ASSOCIATION OF COMORBID RISK FACTORS TO MORTALITY OF CHRONIC KIDNEY DISEASE PATIENTS UNDERGOING HEMODIALYSIS

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ABSTRACT

Introduction: Chronic Kidney Disease (CKD) is a condition of decreased kidney function with LFG < 60 ml/minute per 1.73 m2, which occurs within three months. The global prevalence of CKD in 2017 reached 9.1% or 697.5 million cases in the world, where women were 9.5% and men 7.3% cases and 1.2 million deaths. In Indonesia, according to Riskesdas, in 2013, the prevalence of CKD increases with age, with men by 0.3% while women by 0.2%. Comorbidities are known to increase the risk of death of CKD patients on hemodialysis. In this study, comorbidities taken include hypertension, diabetes mellitus, heart failure, stroke, and urinary tract infections. This study aims to determine and analyze the relationship of comorbid risk factors to the mortality of chronic kidney disease patients undergoing hemodialysis.
Methods: This study is observational analytic with a case-control design. The subjects of this study were end-stage CKD patients on hemodialysis at the regional general hospital Dr Moewardi in 2017-2021, with a total of 150 samples. Sampling using purposive sampling method based on inclusion and exclusion criteria. Data analysis using SPSS 22 statistical software application with chi-square test as bivariate analysis.
Results: Univariate analysis showed that the age of 51-60 years was the largest group that experienced the incidence of CKD, which was 64 people (42.67%). Women experience more CKD incidence than men. The most comorbidities that appeared in the group of cases (died) were UTIs (Urinary Tract Infections) with a total of 40 people (53.33%), followed by hypertension as many as 31 people (41.33%), diabetes mellitus as many as 24 people (32%), heart failure as many as 16 people (21.33%), and stroke as many as 16 people (21.33%). Bivariate analysis using the chi-square test showed that there was a significant association between comorbid hypertension (P = 0.038; OR = 2.077), diabetes mellitus (P = 0.037; OR = 2.244), heart failure (P = 0.041; OR = 2.634), stroke (P = 0.021; OR = 3.119), and urinary tract infections (P = 0.049; OR = 1.918) on mortality of chronic kidney disease patients undergoing hemodialysis. Multivariate analysis using logistic regression showed no factor most influential on mortality of chronic kidney disease patients on hemodialysis.
Conclusion: Risk factors for hypertension, diabetes mellitus, heart failure, stroke, and urinary tract infections have a significant relationship with mortality rates of chronic kidney disease patients undergoing hemodialysis. Other factors that affect the mortality of CKD patients on hemodialysis are older age and female sex.

Keywords: CKD; Comorbidity; Mortality.

INTRODUCTION

Chronic Kidney Disease (CKD) is still a problem that clinicians in the health sector must solve because of its high mortality rate with the increasing incidence of the disease, including in Indonesia. The definition of Chronic Kidney Disease (CKD) based on the latest international consensus is a condition in which decreased kidney function is indicated by the results LFG < 60 ml/minute per 1.73 m^2 that occurs within three months without or accompanied by an underlying cause [1].

An epidemiological study through a new analysis in 2017 estimated that the global prevalence of CKD reached 9.1% or around 697.5 million cases in the world, where women were more at 9.5% than men with 7.3% of cases and 1.2 million cases of death which caused CKD to enter the 12th rank in the world as the cause of death [2].

Comorbid conditions are the emergence of additional clinical entities different from previous diseases that worsen the patient's health [3]. CKD is often accompanied by pathological conditions (comorbid conditions) that appear along with the disease. Prospective research based on cohort analysis that has been conducted for ten years shows that patients with Chronic Kidney Disease (CKD) stages 3-5 aged ≥ 65 years have a more significant number than < 65 years of age and have more than one comorbidity or multimorbidity [4].

Research shows that CKD patients who have undergone hemodialysis at the age of 65-74 years have a 2.25 times higher risk of mortality, while the age of ≥ 75 has a 2.62 times higher risk of mortality than the age of < 65 years with various causes, namely cardiovascular disorders (34.2%), infections (13.8%), malignancy (9.9%), staying at home (13.2%), miscellaneous (16.1%), withdrawal (12,8%) [5]. Research in Indonesia shows that comorbidities that cause death are coronary heart disease, congestive heart failure, stroke, TB, sepsis, and pneumonia in patients with chronic renal failure (CRF) [6].

The mortality cases of CKD patients after hemodialysis are also relatively high. In an epidemiological study in Sichuan Province, China, it was found that as many as 80% of CKD patients post-hemodialysis died at the age of ≥ 60 years and was most commonly caused by cardiovascular disease (24.5%), sudden death (21.8%), cerebrovascular disease (21.7%), infection (11.7%), and gastrointestinal bleeding (6.4%) [7].

Based on the performance report at Regional General Hospital, dr. Moewardi regarding the number of hemodialysis procedures performed increased from 2019 to 2020 as of March. In 2019, hemodialysis procedures were carried out in 4,567 patients, while in 2020, with the same period, hemodialysis procedures totalled 4,749 patients [8].

Research that has been conducted shows the prevalence of comorbidities in stage 3-5 CKD patients. As much as 41.9% have more than one comorbid or multimorbid. The three comorbidities with the highest prevalence were hypertension, diabetes, and hyperlipidemia. However, they were not accompanied by data on the number of deaths of CKD patients [4]. Research in Indonesia shows that comorbidities that cause death are coronary heart disease, congestive heart failure, stroke, TB, sepsis, and pneumonia in patients with chronic renal failure (CRF) [6]. With the increasing mortality rate of patients on hemodialysis, researchers are interested in conducting research on comorbid risk factors for the mortality rate of CKD patients after hemodialysis.

METHODS

Study Design

This study is an analytical observational study using a case-control research design. This research was conducted at the Medical Record Installation Section of Regional General Hospital Dr. Moewardi Surakarta. The samples in this study were all patients diagnosed with end-stage CKD with hemodialysis at Regional General Hospital Dr Moewardi Surakarta. The inclusion criteria in this study were end-stage CKD patients on hemodialysis aged 18−60 years and alive or dead. The exclusion criteria are end-stage CKD patients on hemodialysis die from immunocompromised diseases and without comorbidities. The purposive sampling method uses the researcher to

select the sample following the inclusion and exclusion criteria. The sample size is calculated using a hypothesis test for odds ratio (OR) estimation. Based on the calculation of the minimum sample size required with a tolerable error rate of 5%, test strength of 80%, and the minimum odd ratio used is 2, which is 75 samples. This study has two groups, namely the case group and control, so the minimum number of samples required is 150. The independent variables in this study were comorbidities, which included hypertension, diabetes mellitus, heart failure, stroke, and urinary tract infections. The dependent variable used is the mortality of CKD patients on hemodialysis. Univariate data analysis was performed to describe the distribution of samples, including age, sex, and comorbid patients. At the same time, bivariate analysis uses the SPSS 22 application with a chi-square test. This research has received ethical clearance from the Health Research Ethics Commission of Regional General Hospital Dr. Moewardi Surakarta with number 670 / VI / HREC / 2021.

RESULTS

This research was carried out from July - August 2021 in the medical record installation section of Regional General Hospital Dr Moewardi Surakarta. Research sampling using medical records of Chronic Kidney Disease patients hospitalized at Regional General Hospital Dr. Moewardi Surakarta from January 2017 – May 2021. The number of samples of this study was 150 inpatients with details of 75 CKD patients with death status and 75 CKD patients with a return to life status. The dependent variable in this study was mortality of CKD patients, while the independent variable was comorbid. Comorbidities used by researchers include hypertension, diabetes mellitus, heart failure, stroke, and UTIs.

Table 1. Age Sample Distribution

Age Group (Years)	Total (N)	Percentage (%)
18-30	15	10
31-40	22	14,67
41-50	49	32,67

Sample Distribution

Based on the age distribution (Table 1) in CKD patients, it was found that the age group of 51-60 years became the largest group that experienced the incidence of CKD, which was 64 people (42.67%). Based on the sex distribution (Table 2) in CKD patients, it was found that women experienced more CKD incidence than men.

Table 2. Gender Sample Distribution

Jenis Kelamin	Total (N)	Percentage (%)
Man	74	49,33
Woman	76	50,67
Total	150	100

Table 3. Comorbid Sample Distribution

Comorbid	Died (N = 75)	Live (N = 75)
	Amount (%)	Amount (%)
Hypertensive	31 (41,33)	19 (25,33)
Diabetes Mellitus	24 (32)	13 (17,33)
Heart Failure	16 (21,33)	7 (9,33)
Stroke	16 (21,33)	6 (8)
ISK	40 (53,33)	28 (37,33)

Based on the comorbid distribution of CKD patients (Table 3), it was found that the most comorbidities that appeared in the group of cases (died) were UTIs (Urinary Tract Infections) with 40 people (53.33%). While in the control group (returning home), the most were found in UTIs with 28 people (37.33%).

Data Analysis Results

Based on the *chi-square* test table (Table 4), it can be concluded that there is a significant relationship between comorbid hypertension and mortality of CKD patients undergoing hemodialysis with a P value of 0.038 (P < 0.05). Meanwhile, the OR (Odd Ratio) value calculation results in OR = 2.077. From these results, it can be interpreted that CKD patients who have comorbid hypertension have a risk of dying 2,077 times higher than CKD patients who do not have comorbid hypertension.

Table 4. Chi-Square Test Results of Hypertension with CKD Mortality

Variable		Mortalitas		Total (%)	P Value
		No (%)	of (%)		
HT	No	56 (74,7)	44 (58,7)	100 (66,7)	0,038
	Yes	19 (25,3)	31 (41,3)	50 (33,3)	
	Total	75 (100)	75 (100)	150 (100)	

Based on the *chi-square* test table (Table 5), it can be concluded that there is a significant relationship between comorbid diabetes mellitus and mortality of CKD patients undergoing hemodialysis with a P value of 0.037 (P < 0.05).

Table 5. Chi-Square Diabetes Mellitus Test Results with CKD Mortality

Variable		Mortalitas		Total (%)	P Value
		No (%)	of (%)		
DM	No	62 (82,7)	51 (68,0)	113 (75,3)	0,037
	Yes	13 (17,3)	24 (32,0)	37 (24,7)	
	Total	75 (100)	75 (100)	150 (100)	

Meanwhile, the OR (Odd Ratio) value calculation results in OR = 2.244. From these results, it can be interpreted that CKD patients who have comorbid diabetes mellitus have a risk of dying 2,244 times higher than CKD patients who do not have comorbid diabetes mellitus.

Based on the *chi-square* test table (Table 6), it can be concluded that there is a significant relationship between comorbid heart failure and mortality of CKD patients undergoing hemodialysis with a P value of 0.041 (P < 0.05). Meanwhile, from the calculation of the OR (Odd Ratio) value, the result OR = 2.634 is obtained. From these results, it can be interpreted that CKD patients who have comorbid heart failure have a 2,634 times higher risk of dying compared to CKD patients who do not have comorbid heart failure.

Table 6. Chi-Square Test Results of Heart Failure with CKD Mortality

Variable		Mortalitas		Total (%)	P Value
		No (%)	of (%)		
Heart Failure	No	68 (90,7)	59 (78,7)	127 (84,7)	0,041
	Yes	7 (9,3)	16 (21,3)	23 (15,3)	
	Total	75 (100)	75 (100)	150 (100)	

Based on the *chi-square* test table (Table 7), it can be concluded that there is a significant relationship between comorbid stroke and mortality of CKD patients undergoing hemodialysis with a P value of 0.021 (P < 0.05). Meanwhile, from calculating the OR value (Odd Ratio), the result OR = 3.119. From these results, it can be

interpreted that CKD patients who have a comorbid stroke have a risk of death 3,119 times higher than CKD patients who do not have a comorbid stroke.

Table 7. Chi-Square Stroke Test Results with CKD Mortality

Variable		Mortality		Total (%)	P Value
		No (%)	of (%)		
Stroke	No	69 (92,0)	59 (78,7)	128 (85,3)	0,021
	Yes	6 (8,0)	16 (21,3)	22 (14,7)	
	Total	75 (100)	75 (100)	150 (100)	

Based on the *chi-square* test table (Table 8), it can be concluded that there is a significant relationship between comorbid UTIs and mortality of CKD patients undergoing hemodialysis with a P value of 0.049 (P < 0.05). Meanwhile, from the calculation of the OR (Odd Ratio) value, the result OR = 1.918 is obtained. From these results, it can be interpreted that CKD patients who have comorbid UTIs have a 1,918 times higher risk of dying compared to CKD patients who do not have comorbid UTIs.

Table 8. Chi-Square UTI Test Results with CKD Mortality

Variable		Mortalitas		Total (%)	P Value
		No (%)	of (%)		
UTI	No	47 (62,7)	35 (46,7)	82 (54,7)	0,049
	Yes	28 (37,3)	40 (53,3)	68 (45,3)	
	Total	75 (100)	75 (100)	150 (100)	

Multivariate analysis with logistic regression showed insignificant results on all variables, which means no more dominant variable could affect the mortality of chronic kidney disease patients on hemodialysis. These results also show that hypertension, diabetes mellitus, heart failure, stroke, and UTI are variables that mutually influence the mortality of CKD with hemodialysis.

Table 9 Results of Multivariate Analysis of Logistic Regression

Variable	Coefficient	P Value
Hypertensive	38,362	0,995
Diabetes Mellitus	38,847	0,995
Heart Failure	58,217	0,994
Stroke	57,966	0,994
ISK	57,983	0,994

DISCUSSION

Age

In this study, the highest age group in chronic kidney disease patients undergoing hemodialysis was in the age group of 51-60 years, as many as 64 people (42.67%). This is in line with research from the CDC (Centers for Disease Control and Prevention), which suggests CKD is more common in the age group of 45-64 years (12%) than in 18-44 years (6%)9. Old age has more comorbidities than young age, so these factors also play a role in the increased risk of CKD mortality [4]. Research results by Hallan et al. show that old age increases the risk of death in CKD patients because, with age, there is a periodic decrease in LFG and an increasing number of comorbidities in these patients [10].

Sex

In this study, chronic kidney disease patients undergoing hemodialysis were more likely to be found in women, namely 76 people (50.67%) compared to 74 men (49.33%). This is following research in 2019 on the prevalence and relationship of risk factors in CKD patients, which showed that women experienced more incidence of CKD, which was 56.3% compared to men, which amounted to 43.7% of the total population [11]. Women experience more CKD because they are at risk for urinary tract infections (UTIs) that can cause kidney damage. In pregnant women with hypertension or eclampsia also increases the risk of damage to the kidneys [12].

The results of other studies show that women have a longer life expectancy, and it is also possible to cause overdiagnosis using the glomerular filtration rate equation [13]. Women also get less kidney transplant therapy because of higher antibody levels, and the effects caused after transplantation are worse than men because the symptoms that appear more severe reduce the quality of life [14].

Comorbid

This study showed that the most comorbidities in the case and control groups were UTIs, totalling 68 people. This follows observational studies showing that CKD is a chronic inflammatory disease that causes a decrease in the body's immune system response, increasing the risk of infection, especially the most common infection, namely UTI (Urinary Tract Infection) [15**]**. Fraser's research et al. show that hypertension is still comorbid and is often found in chronic kidney disease patients, as much as 88% of the total sample, where as many as 23% have ischemic heart disease, and 17% have diabetes [16**]**.

Heart failure is still a comorbid that can increase the risk of death in CKD. This is in line with Thompson's research et al., which explains that the most common cause of death found in CKD patients is accompanied by a decrease in LFG <60 ml/min per 1.73 m2, which is a cardiovascular disease [17**]**. Research by Lee et al. shows that the number of comorbidities present in CKD patients correlates with the progressiveness of worsening kidney function. It is known that patients with at least three comorbidities should receive multidisciplinary treatment as a predictor for immediate dialysis [18**]**.

Relationship between Hypertension and CKD Mortality

Based on the chi-square test results, a significant relationship was found between comorbid hypertension and mortality of CKD patients undergoing hemodialysis with a P value of 0.038 ($P < 0.05$, OR = 2.007). These results are in line with Bansal's research et al., which suggests that CKD patients undergoing hemodialysis with chronic hypertension marked increased systolic pressure may increase the risk of mortality ($P < 0.05$) [19]. Similar research results from Pugh et al. explain that uncontrolled hypertension can increase the risk of further kidney damage in CKD as well as cardiovascular disease [20].

The mechanism of hypertension in CKD is very complex and influenced by various factors. CKD can increase the activity of RAAS (Renin Angiotensin Aldosterone System), which causes decreased blood flow in the peritubular capillaries so that the glomerulus will hypersecretion renin, which also increases angiotensin II, which will cause vasoconstriction accompanied by an increase in systemic vascular resistance and blood pressure [21]. Aldosterone plays a role in increasing blood pressure by hyperabsorption of sodium in the Na-Cl channel in the distal tubule, NO inhibition, hyperfiltration and proteinuria, glomerular inflammation and hypertrophy, and podocyte damage due to ROS formation by aldosterone [22].

Increased activation of the sympathetic nervous system in the kidneys can lead to hypertension through the mechanism of renal vasoconstriction with receptors α1A adrenergic in arteries experiencing resistance, stimulation of renin through receptors β1 adrenergic in juxtaglomerular granule cells, and increased absorption of sodium and water through α receptors1B adrenergic in renal tubular epithelial cells [23].

Endothelial dysfunction, impaired NO production, oxidative stress, and increased endothelin can lead to hypertension in CKD patients [21]. Decreased NO production in the medullary circulation can increase renal vascular resistance, augmentation of salt reabsorption results, and increased natriuresis pressure [23]. In contrast, oxidative stress will stimulate oxidative molecules or ROS (Reactive Oxygen Species). ROS can cause

hypertension through increased sensitivity to salt with a mechanism of decreasing NO availability due to renal vascular vasoconstriction, sodium reabsorption, and disturbances in natriuresis [22].

Relationship between Diabetes Mellitus and CKD Mortality

Based on the chi-square test results, a significant relationship was found between comorbid diabetes mellitus and CKD patients undergoing hemodialysis mortality with a P value of 0.037 (P < 0.05, OR = 2.244). This result is in line with Wen's research et al., which revealed that chronic kidney disease patients with diabetes experienced twice the mortality rate (HR = 2.01) than those without diabetes [24]. Diabetes in CKD is known as DKD (Diabetic Kidney Disease). Diabetes will trigger hemodynamic disorders, inflammation, fibrosis in the kidneys and hyperaminoacidemia conditions. Excess amino acids in the blood give rise to hyperfiltration, hyperperfusion, and hyperglycemia [25].

Hyperfiltration in the glomerulus is known to occur due to increased glucose reabsorption in the proximal tubule through sodium-glucose cotransporter 2 (SGLT 2), which can reduce the distribution of solutes in the form of sodium chloride to the distal part in the macula densa [26]. This condition causes dilatation of the afferent arterioles to increase glomerular perfusion. On the other hand, there is an increase in angiotensin II production in the efferent arterioles for the vasoconstriction process, which ultimately leads to an increase in intraglomerular pressure and hyperfiltration of the glomerulus [27].

In DKD, glomerular vascular lesions occur, which decrease oxygen supply, causing hypoxia in the renal medulla and renal tubular dysfunction. Without adequate oxygen supply, there will be a release of free radicals such as HIF (Hypoxia Inducible Factor) that cause tissue damage, plus hyperglycemia conditions will also cause tissue fibrosis [28].

In addition to ischemia, DKD also causes inflammatory processes due to activation of the innate immune system / Innate. Hyperglycemia can increase the expression of the NF-kB transcription factor, which correlates with persistent proteinuria conditions where NF-Kb May cause inflammatory reactions in the glomerulus, interstitial tissue, and tubular epithelial cells [29]. The JAK/STAT protein also activates the innate immune system in the kidneys through chemokines, cytokines, and angiotensin receptors. Expression of JAK2 in podocyte cells in the glomerulus can cause worsening in DKD [30].

The presence of inflammatory cytokines such as TNF-α and interleukins 1, 6, and 18 in DKD can increase albumin excretion, causing albuminuria. In addition, these cytokines can also increase endothelial cell permeability, impacting glomerular hypercellularity and GBM thickening (Glomerular Basement Membrane), which induces endothelial cell apoptosis and renal toxicity [31].

Relationship between Heart Failure and CKD Mortality

Based on the results of the chi-square test, a significant relationship was found between comorbid heart failure and mortality of CKD patients undergoing hemodialysis with a P value of 0.041 (P < 0.05, OR = 2.634). These results are consistent with Wan's research et al., which explains that CKD patients with comorbid heart failure increase the risk of death 2.63 times higher than patients without these comorbidities [32]. Sud research results et al. also explained that heart failure increases the risk of ESRD (HR = 4.89) and death before ESRD in CKD patients (HR = 3.30) [33].

The presence of heart failure leads to increased activity of the sympathetic nervous system and RAAS. Both will improve afterload so that there is a decrease in cardiac output [34]. Increased afterload and preload will increase the work of the heart and can lead to LVH (Left Ventricular Hypertrophy). Preload elevated LVH due to hypovolemia, anaemia and high blood flow in arteriovenous fistulas in CKD patients undergoing hemodialysis [35].

Besides volume overload, CKD patients with LVH will cause changes in myocardial cells and remodelling in the left ventricle36. LVH can cause myocardial fibrosis due to uremic cardiomyopathy in CKD patients [37]. Fibrosis is due to collagen deposits that diffuse between capillaries and cardiomyocytes that enter the ventricles and hypertrophy with cardiac dilatation [38].

RAAS activity will trigger sodium and water retention, increasing central venous pressure. Volume retention and increased vascular tone can give rise to hypertension in CKD. Increased blood pressure results in an increase in the amount of extracellular volume with an increased compensation cardiac output [39]. Increased central venous pressure also results in hypertension of the renal veins, increased renal resistance, and impaired blood flow within the kidneys, which often occurs in patients with acute heart failure [40].

Excessive angiotensin II secretion can accumulate in the heart. It can result in cardiomyocyte hypertrophy, interstitial fibrosis, and microvascular diseases such as cardiac conduction disorders and arrhythmias [41]. Decreased LFG and chronic endothelial dysfunction can cause kidney dysfunction due to increased central venous pressure, resulting in venous congestion in patients with acute heart failure [42].

Relationship between Stroke and CKD Mortality

Based on the results of the chi-square test, a significant relationship was found between comorbid stroke and mortality of CKD patients undergoing hemodialysis with a P value of 0.021 ($P < 0.05$, OR = 3.199). This is following the results of the study by Nicole L. De La Mata et al., which shows that end-stage CKD / ESRD patients with stroke have a risk of death three times higher than CKD patients without stroke. The highest mortality is type stroke Intracerebral haemorrhages [43]. Results of a similar study by Cherng et al. showed that stroke patients with end-stage CKD / ESRD who were hospitalized had a 2.62 times higher risk of mortality than patients without kidney disease [44].

Recent research has mentioned that CKD is related to the process of thrombosis that occurs in such a way that clot which is formed in CKD patients structure and function differently from clot which is formed when kidney function is expected, which also explains that CKD patients are at high risk of thrombosis and also at high risk of bleeding [45]. Patients with decreased GFG may reduce the effectiveness of cerebral autoregulation. This autoregulatory disorder is due to hypoperfusion and microvascular injury resulting in bleeding [46].

The mechanism of bleeding occurs after the thrombolysis process in CKD patients with stroke. Endogenous accumulation of tPA in circulation due to abnormal tPA/PAI ratio and exogenous transmission affecting excess influx of circulating tPA into ischemic tissue. Overaccumulation of extracellular matrix components, urea, oxidative stress, and energy failure affect the entry of circulating tPA into cells. Bleeding complications in CKD patients with stroke are mediated by MMP-9 activation along with cytokine activity of tPA, urea toxin, and excessive extracellular matrix [47].

Acute kidney disease causes increased cerebral microvascular permeability and damage to the blood-brain barrier, especially in patients with reversible posterior encephalopathy syndrome, which can decrease brain autoregulation and endothelial dysfunction, leading to hypoperfusion with proteins and extravasation of fluid into the brain parenchyma [48]. The condition of uremia can cause protein carbonylation that causes the effect of atherosclerosis with dyslipidemia, which will also interfere with the platelet adhesion process and interaction with endothelium, which can increase the risk of hemorrhagic stroke [49].

Relationship between UTIs and CKD Mortality

Based on the chi-square test results, a significant relationship was found between comorbid UTIs and CKD patients undergoing hemodialysis mortality with a P value of 0.049 ($P < 0.05$, OR = 1.918). This is in line with Kuo's research et al., who explains that UTI patients can be at higher risk of end-stage CKD, progressive decline in kidney function, and higher risk of death than patients without UTI (HR = 1.63, $P < 0.001$) [50]. Equal Revenue by Money et al. shows that CKD patients with reduced LFG and albuminuria increase the risk of mortality when accompanied by infectious diseases [51].

A urinary tract infection (UTI) begins when bacteria residing in the intestinal tract contaminate the periurethral area and can colonize the urethra. The subsequent migration to the bladder by pili intermediaries and adhesin results in colonization and invasion of cells umbrella Superficial. The host's inflammatory response, including neutrophil infiltration, begins to attack the pathogen. Some bacteria evade the immune system through host cell invasion or morphological changes, resulting in neutrophil resistance. Then, these bacteria multiply and

form biofilms. These bacteria produce toxins and proteases that induce host cell damage, releasing certain substances that promote bacterial survival and ascending to the kidneys. Kidney colonization results in the production of bacterial toxins and damage to host tissues. If untreated, UTIs can eventually progress to bacteremia if the pathogen crosses the kidney's tubular epithelium [52]. CKD patients on hemodialysis are at risk of infection. Using a central venous catheter is a risk factor for infection through the bloodstream in CKD patients, with the most frequent bacterial cause being Staphylococcus aureus [53].

Multivariate Analysis

Based on multivariate analysis with logistic regression, insignificant results were obtained with a P value> 0.05 on all variables. These results show that no dominant variable can affect the mortality of CKD patients on hemodialysis. This shows that the variables of hypertension, diabetes mellitus, heart failure, stroke, and UTI influence each other on CKD mortality.

These results were also contained in the study of Skupien et al., which explained that there was no significant difference in mortality of patients not related to ESRD, in this case, patients with type 1 DM. In addition, the risk of death from type 1 DM in ESRD also did not show significant results (P = 0.063) [54]. Another study from Bansal et al. showed no independent or significant association between high systolic blood pressure and mortality of hemodialysis CKD patients with an eGFR of <30 mL/min/1.73 m2 per increase of 10 mmHg (P = 0.3)19. While research from Saeed et al. explained that increased age and congestive heart failure are risk factors for death in CKD patients, the results of multivariate analysis found no meaningful interaction between these variables [55].

Research Limitations

Limitations in this study are that the variables hypertension, DM, heart failure, stroke, and UTI were not further classified according to the degree and type of disease, the most dominant variables for mortality of CKD patients on hemodialysis did not show significant results, and confounding factors such as smoking habits and alcohol consumption were not contained in this study.

CONCLUSION

Based on the results of research that has been conducted, it can be concluded that risk factors for hypertension, diabetes mellitus, heart failure, stroke, and urinary tract infections have a significant relationship with the mortality rate of chronic kidney disease patients undergoing hemodialysis. In addition to comorbid risk factors, age and gender also affect the mortality rate of CKD patients on hemodialysis. The most common comorbid found in CKD patients with hemodialysis is UTIs. However, the highest risk factor for death is hemodialysis CKD patients with comorbid stroke.

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CONFLICT OF INTEREST

The author declares there is no conflict of interest.

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