between malignancy disease and sepsis mortality in this study may be due to several things, such as differences in the location of malignancy and patient therapy choices that have different influences on patient mortality [23]. In addition, it is caused by differences in the malignancy stage that affects patients' relative survival [24].

Researchers have tried their best to work on this research. However, there are several limitations to this study, namely: 1) Sepsis patients in this study sample have comorbid diseases that are very diverse, so multimorbidity confounding factors cannot be controlled. 2) Sepsis patients with CKD hemodialysis mostly have had complications of cardiovascular disease. Therefore, researchers cannot control the confounding factors of cardiovascular disease.

CONCLUSION

Based on the study's results, it can be concluded that chronic kidney disease affects sepsis mortality significantly and increases the risk of sepsis death by 2,531 times.

ACKNOWLEDGMENTS

Praise the author to Allah SWT, God Almighty, because thanks to His great mercy, the author completed a thesis entitled "The Effect of Chronic Kidney Disease on the Death Rate of Sepsis Patients". The author would like to express his gratitude to Agung Susanto as the examiner who has provided guidance and advice to improve the shortcomings of writing this thesis. Thank also to the Department of Internal Medicine Dr Moewardi Hospital and the Medical Record Installation Department of Dr Moewardi Hospital for providing direction during the thesis writing process and data collection

CONFLICT OF INTEREST

None

BIBLIOGRAPHY

1. Singer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315(8):801.
2. Rudd et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020;395(10219):200–211.
3. Fathi M, Markazi-Moghaddam N, and Ramezankhani A. A systematic review of risk factors associated with sepsis in patients admitted to intensive care units. Australian Critical Care. 2016;32(2):155–164.
4. Centres for Disease Control and Prevention. What is sepsis? https://www.cdc.gov/sepsis/what-is-sepsis.html (Diakses 27 Januari 2021)
5. KDIGO. Chapter 1: Definition and Classification of CKD. Kidney International Supplements. 2013;3(1):19–62.
6. Vaidya SR and Aeddula NR. Chronic Renal Failure. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing: 2020.
7. Wang HE, Gamboa C, Warnock DG, Muntner P. Chronic Kidney Disease and Risk of Death from Infection. Am J Nephrol. 2011;34(4):330–6.
8. Mansur A et al. Chronic kidney disease is associated with a higher 90-day mortality than other chronic medical conditions in patients with sepsis. Scientific Reports. 2015:8.
9. Chang C-H, Fan P-C, Kuo G, Lin Y-S, Tsai T-Y, Chang S-W, et al. Infection in Advanced Chronic Kidney Disease and Subsequent Adverse Outcomes after Dialysis Initiation: A Nationwide Cohort Study. Sci Rep. 2020 Dec;10(1):2938.
10. Kurts C, Panzer U, Anders H-J, Rees AJ. The immune system and kidney disease: basic concepts and clinical implications. Nat Rev Immunol. 2013 Oct;13(10):738–53.
11. Syed-Ahmed M, Narayanan M. Immune Dysfunction and Risk of Infection in Chronic Kidney Disease. Advances in Chronic Kidney Disease. 2019 Jan;26(1):8–15.
12. Xu J, Tong L, Yao J, Guo Z, Lui KY, Hu X, et al. Association of Sex With Clinical Outcome in Critically Ill Sepsis Patients: A Retrospective Analysis of the Large Clinical Database MIMIC-III. Shock. 2019 Aug;52(2):146–51.
13. Bösch F, Angele MK, Chaudry IH. Gender differences in trauma, shock and sepsis. Military Med Res. 2018 Dec;5(1):35.
14. Madsen TE et al. The DISPARITY Study: do gender differences exist in Surviving Sepsis Campaign resuscitation bundle completion, completion of
individual bundle elements, or sepsis mortality?, Journal of Critical Care. 2014;29(3):473.e7-473.e11.
15. Pietropaoli AP, Glance LG, Oakes D, Fisher SG. Gender differences in mortality in patients with severe sepsis or septic shock. Gender Medicine. 2010 Oct;7(5):422–37.
16. Dossett LA, Swenson BR, Heffernan D, Bonatti H, Metzger R, Sawyer RG, et al. High Levels of Endogenous Estrogens are Associated With Death in the Critically Injured Adult. Journal of Trauma: Injury, Infection & Critical Care. 2008 Mar;64(3):580–5.
17. Lineberry C, Stein DE. Infection, Sepsis, and Immune Function in the Older Adult Receiving Critical Care. Critical Care Nursing Clinics of North America. 2014 Mar;26(1):47–60.
18. Chen C-M, Cheng K-C, Chan K-S, Yu W-L. Age May Not Influence the Outcome of Patients with Severe Sepsis in Intensive Care Units. International Journal of Gerontology. 2014 Mar;8(1):22–6.
19. Centers for Disease Control and Prevention. Does cancer put me at risk for sepsis?. https://www.cdc.gov/sepsis/sepsis-cancer/index.html (Diakses 1 Oktober 2021)
20. Soares M, Bozza FA, Azevedo LCP, Silva UVA, Corrêa TD, Colombari F, et al. Effects of Organizational Characteristics on Outcomes and Resource Use in Patients With Cancer Admitted to Intensive Care Units. JCO. 2016 Sep 20;34(27):3315–24.
21. Liu MA, Bakow BR, Hsu T-C, Chen J-Y, Su K-Y, Asiedu EK, et al. Temporal Trends in Sepsis Incidence and Mortality in Patients With Cancer in the US Population. American Journal of Critical Care. 2021 Jul 1;30(4):e71–9.

22. Cooper AJ, Keller SP, Chan C, Glotzbecker BE, Klompas M, Baron RM, et al. Improvements in Sepsis-associated Mortality in Hospitalized Patients with Cancer versus Those without Cancer. A 12-Year Analysis Using Clinical Data. Annals ATS. 2020 Apr;17(4):466–73.
23. Shvetsov YB, Ogino MH, Glibetic N, Asato CB, Wilkens LR, Le Marchand L, et al. Association of Sepsis Mortality with Specific Cancer Sites and Treatment Type: The Multiethnic Cohort Study. JPM. 2021 Feb 19;11(2):146.
24. McPhail S, Johnson S, Greenberg D, Peake M, Rous B. Stage at diagnosis and early mortality from cancer in England. Br J Cancer. 2015 Mar;112(S1):S108–15.