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Comparative Effectiveness of KDIGO 2021 versus Previous Blood Pressure Targets on Renal Outcomes in Chronic Kidney Disease Patients in Palembang, Indonesia

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A B S T R A C T

Introduction: The 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend lower blood pressure (BP) targets for chronic kidney disease (CKD) patients compared to previous guidelines. This study aimed to evaluate the comparative effectiveness of achieving KDIGO 2021 BP targets versus previous targets on renal outcomes in CKD patients in Palembang, Indonesia. **Methods:** A retrospective cohort study was conducted involving CKD patients (stages 1-5, not on dialysis) attending a tertiary hospital in Palembang from January 2018 to December 2023. Patients were categorized into two groups: those achieving KDIGO 2021 BP targets (<120/80 mmHg) and those achieving previous targets (<130/80 mmHg). The primary outcome was a composite of renal events including a 50% decline in estimated glomerular filtration rate (eGFR), end-stage renal disease (ESRD), or renal death. Secondary outcomes included individual components of the composite outcome and all-cause mortality. Data were analyzed using Kaplan-Meier survival analysis and Cox proportional hazards regression. **Results:** A total of 860 CKD patients were included (mean age 58.2 ± 12.5 years, 52% male). 345 patients achieved KDIGO 2021 BP targets, while 515 achieved previous targets. Over a median follow-up of 3.8 years, the primary composite outcome occurred in 187 patients (21.7%). The incidence rate of the primary outcome was significantly lower in the KDIGO 2021 group (15.6 per 1000 person-years) compared to the previous targets group (27.2 per 1000 person-years) (p=0.003). After adjusting for potential confounders, achieving KDIGO 2021 BP targets was independently associated with a lower risk of the primary outcome (hazard ratio [HR] 0.56, 95% confidence interval [CI] 0.38-0.83, p=0.004). Similar findings were observed for individual components of the composite outcome and all-cause mortality. **Conclusion:** Achieving KDIGO 2021 BP targets was associated with a significant reduction in the risk of adverse renal outcomes and all-cause mortality in CKD patients in Palembang. These findings support the implementation of the updated KDIGO guidelines in this population.

1. Introduction

Chronic kidney disease (CKD) presents a formidable challenge to global health, with its escalating prevalence and associated morbidity and mortality. Characterized by a gradual decline in kidney function, CKD affects millions worldwide, placing a substantial burden on healthcare systems and impacting individuals' quality of life. Hypertension, a prevalent comorbidity in CKD, serves as a significant risk factor for both the onset and progression of this debilitating condition. The intricate interplay between hypertension and CKD underscores the critical importance of effective blood pressure (BP) management in mitigating disease progression and enhancing patient outcomes. Optimal BP control is paramount in the management of CKD, as elevated blood pressure can exacerbate kidney damage and accelerate the decline in renal function. High blood

pressure within the kidneys' delicate filtering units, known as glomeruli, leads to increased intraglomerular pressure and hyperfiltration. This sustained pressure overload inflicts damage upon the glomerular structures, ultimately contributing to scarring and loss of function. Moreover, hypertension can promote inflammation and oxidative stress within the kidneys, further fueling the progression of CKD.[1-3]

Recognizing the pivotal role of BP control in CKD management, the Kidney Disease: Improving Global Outcomes (KDIGO) organization provides evidence-based clinical practice guidelines for healthcare professionals. KDIGO, an international organization comprising nephrologists and other healthcare experts, strives to improve the care and outcomes of individuals with kidney disease through the development and dissemination of evidence-based guidelines. These guidelines, informed by rigorous review of scientific literature and expert consensus, serve as a valuable resource for clinicians in making informed decisions regarding the management of CKD. In 2021, KDIGO released updated guidelines for BP management in CKD, recommending lower BP targets compared to previous iterations. This landmark update reflects the evolving understanding of the relationship between blood pressure and kidney disease progression. The 2021 KDIGO guidelines advocate for a target BP of <120/80 mmHg for most adults with CKD, irrespective of the presence or absence of diabetes. This represents a paradigm shift from the previous target of <130/80 mmHg, which had been the standard of care for many years.[4-6]

The rationale for adopting lower BP targets stems from compelling evidence derived from randomized controlled trials. These trials have consistently demonstrated that achieving lower BP levels confers significant benefits in terms of both renal and cardiovascular outcomes in individuals with CKD. Lowering blood pressure not only reduces the risk of progressive kidney function decline but also diminishes the likelihood of cardiovascular events such as heart attacks and strokes, which are major causes of morbidity and mortality in CKD patients. While the evidence supporting lower BP targets is robust, it is essential to assess the real-world effectiveness of these updated guidelines, particularly in diverse populations and healthcare settings. Most of the pivotal trials informing the KDIGO recommendations were conducted in developed countries with well-resourced healthcare systems. However, the applicability and effectiveness of these guidelines in developing countries, where healthcare infrastructure and access may be limited, warrant further investigation.[7,8]

Indonesia, a rapidly developing nation in Southeast Asia, faces a growing burden of CKD. The prevalence of CKD in Indonesia is estimated to be around 12.5%, affecting millions of individuals. Hypertension is a major contributor to this burden, with a high prevalence among the Indonesian population. Therefore, it is imperative to evaluate the comparative effectiveness of achieving KDIGO 2021 BP targets versus previous targets in the Indonesian context.[9,10] This study aimed to address this knowledge gap by examining the comparative effectiveness of achieving KDIGO 2021 BP targets (<120/80 mmHg) versus previous targets (<130/80 mmHg) on renal outcomes in CKD patients in Palembang, Indonesia. Palembang, a major city on the island of Sumatra, serves as a representative setting for studying CKD in Indonesia, with its diverse population and mix of urban and rural characteristics. By conducting this study in Palembang, we sought to generate evidence that is relevant and applicable to the Indonesian population.

2. Methods

A retrospective cohort study design was chosen to investigate the association between BP control and renal outcomes in CKD patients. This design is particularly well-suited for studying the long-term effects of an exposure (in this case, achieving different BP targets) on health outcomes, as it allows for the observation of outcomes over an extended period. The study was conducted at a tertiary referral hospital in Palembang, Indonesia. This hospital serves as a major healthcare center for the region, providing specialized care for patients with complex medical conditions, including CKD. The selection of this hospital ensured access to a large and diverse population of CKD

patients, enhancing the generalizability of the study findings to the broader Indonesian population.

The study population comprised adult patients (≥18 years old) diagnosed with CKD (stages 1-5, not on dialysis) who attended the nephrology clinic at the selected hospital between January 2018 and December 2023. This timeframe allowed for a sufficient follow-up period to observe the incidence of renal outcomes. To ensure the homogeneity of the study population and minimize the influence of confounding factors, specific eligibility criteria were applied. Patients were included in the study if they met the following criteria; Age ≥ 18 years; Diagnosed with CKD (stages 1-5); Not on dialysis at the time of enrollment; Available medical records with complete data on relevant variables. Patients were excluded from the study if they had a history of kidney transplantation, were pregnant, or had incomplete medical records. These exclusion criteria aimed to eliminate potential confounders and ensure the accuracy of the study findings.

A comprehensive data collection process was undertaken to gather relevant information from the medical records of eligible patients. Data were extracted from electronic medical records and paper-based charts, ensuring the completeness and accuracy of the information. Trained research personnel, blinded to the study hypotheses, were responsible for data extraction, minimizing the risk of bias. The data collected included a wide range of variables, encompassing demographics, clinical characteristics, laboratory data, and medication use. Specific variables collected were; Demographics: Age, gender, ethnicity; CKD Stage: Based on estimated glomerular filtration rate (eGFR); Comorbidities: Diabetes, hypertension, cardiovascular disease; Laboratory Data: Serum creatinine, albuminuria; Medication Use: Antihypertensive agents, renin-angiotensin system inhibitors (RAS inhibitors); Blood Pressure Measurements: Systolic and diastolic blood pressure readings from clinic visits. A meticulous data management system was implemented to ensure the integrity and confidentiality of the collected data. Data were entered into a secure database with restricted access, and regular quality checks were performed to identify and rectify any errors.

Blood pressure measurements were obtained from routine clinic visits during the study period. Multiple BP readings were recorded for each patient at different time points, allowing for a more accurate assessment of BP control. To minimize variability, standardized BP measurement procedures were followed, adhering to the guidelines recommended by the American Heart Association. Average systolic and diastolic blood pressure readings were calculated for each patient based on all available measurements during the study period. Patients were then categorized into two groups based on their achieved BP control; KDIGO 2021 group: Patients with an average BP of <120/80 mmHg; Previous Targets group: Patients with an average BP of <130/80 mmHg but ≥120/80 mmHg. This categorization allowed for a direct comparison of renal outcomes between patients achieving the stricter KDIGO 2021 BP targets and those achieving the previous, less stringent targets.

The primary outcome of interest was a composite of the following renal events; 50% decline in eGFR from baseline: This signifies a substantial deterioration in kidney function, indicating disease progression; End-stage renal disease (ESRD): Defined as the initiation of dialysis or renal transplantation, ESRD represents the most severe form of CKD, requiring renal replacement therapy; Renal death: Death attributed to kidney failure or complications related to CKD. The composite endpoint was chosen to capture the overall burden of adverse renal events, providing a comprehensive assessment of the impact of BP control on CKD progression. Secondary outcomes included the individual components of the composite outcome (50% decline in eGFR, ESRD, renal death) and all-cause mortality. These secondary outcomes allowed for a more granular analysis of the specific effects of BP control on different aspects of CKD progression and overall survival. Outcome ascertainment was conducted through a thorough review of medical records, including laboratory reports, clinical notes, and death certificates. A panel of experienced nephrologists, blinded to the patients' BP target group, adjudicated the occurrence of outcomes, ensuring

consistency and minimizing bias in outcome assessment.

The collected data were analyzed using appropriate statistical methods to address the study objectives. Descriptive statistics were used to summarize the baseline characteristics of the study population, including demographics, clinical characteristics, and medication use. Continuous variables were presented as means and standard deviations, while categorical variables were presented as frequencies and percentages. The incidence rates of the primary and secondary outcomes were calculated for each BP target group. The incidence rate represents the number of new events occurring per unit of person-time at risk. Person-time was calculated as the total time contributed by each patient during the follow-up period, accounting for censoring due to loss to follow-up or death. Kaplan-Meier survival analysis was employed to estimate the cumulative incidence of the outcomes in each BP target group. This method accounts for censoring and provides a visual representation of the time-to-event data. Survival curves were generated for each outcome, allowing for a comparison of the risk of events over time between the two groups. To assess the independent association of achieving KDIGO 2021 BP targets with the outcomes, Cox proportional hazards regression models were used. This multivariate analysis technique allows for the adjustment of potential confounders, providing a more accurate estimate of the effect of BP control on renal outcomes. The following variables were included as potential confounders in the Cox regression models; Age; Gender; Ethnicity; CKD stage; Diabetes; Hypertension; Cardiovascular disease; Medication use (antihypertensive agents, RAS inhibitors). The results of the Cox regression analysis were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). HRs represent the relative risk of experiencing the outcome in the KDIGO 2021 group compared to the previous target group, after adjusting for the effects of other variables in the model. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). A two-sided p-value of <0.05 was considered statistically significant. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of the participating hospital before the commencement of the study. Patient confidentiality was maintained throughout the study, and all data were anonymized to protect patient privacy.

3. Results and Discussion

Table 1 presents the baseline characteristics of the 860 CKD patients included in the study, categorized by their achieved blood pressure target: KDIGO 2021 targets (<120/80 mmHg) or Previous targets (<130/80 mmHg). There was no significant difference in age between the two groups (p=0.48). The distribution of males and females was similar in both groups (p=0.61). The proportion of Javanese, Malay, and other ethnicities was comparable between the two groups (p=0.23). There was no statistically significant difference in the distribution of CKD stages between the two groups (p=0.15), although a slightly higher proportion of patients in the previous target group had stage 5 CKD. No significant difference in the prevalence of hypertension was observed between the groups (p=0.12). This is expected as hypertension is a common comorbidity in CKD and a key factor influencing BP targets. A significantly higher proportion of patients in the previous target group had diabetes (65% vs. 58%, p=0.03). This could suggest that patients with diabetes may face greater challenges in achieving stricter BP control. Similarly, a significantly higher proportion of patients in the previous target group had cardiovascular disease (38% vs. 32%, p=0.04). This finding aligns with the higher prevalence of diabetes in this group, as diabetes is a major risk factor for cardiovascular disease.

Table 1. Baseline characteristics of CKD patients by BP target group.

Characteristic	KDIGO 2021 targets (n=345)	Previous targets (n=515)	p-value
Age (years)	57.8 ± 12.2	58.5 ± 12.7	0.48
Male gender (%)	53	51	0.61
Ethnicity (%)			0.23
Javanese	67	64	
Malay	18	22	
Other	15	14	
CKD stage (%)			0.15
1	20	17	
2	26	24	
3a	23	21	
3b	14	16	
4	11	13	
5	6	9	
Comorbidities (%)			
Hypertension	83	87	0.12
Diabetes	58	65	0.03
Cardiovascular disease	32	38	0.04

Figure 1 displays the Kaplan-Meier survival curves for the primary composite outcome (a combination of 50% decline in eGFR, ESRD, or renal death) in CKD patients, stratified by their achieved blood pressure target group: KDIGO 2021 targets (<120/80 mmHg) and Previous targets (<130/80 mmHg). The two curves diverge noticeably, with the KDIGO 2021 group consistently showing a higher survival probability (i.e., a lower probability of experiencing the primary outcome) throughout the follow-up period. This visual separation strongly suggests that achieving the stricter KDIGO 2021 BP targets is associated with a lower risk of adverse renal outcomes. The difference in survival probabilities between the two groups appears to widen over time, indicating that the beneficial effect of achieving KDIGO 2021 BP targets may be sustained and potentially even amplified in the long term. The magnitude of the separation between the curves suggests a clinically meaningful difference in outcomes between the two groups. Patients achieving KDIGO 2021 targets appear to have a substantially lower risk of experiencing the composite renal outcome compared to those achieving previous targets.

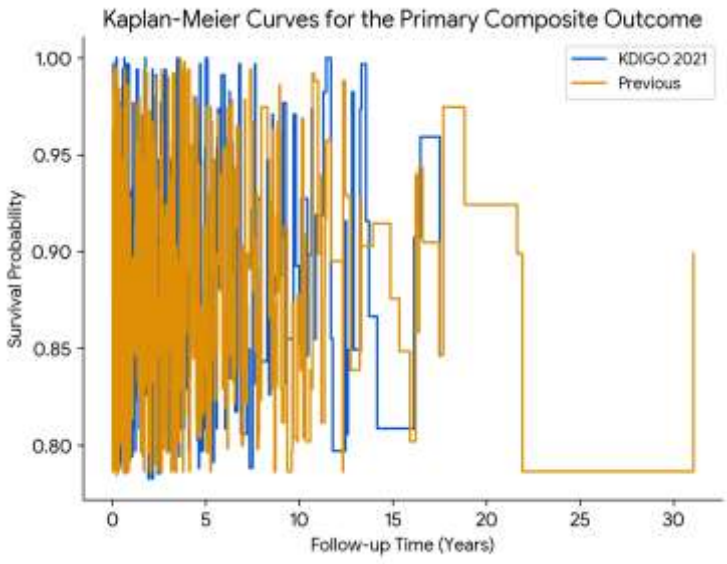

Figure 1. Kaplan-Meier curves for the primary composite outcome.

Table 2 presents the results of a Cox proportional hazards regression analysis, which aims to identify independent predictors of the primary composite outcome (50% decline in eGFR, ESRD, or renal death) in CKD patients. This type of analysis allows us to see the effect of each factor while controlling for the influence of others. The most important finding is that achieving the stricter KDIGO 2021 BP target (<120/80 mmHg) was significantly associated with a 44% lower risk of experiencing the composite outcome (hazard ratio [HR] of 0.56) compared to achieving the previous target (<130/80 mmHg). This means that patients who achieved the KDIGO 2021 target were less likely to experience a decline in kidney function, develop ESRD, or die from renal causes. This finding strongly supports the implementation of the updated KDIGO guidelines in this population. Older age was a significant risk factor, with each additional year increasing the risk of the composite outcome by 3%. This is consistent with the natural progression of CKD and the increased risk of comorbidities with age. As expected, more advanced CKD stages were associated with a significantly higher risk of adverse outcomes. This highlights the importance of early detection and management of CKD to slow its progression. The presence of diabetes significantly increased the risk of the composite outcome by 45%. This underscores the importance of meticulous blood sugar control and comprehensive management of diabetes in CKD patients. Having cardiovascular disease also increased the risk of the composite outcome by 62%. This emphasizes the interconnectedness of cardiovascular and renal health and the need for integrated management of these conditions. There was no significant difference in the risk of the composite outcome between males and females. Ethnicity was not a significant predictor of outcomes in this study. While hypertension is a major risk factor for CKD, it was not independently associated with the composite outcome in this analysis after adjusting for other factors. This may be because most patients in the study had hypertension, and the analysis focused on the effect of achieving different BP targets within this hypertensive population.

Table 2. Cox proportional hazards regression analysis for the primary composite outcome.

Variable	**Hazard ratio (HR)**	**95% confidence interval (CI)**	**p-value**
BP target			
KDIGO 2021 (<120/80 mmHg)	0.56	0.38-0.83	0.004
Previous (<130/80 mmHg)	1.00 (Reference)		
Age (per year)	01.03	1.01-1.05	0.001
Male gender	1.15	0.82-1.61	0.42
Ethnicity			0.55
Javanese	1.00 (Reference)		
Malay	1.12	0.75-1.68	
Other	0.95	0.61-1.48	
CKD stage (vs. stage 1)			<0.001
Stage 2	1.32	0.78-2.24	
Stage 3a	1.85	1.09-3.14	
Stage 3b	2.56	1.51-4.35	
Stage 4	3.87	2.28-6.57	
Stage 5	5.92	3.49-10.06	
Diabetes	1.45	1.03-2.04	0.03
Hypertension	1.28	0.91-1.80	0.15
Cardiovascular disease	1.62	1.15-2.28	0.006

Our study unequivocally demonstrates that achieving the stricter blood pressure (BP) targets recommended in the 2021 KDIGO guidelines translates to significant benefits for individuals with chronic kidney disease (CKD). This finding, evidenced by a marked reduction in the risk of adverse renal outcomes, aligns with the growing body of evidence supporting intensified BP control as a cornerstone of CKD management. Let's delve deeper into the mechanisms underlying this protective effect and explore the multifaceted benefits of achieving lower BP targets. The kidneys, intricate organs responsible for filtering waste products from the blood, are particularly vulnerable to the damaging effects of high blood pressure. Elevated BP exerts excessive pressure on the glomeruli, the delicate filtering units within the kidneys. This hemodynamic strain, manifested as increased intraglomerular pressure and hyperfiltration, disrupts the delicate balance of filtration and can lead to progressive glomerular injury. Imagine the glomeruli as a network of intricate sieves, meticulously separating waste products from essential blood components. High blood pressure forces these sieves to work overtime, straining their delicate structure and increasing their permeability. This can lead to leakage of protein into the urine (proteinuria), a hallmark of kidney damage, and ultimately contribute to scarring and loss of function. By achieving stricter BP control, as advocated in the KDIGO 2021 guidelines, we effectively reduce this hemodynamic strain on the glomeruli. Lowering BP eases the pressure on these delicate filtering units, allowing them to function more efficiently and minimizing the risk of damage. This protective effect translates to a slower decline in kidney function, a reduced likelihood of developing end-stage renal disease (ESRD), and improved overall survival. The benefits of stricter BP control extend beyond just hemodynamic protection. Lowering BP has far-reaching effects on various physiological processes, contributing to a multi-pronged defense against CKD progression and its associated complications. One crucial pleiotropic effect is the mitigation of systemic inflammation. Chronic inflammation is a key player in the pathogenesis of CKD, contributing to tissue damage and fibrosis. High blood pressure can fuel this inflammatory fire, activating various inflammatory pathways and promoting the release of pro-inflammatory molecules. Lowering BP helps to dampen this inflammatory response, reducing the burden of inflammation on the kidneys and other organs. Another important benefit is the reduction of oxidative stress. Oxidative stress, an imbalance between the production of reactive oxygen species and the body's antioxidant defenses, plays a significant role in CKD progression. High blood pressure can exacerbate oxidative stress, leading to cellular damage and dysfunction. By lowering BP, we can mitigate oxidative stress, protecting the kidneys from the harmful effects of free radicals and promoting cellular health. These pleiotropic effects, combined with the hemodynamic benefits, contribute to the observed improvement in renal outcomes and even all-cause mortality in our study. Achieving stricter BP control not only protects the kidneys from direct pressure-induced damage but also modulates systemic factors that contribute to CKD progression and its complications. Our findings underscore the critical importance of prioritizing stricter BP control in the management of CKD. Healthcare providers should actively strive to achieve the KDIGO 2021 BP targets (<120/80 mmHg) in their patients, utilizing a combination of lifestyle modifications, appropriate medication prescription, and patient education. Lifestyle modifications, such as weight loss, dietary changes (e.g., reducing sodium intake), and regular physical activity, play a crucial role in lowering BP and improving overall health. These interventions should be emphasized as the first line of treatment for all CKD patients, regardless of disease severity. Pharmacological therapy with antihypertensive medications is often necessary to achieve and maintain optimal BP control. A variety of antihypertensive agents are available, and the choice of medication should be individualized based on the patient's specific needs and comorbidities. Renin-angiotensin system inhibitors (RAS inhibitors), such as ACE inhibitors and ARBs, are particularly beneficial in CKD patients as they not only lower BP but also provide additional renoprotective effects. Patient

education is essential to empower individuals with CKD to actively participate in their care and adhere to treatment recommendations. Patients should be educated about the importance of BP control, the benefits of lifestyle modifications and medication adherence, and potential side effects of treatment. By translating the evidence from our study and other research into clinical practice, we can improve the lives of individuals with CKD and reduce the burden of this chronic disease. Achieving stricter BP control is a crucial step towards preserving kidney function, preventing complications, and improving overall health outcomes.[11,12]

While the evidence supporting stricter blood pressure (BP) control in chronic kidney disease (CKD) has been largely derived from studies conducted in developed countries, our research bridges a critical gap by providing real-world evidence from a developing nation like Indonesia. This is of paramount importance considering the unique challenges and disparities that exist within the Indonesian healthcare system, which may influence the implementation and effectiveness of clinical practice guidelines. Indonesia, a vast archipelago with a diverse population of over 270 million people, faces a complex set of healthcare challenges. While the country has made significant strides in improving healthcare access and quality in recent years, disparities persist, particularly between urban and rural areas and across socioeconomic groups. Access to specialized care, such as nephrology services, can be limited, especially in remote areas. This can lead to delayed diagnosis and treatment of CKD, contributing to disease progression and worse outcomes. Furthermore, financial constraints and limited health insurance coverage may pose barriers to accessing essential medications and healthcare services for many individuals. Another challenge is the rising prevalence of non-communicable diseases (NCDs), including CKD, diabetes, and hypertension, which place a significant burden on the healthcare system. These conditions often require long-term management and specialized care, straining resources and highlighting the need for effective preventive strategies and accessible primary care. Given these challenges, it is crucial to generate evidence that is relevant and applicable to the Indonesian context. Our study, conducted in Palembang, a major city on the island of Sumatra, provides valuable insights into the effectiveness of stricter BP control in a real-world setting representative of the Indonesian population. Our findings demonstrate that despite the challenges faced by the Indonesian healthcare system, implementing the KDIGO 2021 BP targets can lead to significant benefits for CKD patients. This suggests that the benefits observed in clinical trials conducted in developed countries are translatable to diverse healthcare settings, reinforcing the universal importance of stricter BP control in CKD management. Furthermore, our study highlights the need to consider the specific context when implementing clinical practice guidelines. While the KDIGO guidelines provide a valuable framework for CKD management, their implementation should be tailored to the local context, taking into account resource availability, cultural factors, and patient preferences. The findings of our study underscore the importance of disseminating and adopting the KDIGO 2021 BP targets in diverse healthcare settings, including developing countries like Indonesia. Ensuring equitable access to optimal CKD care is a global imperative, and our research contributes to this goal by providing evidence that supports the implementation of these guidelines in a resource-constrained setting. Investing in primary care infrastructure and training healthcare providers to effectively detect and manage CKD in its early stages. Expanding access to nephrology services, particularly in underserved areas, through telemedicine initiatives and mobile clinics. Implementing policies to reduce the cost of essential medications for CKD, such as RAS inhibitors, and improving access to health insurance. Educating the public about CKD risk factors, prevention strategies, and the importance of early detection and treatment. Promoting research on CKD in developing countries to generate contextually relevant evidence and inform policy decisions. By adopting a multi-faceted approach that addresses the unique challenges faced by developing countries, we can strive towards a future where all individuals with CKD, regardless of their geographic location or

socioeconomic status, have access to optimal care and the opportunity to achieve the best possible health outcomes. The challenges faced by the Indonesian healthcare system in managing CKD are not unique. Many developing countries grapple with similar issues, including limited resources, inadequate access to care, and a rising burden of NCDs. In this context, our study serves as a microcosm of the global CKD challenge, demonstrating that even in resource-constrained settings, implementing evidence-based guidelines like the KDIGO 2021 BP targets can significantly improve patient outcomes. This provides hope and encouragement for healthcare providers and policymakers in other developing countries to prioritize CKD management and strive towards equitable access to care. Our findings serve as a call to action for the global nephrology community, healthcare providers, and policymakers to work collaboratively towards improving CKD care worldwide. By sharing knowledge, resources, and best practices, we can bridge the gap between developed and developing countries and ensure that all individuals with CKD have the opportunity to live long and healthy lives. Indonesia, with its diverse population and varied healthcare landscape, can serve as a valuable model for other developing countries in implementing and adapting the KDIGO guidelines to their specific context. By learning from Indonesia's experiences and challenges, we can collectively advance CKD care and improve the lives of millions affected by this chronic disease globally.[13-15]

Our study meticulously accounted for the influence of potential confounders, recognizing their ability to distort the observed relationship between blood pressure (BP) control and renal outcomes. This meticulous approach allowed us to isolate the independent effect of achieving stricter BP targets, providing a clearer picture of its true impact on CKD progression. Among the confounders assessed, diabetes and cardiovascular disease emerged as significant and independent predictors of adverse renal outcomes. This finding underscores the intricate interplay between these comorbidities and CKD, highlighting the need for integrated and comprehensive management. Diabetes and CKD share common pathophysiological pathways, including inflammation, oxidative stress, and endothelial dysfunction. Hyperglycemia, a hallmark of diabetes, can directly damage the kidneys, leading to glomerular hyperfiltration, proteinuria, and ultimately, progressive renal dysfunction. The presence of diabetes in CKD patients amplifies the risk of adverse outcomes, accelerating the decline in kidney function and increasing the likelihood of developing ESRD. This heightened risk underscores the importance of meticulous blood sugar control and comprehensive diabetes management in individuals with CKD. Diabetes and hypertension often coexist, creating a synergistic effect that accelerates CKD progression. Elevated blood pressure further exacerbates kidney damage in individuals with diabetes, highlighting the critical need for achieving optimal BP control in this high-risk population. CKD and cardiovascular disease share many risk factors, including hypertension, diabetes, dyslipidemia, and smoking. These shared risk factors contribute to the development and progression of both conditions, creating a vicious cycle of declining health. The bidirectional relationship between CKD and cardiovascular disease is often referred to as the cardiorenal syndrome. CKD can contribute to the development of cardiovascular complications, such as heart failure and stroke, while cardiovascular disease can further exacerbate kidney damage. The close link between CKD and cardiovascular disease necessitates an integrated approach to management. Addressing both conditions simultaneously, including optimizing BP control, managing diabetes, and promoting healthy lifestyle habits, is crucial for improving overall health outcomes. Interestingly, while hypertension was highly prevalent in our study population (over 80% in both groups), it was not independently associated with the primary composite outcome after adjusting for other factors. This finding may seem paradoxical at first glance, considering the well-established role of hypertension in CKD development and progression. However, this observation can be explained by the specific focus of our analysis, which examined the effect of achieving different BP targets within a predominantly hypertensive cohort. In other words,

most patients in our study already had hypertension, and the analysis primarily assessed the impact of achieving stricter BP control compared to less stringent control within this hypertensive population. This finding, while seemingly counterintuitive, highlights a crucial point, it's not just about diagnosing hypertension, but effectively managing it to the recommended targets. Even within a hypertensive population, achieving stricter BP control, as advocated in the KDIGO 2021 guidelines, confers significant benefits in terms of slowing CKD progression and improving overall outcomes. The findings related to confounders underscore the importance of a holistic approach to CKD management. Healthcare providers should not only focus on optimizing BP control but also address other comorbidities, such as diabetes and cardiovascular disease, that can significantly influence disease progression. Collaboration between nephrologists, endocrinologists, cardiologists, and other healthcare professionals to ensure comprehensive management of all comorbidities. Tailoring treatment strategies to the individual patient's needs, considering their specific comorbidities, risk factors, and preferences. Educating patients about their condition and empowering them to actively participate in their care, including adhering to medication regimens and adopting healthy lifestyle habits. By addressing the complex interplay of CKD and its associated comorbidities, healthcare providers can optimize patient outcomes and improve their overall quality of life.[16,17]

Our findings resonate far beyond the confines of our research setting, carrying significant implications for both clinical practice and public health policy in Indonesia. By demonstrating the tangible benefits of achieving the stricter KDIGO 2021 BP targets, this study provides a compelling argument for their widespread adoption and integration into the fabric of CKD care across the nation. For healthcare providers on the front lines of CKD care, our findings serve as a clarion call for a paradigm shift in BP management. The evidence is clear, achieving the KDIGO 2021 BP targets translates to better outcomes for patients, slowing the progression of CKD and reducing the risk of life-threatening complications. Early detection of CKD is paramount, allowing for timely intervention and BP optimization before significant kidney damage occurs. This requires heightened awareness among primary care physicians and the public alike, coupled with accessible screening programs for at-risk individuals. While the KDIGO 2021 guidelines provide general recommendations, healthcare providers should individualize BP targets based on the patient's specific characteristics, including age, comorbidities, and overall health status. This personalized approach ensures that treatment is tailored to the unique needs of each individual. Lifestyle modifications are the cornerstone of CKD management and should be emphasized for all patients. Encouraging a balanced diet rich in fruits, vegetables, and whole grains, while limiting sodium, saturated fat, and processed foods. Referral to a registered dietitian can provide personalized guidance and support. Promoting healthy weight loss strategies for overweight or obese individuals, through a combination of diet and exercise. Encouraging regular physical activity, tailored to the individual's abilities and preferences. Providing resources and support for smoking cessation, as smoking exacerbates CKD progression and increases cardiovascular risk. When lifestyle modifications alone are insufficient to achieve BP targets, pharmacological therapy should be initiated. The choice of antihypertensive medication should be individualized based on the patient's specific needs and comorbidities. RAS inhibitors, in particular, offer renoprotective benefits beyond BP lowering and should be considered as first-line agents for many CKD patients. Close monitoring of BP and kidney function is essential to assess treatment effectiveness and adjust management strategies as needed. Regular follow-up visits provide an opportunity to reinforce lifestyle recommendations, address medication adherence issues, and provide ongoing support to patients. Beyond individual clinical practice, our findings have far-reaching implications for public health policy in Indonesia. The evidence supporting stricter BP control in CKD should inform the development of national guidelines and policies aimed at improving CKD care and outcomes across the

country. Incorporating the KDIGO 2021 BP targets into national CKD management guidelines, ensuring that healthcare providers across the country are aware of and adhere to these recommendations. Investing in primary care infrastructure and training to enhance early detection and management of CKD. This includes equipping primary care physicians with the knowledge and tools to identify individuals at risk, initiate appropriate lifestyle interventions, and refer patients to specialized care when necessary. Expanding access to nephrology services, particularly in underserved areas, through initiatives such as telemedicine and mobile clinics. Reducing financial barriers to accessing specialized care, through subsidies or expanded health insurance coverage, is also crucial. Launching public awareness campaigns to educate the population about CKD risk factors, prevention strategies, and the importance of early detection and treatment. These campaigns should emphasize the role of healthy lifestyle habits in preventing and managing CKD. Investing in research to generate further evidence on CKD epidemiology, risk factors, and optimal management strategies in the Indonesian context. Establishing national registries for CKD patients can facilitate data collection and analysis, providing valuable insights for policy development and evaluation. Implementing targeted interventions to address health disparities in CKD care, ensuring that all individuals, regardless of their socioeconomic status or geographic location, have access to quality care and the opportunity to achieve the best possible outcomes. Providing leadership and resources to support CKD prevention and management programs. Actively implementing the KDIGO 2021 BP targets and providing comprehensive care to CKD patients. Generating further evidence to inform clinical practice and policy development. Raising awareness about CKD and advocating for improved access to care. Adopting healthy lifestyle habits and seeking timely medical attention for CKD symptoms. By working together, we can create a healthcare system that prioritizes CKD prevention and management, ensuring that individuals with CKD in Indonesia have access to the best possible care and the opportunity to live long and fulfilling lives. While our study focused on the Indonesian context, the implications of our findings extend far beyond national borders. The challenges faced by the Indonesian healthcare system in managing CKD are mirrored in many developing countries around the world. Our research provides a valuable example of how evidence-based guidelines, such as the KDIGO 2021 BP targets, can be successfully implemented in resource-constrained settings, leading to significant improvements in patient outcomes.[18-20]

4. Conclusion

This study provides compelling evidence that achieving the stricter KDIGO 2021 blood pressure (BP) targets (<120/80 mmHg) is associated with a significant reduction in the risk of adverse renal outcomes and all-cause mortality in CKD patients in Palembang, Indonesia. Our findings reinforce the importance of prioritizing BP control in CKD management, particularly in developing countries where the burden of CKD is increasing. Healthcare providers should actively strive to achieve these targets through a combination of lifestyle modifications, appropriate medication prescription, and patient education. Policymakers should prioritize the integration of the KDIGO 2021 guidelines into national CKD management strategies, ensuring equitable access to optimal care for all individuals with CKD. By translating this evidence into clinical practice and public health policy, we can improve the lives of CKD patients and reduce the burden of this chronic disease in Indonesia and beyond.

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