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The Impact of Antidiabetic Dose Appropriateness Based on Renal Function on Therapeutic Outcomes among Geriatric at Bali, Indonesia

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Abstract

Background*: Diabetes mellitus is a significant global health issue, especially in the older population. Appropriate drug dosing is crucial in geriatric patients because renal function generally declines with age. A decline in renal function is directly associated with the adverse effects of antidiabetic drugs, particularly hypoglycemia, rather than their therapeutic efficacy.* ***Objective****: The objective of the present study was to assess the effect of antidiabetic dose appropriateness according to renal function on therapeutic outcomes among geriatric patients at three hospitals in Bali Province.* ***Methods****: The research was designed as an observational analytic study with a cross-sectional design. The study involved patients with diabetes aged ≥ 60 years, with or without renal function impairment. Medical records from January to December 2024 were also reviewed for this study. The suitability of antidiabetic drug dosing was evaluated using the estimated glomerular filtration rate (eGFR) calculated using the Cockcroft–Gault equation. The prescribed doses were compared with the dosage guidelines based on the renal function. A Chi-square analysis was performed to assess the relationship between the appropriateness of the antidiabetic dose and the therapeutic outcomes. Moreover, multivariate analysis was performed using logistic regression after adjusting for other factors.* ***Results****: Among the included patients, 27.6% were diagnosed with CKD and 28.4% had renal function classified as stage G2. A total of 51.5% of patients received appropriately adjusted antidiabetic doses. Dose appropriateness was significantly associated with primary clinical outcomes ($p<0.05$) but not with secondary clinical outcomes.* ***Conclusion****: In conclusion, appropriate dose adjustment is essential for enhancing diabetes treatment strategies for geriatric patients with diverse stages of kidney dysfunction.*

Keywords: *diabetes mellitus, elderly, dose adjustment, renal function, therapeutic outcomes*

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INTRODUCTION

Diabetes mellitus (DM) has emerged as a prominent global health concern in recent years (Perkumpulan Endokrinologi Indonesia 2021). In 2021, diabetes affected approximately 10.5% of the global population, with estimates indicating a potential increase of 12.2% by 2045. Indonesia ranks fifth among countries with the highest prevalence of diabetes (International Diabetes Federation 2021). Data from the 2023 Indonesia Health Survey indicate that the rate of diabetes grew from 10.9% in 2018 to 11.7% (Badan Kebijakan Pembangunan Kesehatan, 2023). The majority of affected individuals are elderly, reflecting the growing geriatric population in Indonesia. This population continues to rise and is projected to become the largest demographic group in the country (Basrowi et al., 2021). The prevalence of type 2 diabetes mellitus (T2DM) in Bali has reached 52%, surpassing the national rate of 50.2%. Data from the Provincial Health Office indicate that the number of diabetes cases in Bali nearly doubled between 2017 and 2023. Bali also has a significant elderly population (Bali Provincial Health Service, 2017, 2023; Kemenkes RI, 2023).

Geriatric patients often experience multiple comorbidities due to a decline in organ function, including renal function (Kemenkes RI 2014). It can also affect the pharmacokinetics and pharmacodynamics of the drugs. Patients with type 2 diabetes mellitus are vulnerable to developing critical and life-threatening conditions (International Diabetes Federation, 2021), resulting in increased healthcare demands and a higher likelihood of progression to end-stage renal disease. Approximately 9.3% of the Indonesian population experiences impaired renal function due to diabetes (Riyadina et al. 2020).

As renal function declines with age, drug excretion becomes impaired, necessitating dose adjustment and, in some cases, drug discontinuation. Impaired drug excretion can lead to the accumulation of drugs or their metabolites at toxic concentrations. When certain medications are essential, close monitoring of adverse effects is crucial (Garza&Park, 2023). A decline in renal function can also be reflected by a decreased glomerular filtration rate (GFR). Dose adjustments for antidiabetic medications should not be limited to patients already diagnosed with kidney failure but must also consider age. Drug dosing and severity of renal impairment are commonly evaluated using creatinine clearance (CrCl) values (Xu et al., 2024). Several studies have reported that more than 30% of patients receive inappropriate antidiabetic drug doses based on renal function. Thus, geriatric patients diagnosed with T2DM require special attention to ensure that antidiabetic drug doses are appropriate according to their renal function (Noronha et al., 2022). The findings suggest that inappropriate sitagliptin dosing was primarily due to the failure to adjust the dose according to the patients renal function. Variations in the glomerular filtration rate (GFR) may lead to previously appropriate doses becoming unsuitable, highlighting the importance of continuous renal function monitoring to maintain the safety and efficacy of medications (Snyder et al., 2021; Sohn, 2012).

The geriatric population with T2DM is often considered vulnerable in healthcare services. This group requires special attention in terms of medication dose adjustment due to the high risk of complications and decreased quality of life (Hailu et al., 2020; Taha, 2021). A study reported that the appropriateness of oral antidiabetic drug (OAD) prescriptions according to guidelines and patient-specific factors was only 86% (Rusli et al., 2025). Furthermore, the accumulation of several comorbidities tends to increase the probability of patients being exposed to polypharmacy (Tamene et al., 2025). Health conditions frequently found in older adults, including diabetes and cardiovascular disorders, have the potential to impair renal functions. These conditions are linked to higher rates of albuminuria among older adults and may result in pathological changes, such as glomerular sclerosis, tubular degeneration, and vascular stiffening, as evidenced by kidney biopsy findings. Consequently, this elevates the risk of cardiovascular mortality, and a low eGFR correlates with poor clinical outcomes (Noronha et al., 2022). Appropriate selection of OADs and their dosing is expected to help achieve the desired therapeutic outcomes. Both national and international diabetes management guidelines recommend evaluating diabetes treatment outcomes using parameters such as HbA1c, fasting blood glucose, blood pressure, and lipid profiles. Assessing dosage appropriateness as a personalized medicine is essential to ensure safety while maintaining therapeutic effectiveness (Nova & Virginia, 2023; Perkumpulan Endokrinologi Indonesia, 2021; Virginia et al., 2021).

Therapeutic outcome targets will not be achieved if there is a gap between clinical guidelines and their practical implementation in the field. This includes variations in prescribing practices among healthcare professionals, a lack of awareness regarding dose adjustment based on renal function, and limited monitoring of renal function in routine clinical settings.

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Evidence-based medicine is needed to address the lack of local data on prescribing patterns. Therefore, optimizing diabetes therapy in geriatric patients is essential, highlighting the need for research focused on specific populations in Indonesia, such as the elderly, as an innovative step to improve patient safety and clinical therapeutic outcomes (Kieho 2012; Li et al. 2023). Therefore, this study aimed to investigate the relationship between the renal function–based appropriateness of OADs and therapeutic effectiveness in older adults residing in Bali, Indonesia.

MATERIALS AND METHODS

Study design and patients

This study utilized an analytical observational method with a cross-sectional design and was conducted between February and May 2025 to collect patient medical record data from three hospitals in Bali. The study population comprised all individuals who visited the outpatient clinic. The sample was drawn from the medical records of patients with diabetes who fulfilled the inclusion requirements: patients aged ≥60 years, diagnosed with T2DM, receiving antidiabetic treatment, and who underwent medical examinations between January and December 2024. The exclusion criteria were incomplete data in the medical records, including body weight, sex, blood pressure, serum creatinine, fasting blood glucose, random blood glucose, and lipid profile.

Data collection

Patient data were extracted from the medical records of patients with a confirmed diagnosis of type 2 diabetes mellitus (T2DM). Ethical approval for the study was obtained to allow access to patient medical records (approval number: KE/FK/1807/EC, dated December 2, 2024). Ethical approval for this study was obtained to protect the rights, dignity, and well-being of the research participants, ensure that the study was conducted in accordance with ethical principles, provide legal and institutional legitimacy, and guarantee data security and confidentiality. Medical records were retrieved from the Medical Records Department between January and December 2024. Information extracted from the medical records comprised the patient's identification number, full name, sex, age, body weight, diagnosis, laboratory examination results, and prescribed therapy (active ingredient(s), dosage, quantity, and administration instructions), as shown in Table 1.

The collected information was analyzed to assess whether the dosages of antidiabetic medications administered to geriatric patients were appropriate in relation to their renal function and to evaluate treatment outcomes. Therapeutic outcomes were categorized into primary outcomes, including fasting blood glucose, random blood glucose, and HbA1c levels, and secondary outcomes, which comprised blood pressure and lipid profile measurements. The estimation of glomerular filtration rate (eGFR) in this study was estimated using the Cockcroft–Gault equation. Subsequently, the prescribed antidiabetic doses were compared with the established dosage recommendations adjusted for renal function (Ashley & Currie, 2009; Hahr & Molitch, 2022; National Kidney Foundation, 2007; Perkumpulan Endokrinologi Indonesia, 2021). The Cockcroft–Gault formula was used because the CrCl value calculated using this equation has been historically applied in pharmacokinetic studies and drug dosage adjustment guidelines; many drug labels and regulatory recommendations (e.g., FDA) refer to the eCrCl derived from the Cockcroft–Gault formula for dosing purposes(CDER, 2024). The CG formula is easy to calculate (requiring only age, body weight, and serum creatinine), making it practical for everyday clinical decision-making, particularly for drug dose adjustments(Scappaticci & Regal, 2017).

Statistical analysis

The relationship between the appropriateness of antidiabetic drug dosing based on renal function and therapeutic outcomes was examined using the chi-square test. Logistic regression analysis was performed to control for the confounding variables. Statistical significance was set at $p<0.05$.

RESULTS AND DISCUSSION

Results

The patient selection flowchart for those who met the inclusion criteria is shown in Figure 1. A total of 134 T2DM patients aged ≥ 60 years with available serum creatinine data were included in the study.

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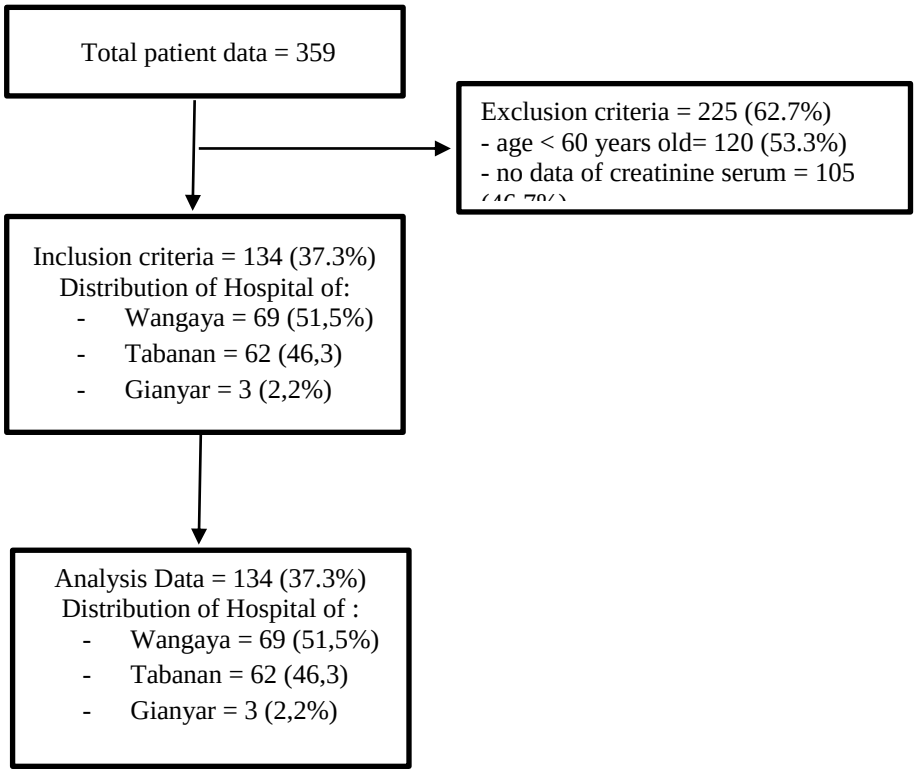

Figure 1. Flowchart of patient selection who met the inclusion criteria

Table 1 provides a summary of patient demographics, showing that most respondents were female, predominantly aged 60 years, and more than half were overweight. A total of 27.6% of the respondents had been diagnosed with CKD, and 28.4% had renal function classified as stage G2. Most of our respondents were non-smokers and had well-controlled glycemic indicators, blood pressure, and lipid profiles (except LDL).

Figure 2 shows that 74 respondents received two-drug combination therapy. Figure 3 shows that 51.5% of patients consumed antidiabetic drugs at an appropriate dose according to the eGFR. As shown in Figure 4, 65.6% of patients were not prescribed insulin. Figure 5 shows that the most inappropriate dose was that of sitagliptin.

Figure 6 shows the crude odds ratio of the appropriate diabetic drug dose for primary and secondary clinical outcomes. The appropriateness of the diabetic dose was significantly associated with primary clinical outcomes (FBG, RBG, and HbA1c) but not with secondary outcomes (blood pressure and lipid profile). An appropriate antidiabetic dose could increase controlled FBG ($p = 0.000$; OR = 4.93, 95%CI = 2.24 – 10.83), enhance controlled RBG ($p = 0.008$; OR = 2.83, 95%CI = 1.30 – 6.18), and improve controlled HbA1c ($p = 0.000$; OR = 4.24, 95%CI = 1.89 – 9.50).

The findings of the multivariate analysis are shown in Table 2. After controlling for age, body mass index (BMI), and smoking habits, appropriate antidiabetic dosing significantly enhanced the primary clinical outcomes. The effect to FBG was OR = 5.65, 95% CI = 2.44 – 13.12; RBG was OR = 3.01, 95%CI = 1.35 – 6.72, and HbA1c was OR = 4.22, 95%CI = 1.88 – 9.48. However, adjusting for age, BMI, and smoking status did not affect secondary outcomes. The interesting finding was that DBP showed a significant association with the appropriate diabetic dose as a result of multivariate analysis after adjusting for primary outcomes, age, BMI, and smoking status (OR(95%CI) = 0.16 (0.02 – 0.61)).

P-ISSN: 2406-9388
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Table 1. Patient characteristics

Patient Characteristics	n (%)	Patient Characteristics	n (%)
Sex all(n=359), inklusi(n=134)		Systolic Blood Pressure (n=132)	
Female	188 (52,37), 58 (43.3)	Mean±SD: 135.20 ± 18.68 mmHg	
		Controlled	93 (70.5)
Male	171 (47,63), 76 (56.7)	Uncontrolled	39 (29.5)
Age	359 (100.0)	Diastolic Blood Pressure (n=132)	
Mean±SD: 62.32 ± 6.1 years of age		Mean±SD: 72.98 ± 12.93 mmHg	
<65 years of age	223 (62.1)	Controlled	123 (93.2)
≥65 years of age	136 (37.9)	Uncontrolled	9 (6.8)
CKD diagnosis (n=134)		LDL (n=76)	
Yes	37 (27.6)	Mean±SD: 116.25 ± 39.90 mg/dL	
No	97 (72.4)	Controlled	32 (42.1)
		Uncontrolled	44 (57.9)
Smoking status (n=134)		HDL (n=69)	
Yes	18 (13.4)	Mean±SD: 51.17 ± 18.05 mg/dL	
No	116 (86.6)	Controlled	38 (55.1)
		Uncontrolled	31 (44.9)
Body Mass Index (n=134)		Triglycerides (TG) (n=75)	
Mean±SD: 25.70 ± 10.51 kg/m^2		Mean±SD: 153.61 ± 105.15 mg/dL	
Underweight	2 (1.5)	Controlled	43 (57.3)
Normal	36 (26.9)	Uncontrolled	32 (42.7)
Overweight	96 (71.6)		
Fasting Blood Glucose (n=116)		Total Cholesterol (TC) (n=71)	
Mean±SD: 135.69 ± 47.66 mg/dL		Mean±SD: 193.01 ± 40.62 mg/dL	
Controlled	62 (53.4)	Controlled	39 (54.9)
Uncontrolled	54 (46.6)	Uncontrolled	32 (45.1)
Random Blood Glucose (n=115)		Serum Creatinine (SrCr) (n=134)	134 (100.0)
Mean±SD: 180.15 ± 79.48 mg/dL		Mean±SD: 1.34 ± 1.20 mg/dL	
Controlled	70 (60.9)		
Uncontrolled	45 (39.1)		
HbA1c (n=107)		CKD Classification (n=134)	
Mean±SD: 7.42 ± 1.95 **%**		Mean±SD: 62.08 ± 42.09 mL/m^2	
Controlled	54 (50.5)	G1	20 (14.9)
Uncontrolled	53 (49.5)	G2	38 (28.4)
		G3a	34 (25.4)
		G3b	23 (17.2)
		G4	17 (12.7)
		G5	2 (1.5)

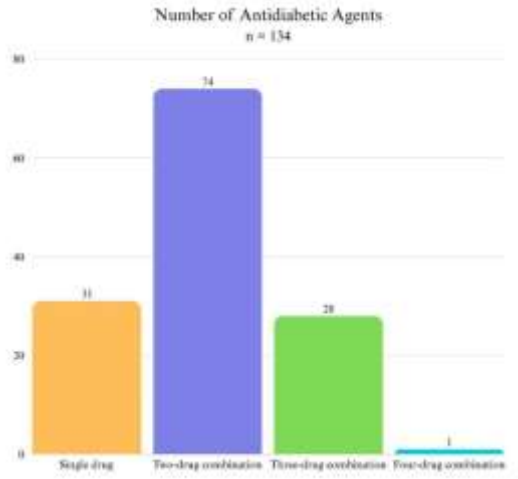

Figure 2. Number of antidiabetic agents

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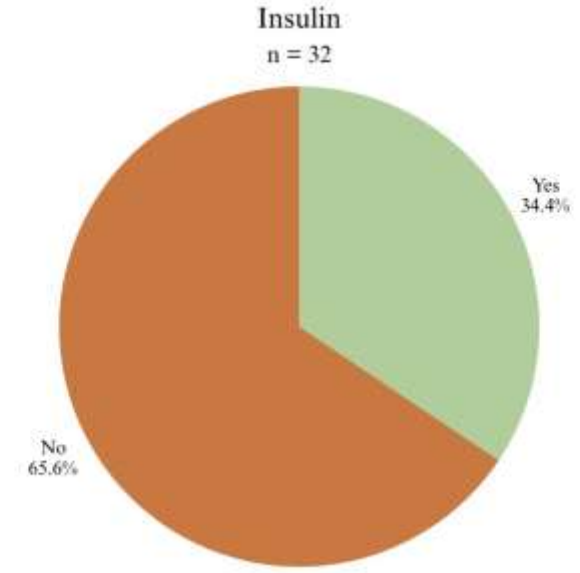

Figure 3. Insulin prescribing pattern

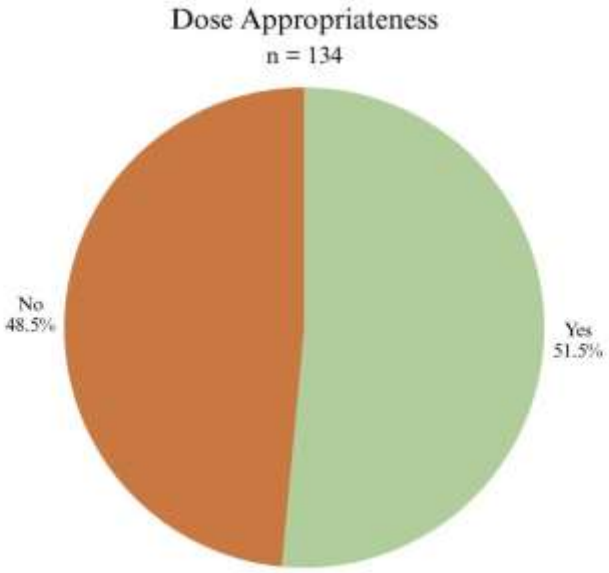

Figure 4. Dose appropriateness of antidiabetic agents

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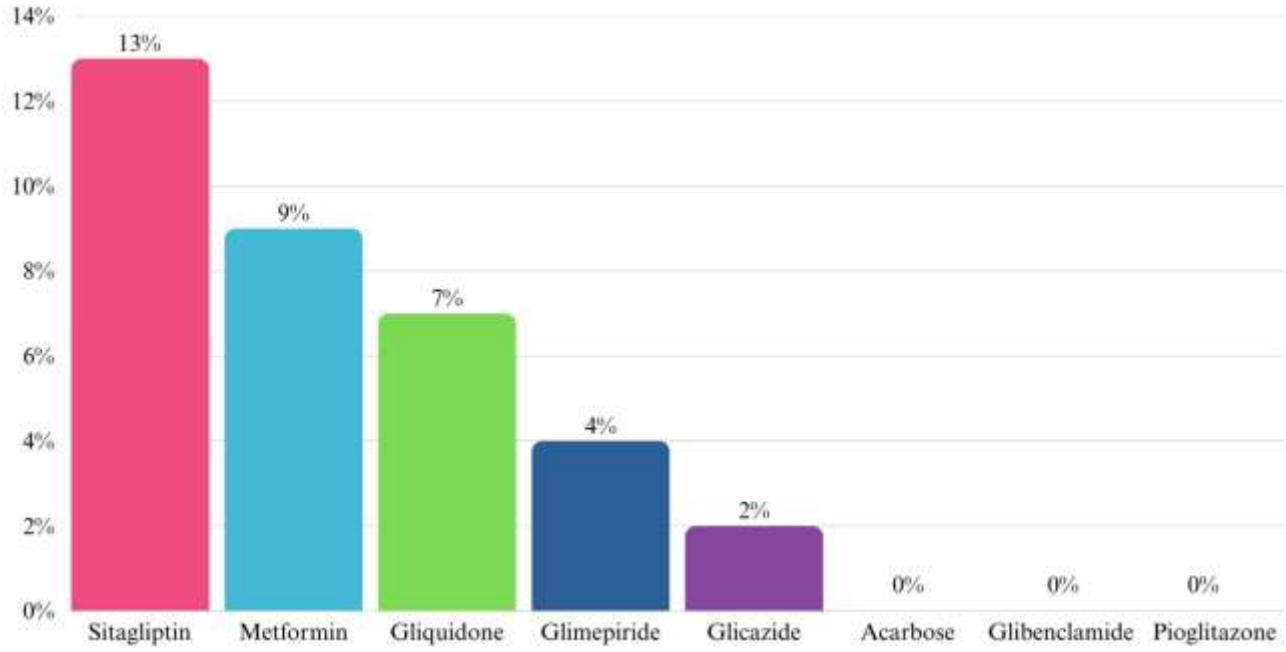

Figure 5. Inappropriate antidiabetic drug dosage according to renal adjustment dosage

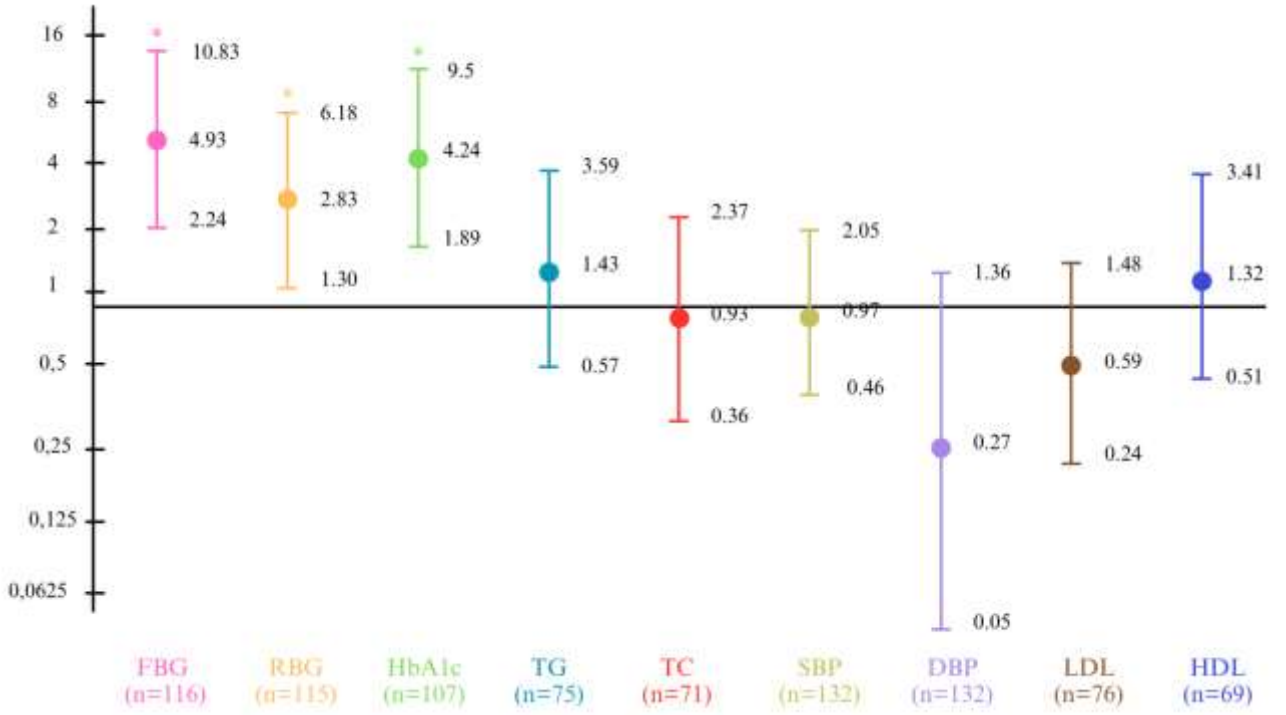

Figure 6. Crude odds ratio of the appropriateness of diabetes dose for primary and secondary clinical outcomes.
*p-value<0.05
FBG: fasting blood glucose, RBG: random blood glucose, TG = triglycerides, TC = total cholesterol, SBP = systolic blood pressure, DBP = diastolic blood pressure, LDL = low density lipoprotein, HDL = high density lipoprotein

The relationship between the appropriateness of antidiabetic drug dosing adjusted for renal function and treatment outcomes in geriatric patients was analyzed using multivariate analysis. Table 2 presents multivariate analysis.

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Table 2. Multivariate analysis of association appropriateness antidiabetic dose and clinical outcomes

Clinical outcomes	AOR (95%CI)[1]	AOR (95%CI)[2]
Primary outcomes		
FBG (n=116)	5.65 (2.44 – 13.12)*	
RBG (n=115)	3.01 (1.35 – 6.72)*	
HbA1c (n=107)	4.22 (1.88 – 9.48)*	
Secondary outcomes		
SBP (n=132)	0.96 (0.45 – 2.04)	0.58 (0.20 – 1.67)
DBP (n=132)	0.25 (0.05 – 1.29)	0.16 (0.02 – 0.61)*
LDL (n=76)	0.54 (0.21 – 1.42)	0.30 (0.06 – 1.46)
HDL (n=69)	1.25 (0.48 – 3.30)	1.35 (0.27 – 6.70)
TG (n=75)	1.40 (0.54 – 3.59)	0.67 (0.13 – 3.33)
TC (n=71)	0.96 (0.35 – 2.63)	0.57 (0.13 – 2.51)

[1]adjusted for age, BMI, smoking status
[2]adjusted for primary outcomes, age, BMI, smoking status
*p-value<0.05
FBG: fasting blood glucose, RBG: random blood glucose, TG = triglycerides, TC = total cholesterol, SBP = systolic blood pressure, DBP = diastolic blood pressure, LDL = low density lipoprotein, HDL = high density lipoprotein

Discussion

The menopausal transition in women, characterized by hormonal changes, including reduced estrogen levels, is frequently associated with increased body fat distribution and a rise in BMI. Most patients were overweight, and an increase in BMI is known to contribute to insulin resistance. Moreover, increased concentrations of sex hormone-binding globulin (SHBG) have been linked to a greater likelihood of developing diabetes, possibly influenced by genetic polymorphisms. Typically, SHBG levels are higher in women than in men (Ciarambino et al., 2022). Gestational diabetes occurs exclusively in women and is a well-established risk factor for the future onset of type 2 diabetes mellitus (Perämäki et al. 2023).

Diabetes mellitus (DM) and chronic kidney disease (CKD) predominantly affect individuals aged ≥55 years (International Diabetes Federation, 2021; Kemenkes RI, 2023). Geriatric patients are older adults with multiple comorbidities and/or functional impairments involving physiological, psychological, social, economic, and environmental factors, requiring integrated healthcare services with a multidisciplinary and interdisciplinary approach (Kemenkes RI 2014). The decline in organ function with aging increases the risk of developing DM or worsening pre-existing diabetes. Therefore, geriatric patients are at a particularly high risk of diabetes diagnosis. As age increases, the kidneys undergo atrophy, and the thickness of the renal cortex decreases by approximately 20% every ten years. By the age of 80 years, only approximately 40% of the nephrons function effectively.

As renal function declines with age, drug excretion becomes impaired, necessitating dosage adjustments and, in some cases, discontinuation of certain medications. Impaired drug excretion leads to the accumulation of drugs or their metabolites at toxic levels. Therefore, careful monitoring of adverse effects is critical (Garza & Park, 2023) Renal function tends to decline in geriatric patients, as indicated by a reduction in glomerular filtration rate (GFR). A decreased GFR may lead to a diagnosis of CKD (Eknoyan et al., 2022). In this study, only 27.6% of patients were diagnosed with CKD. However, most patients were classified as stage G2 patients.

Most patients were managed with dual antidiabetic therapy. For those suffering from both diabetes and CKD, a well-structured and holistic care plan is essential to slow the progression of kidney damage (Basrowi et al., 2021; Eknoyan et al., 2022). The suitability of drug dosing was determined by estimating the glomerular filtration rate (eGFR) using the Cockcroft–Gault equation, as follows: The prescribed doses were compared with those in the existing literature and dosing guidelines, according to renal function. Almost 50% of patients received inappropriate antidiabetic therapy.

Among the appropriately dosaged medications, metformin was the most frequently prescribed in a appropriate doses. Metformin is widely acknowledged as the initial drug of choice in the pharmacological management of type 2 diabetes mellitus. In addition to its role in lowering blood glucose, metformin offers several benefits, such as minimal risk of hypoglycemia and weight gain, decreased likelihood of macrovascular complications, enhanced insulin sensitivity and lipid levels, and affordability (Alhassani et al., 2021; Asif et al., 2020; Lazarus et al., 2018). Recent evidence-based guidelines recommend adjusting metformin dosage

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according to renal function. For patients with an estimated glomerular filtration rate (eGFR) of 45–59 mL/min/1.73 m², the dose should be reduced, while metformin is generally not recommended to be initiated in patients with eGFR below 45 mL/min/1.73 m², and should be discontinued if eGFR falls below 30 mL/min/1.73 m² (Eknoyan et al., 2022; The American Diabetes Association, 2025). This approach minimizes the risk of lactic acidosis while maintaining glycemic control.

The most common medication with inappropriate dosing was sitagliptin, which was observed in 50.9% of the patients. Sitagliptin, an oral agent classified as a DPP-4 inhibitor, is prescribed for the treatment of type 2 diabetes mellitus (T2DM). It functions by stimulating insulin release in response to glucose and suppressing glucagon secretion, thereby aiding in glycemic control (Gonzatti et al., 2023). Sitagliptin is typically administered at a daily dose of 100 mg (Nguyen et al. 2021). It is important to adjust the dosage of sitagliptin according to renal function: patients with a glomerular filtration rate (GFR) between 30 and 50 mL/min are advised to take 50 mg once daily, while those with GFR below 30 mL/min should receive 25 mg daily (Ashley & Currie, 2009; Perkumpulan Endokrinologi Indonesia 2021). The drug reaches peak plasma concentration approximately two hours after administration, and approximately 79% is excreted via urine (Gallwitz, 2019). Consequently, incorrect or excessive dosing may increase the likelihood of side effects, including nasopharyngitis, urinary tract infections, headaches, digestive issues, and possibly aggravation of chronic kidney disease. The findings suggest that inappropriate sitagliptin dosing was primarily due to the failure to adjust the dose according to the patients' renal function. Variations in the glomerular filtration rate (GFR) may lead to previously appropriate doses becoming unsuitable, highlighting the importance of continuous renal function monitoring to maintain medication safety and efficacy (Snyder et al., 2021; Sohn, 2012).

The primary therapeutic outcomes of T2DM are FBG, RBG, and HbA1c levels (American Diabetes Association, 2025; Perkumpulan Endokrinologi Indonesia, 2021). The glycemic parameters of the study participants were generally within the target ranges. In terms of secondary outcomes, most patients had regulated SBP and satisfactory DBP control. Secondary outcomes included assessments of lipid levels, including low-density lipoproteins, high-density lipoproteins, triglycerides, and total cholesterol. All lipid profile parameters were generally well controlled, except for LDL, which showed a predominance of uncontrolled values.

We found that appropriate dosing significantly influenced the controlled FBG levels. Patients receiving appropriate doses were 5.65 (95%CI = 2.44 – 13.12) times more likely to attain controlled fasting blood glucose (FBG) levels than those administered improper doses. With regard to RBG, patients receiving appropriate doses were 3.01 (95%CI = 1.35. – 6.72) times more likely to have controlled RBG levels than those who received the inappropriate dose. For HbA1c, appropriate dosing similarly influenced the outcome, with patients receiving suitable doses being 4.22 (95%CI: 1.88 – 9.48) times more likely to achieve controlled HbA1c levels than those receiving inappropriate doses. All three findings demonstrate that the appropriate antidiabetic dose based on renal function plays a significant role in achieving controlled primary clinical outcomes. This confirms that the appropriateness of OADs dose ensures therapeutic effectiveness (Kumari et al., 2014; Sugandh et al., 2023).

Based on the association between antidiabetic dose appropriateness according to renal function and secondary clinical outcomes related to blood pressure, it was found that dose appropriateness did not significantly influence secondary clinical outcomes, either blood pressure or lipid profile, despite adjustments for age, BMI, and smoking behavior. Several risk factors may affect blood pressure and lipid profiles rather than dose appropriateness. These risk factors include smoking history, lipid profile, diabetes, uric acid levels, obesity, kidney disease, family history, menopause, unhealthy lifestyle, psychosocial factors, socioeconomic conditions (Perhi, 2019), genetics, diet, stress, corticosteroid use, and comorbidities such as diabetes mellitus (Perkumpulan Endokrinologi Indonesia, 2021; Virginia et al., 2022). Our data support the fact that most patients were overweight.

Notably, we found that dose appropriateness affected DBP after adjusting for primary outcomes, age, BMI, and smoking status. It has been highlighted that DBP has a strong correlation with glycemic status. This could be explained by the positive correlation between insulin resistance and DBP (Quesada et al. 2021). In addition, several studies have shown that both SBP and DBP significantly contribute to the risk of ASCVD. Therefore, we should be aware of these findings.

Our study had some limitations, including: (1) the CKD patients included in our study may induce bias, (2) we could not obtain a history of T2DM data that may

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interfere with the outcome, and (3) lifestyle data were not collected, which may affect the outcome. Future studies should consider a prospective cohort design to minimize biases.

CONCLUSION

The appropriateness of antidiabetic dosing based on renal function significantly influences clinical outcomes, particularly primary clinical outcomes. Appropriate antidiabetic prescriptions had a greater impact on achieving target outcomes than inappropriate dosing. Therefore, it is essential to regularly evaluate and adjust treatment in cases of impaired renal function to determine the most suitable therapeutic regimen, thereby ensuring successful treatment outcomes in older adult patients.

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AUTHOR CONTRIBUTIONS

Conceptualization, P.H., D.M.V.; Methodology, P.H., D.M.V.; Validation, P.H., D.M.V.; Formal Analysis, B.N.S., P.H., D.M.V.; Investigation, B.N.S.; Resources, B.N.S.; Data Curation, B.N.S., P.H., D.M.V.; Writing - Original Draft, B.N.S., P.H., D.M.V.; Writing - Review & Editing, B.N.S., P.H., D.M.V.; Visualization, B.N.S., P.H., D.M.V.; Supervision, P.H., D.M.V.; Project Administration, P.H., D.M.V.; Funding acquisition, B.N.S., D.M.V.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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