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(Research/Review) Articlea

Comparison of Cystatin-C Based eGFR and Creatinine Based eGFR to Assess Kidney Function in Patients With Chronic Kidney Disease Stage V Undergoing Hemodialysis at RSUD Dr. Mohamad Soewandhie Surabaya

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Abstract: Chronic kidney disease (CKD) is a global health problem with continuously increasing incidence and mortality, and accurate assessment of kidney function is essential for disease staging and clinical decision making. Estimation of glomerular filtration rate (eGFR) based on serum creatinine using the CKD-EPI 2009 equation is widely used, however it is influenced by nonrenal factors such as age, sex, and muscle mass, whereas cystatin C is considered a more stable biomarker. This observational analytic study with a cross sectional design aimed to analyze the differences and agreement between creatinine based eGFR and cystatin C based eGFR in 53 patients with stage V CKD undergoing hemodialysis at RSUD dr. Mohamad Soewandhie Surabaya prior to dialysis. Creatinine based eGFR was calculated using the CKD-EPI 2009 equation and cystatin C based eGFR using the CKD-EPI 2012 equation. Statistical analysis was performed using the Wilcoxon signed rank test and Bland Altman analysis. The Wilcoxon test showed that all paired data had positive ranks with a Z value of –6.336 and $p < 0.001$, indicating a statistically significant difference. Bland Altman analysis demonstrated a bias of –41.64 mL/min/1.73 m² with limits of agreement ranging from –105.14 to 21.86, indicating that the two methods are not interchangeable. In conclusion, a significant difference exists between creatinine based eGFR and cystatin C based eGFR, and these methods cannot be used interchangeably in clinical practice among patients with stage V CKD at RSUD dr. Mohamad Soewandhie Surabaya.

Keywords: Creatinine; Cystatin-C; Chronic Kidney Disease; Cross-Sectional Study; eGFR.

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1. Introduction

Chronic kidney disease (CKD) is a disorder of kidney structure or function that lasts at least 3 months and has a negative impact on health.(KDIGO, 2024).Globally, there were 697.5 million CKD sufferers in 2017 with a death rate reaching 1.2 million people, an increase of 41.5% compared to 1990.(Global Burden of Disease, 2020)In Indonesia, the prevalence of PGK reaches 0.18%, and in East Java 0.12%.(SKI, 2023)The main causes of stage V CKD in Indonesia include hypertension (35%), diabetic nephropathy (29%), and glomerulopathy (8%).(Indonesian Renal Registry, 2020).

Accurate evaluation of kidney function is essential for staging and clinical management. Glomerular filtration rate (GFR) is the best parameter, but direct measurement is complex and expensive, so estimation of GFR (eGFR) based on endogenous biomarkers such as creatinine and cystatin-C is more widely used. (Inker and Titan, 2021).Creatinine is practical to test and has been widely used, but is affected by age, gender, and muscle mass so its accuracy can be reduced.(Spencer, Desborough and Bhandari, 2023)Meanwhile, cystatin-C is considered more stable because it is not affected by factors that affect creatinine, although its levels can change due to chronic inflammation, obesity, hyperthyroidism, or malignancy. (Spencer, Desborough and Bhandari, 2023; Williams and Gerlach, 2025). EQF equations like the CKD-EPI facilitate the assessment of kidney function but have limitations due to the limited number of elderly participants in the development studies. Therefore, this study selected the 18–65 age group to better reflect the characteristics of the population studied.(Cusumano et al., 2022).

Several international studies have demonstrated the superiority of cystatin-C in assessing kidney function and predicting clinical risk compared to creatinine. Cystatin-C-based GFR estimation has a stronger association with prognosis.(KDIGO, 2024). Cystatin-C provides estimates with a lower degree of bias than creatinine.(Zou et al., 2020)The National Kidney Foundation and the American Society of Nephrology recommend the widespread use of cystatin-C to confirmeGFR creatinine results thereby improving the accuracy of clinical decisions(Delgado et al., 2022)In Indonesia, studies report that cystatin-C levels increase more frequently than creatinine.Shows that cystatin-C is more sensitive than creatinine.(Rachmawati et al., 2023)However, its utilization is still limited due to the high cost of the examination and it is not yet covered by BPJS Kesehatan, while creatinine examination has become a standard service (Minister of Health Regulation No. 3 of 2023).

Dr. Mohamad Soewandhie Regional General Hospital, Surabaya, is a referral hospital that treats many patients with stage V CKD. To date, there has been no research at this hospital comparing the results of creatinine-based and cystatin-C-based eGFR estimation in patients with stage V CKD undergoing hemodialysis. This study is important to determine whether there are significant differences and assess the suitability between the two methods in assessing kidney function. The results of this study are expected to provide a basis for consideration in selecting a kidney function estimation method that is more appropriate to the clinical conditions at Dr. Mohamad Soewandhie Regional General Hospital, Surabaya.

2. Literature Review

Kidney Organ

A. Kidney Anatomy

The oval-shaped kidneys are located retroperitoneally on the posterior abdominal wall, parallel to the T12–L3 vertebrae. Each kidney is located on either side of the vertebral column. Superiorly, on the posterior aspect, the kidneys are adjacent to the diaphragm, which separates them from the pleural cavity and the T12 vertebra. Inferiorly, the posterior surfaces of the kidneys are adjacent to the psoas major muscle medially and the quadratus lumborum muscle. Anterior to the right kidney are the liver, duodenum, and ascending colon. The right kidney is separated from the liver by the hepatorenal recess. Anterior to the left kidney are the stomach, spleen, pancreas, jejunum, and descending colon. The kidneys are reddish-brown in color and measure approximately 10 cm long, 5 cm wide, and 5.5 cm thick, as shown in Figure 2.1.(Dalley and Agur, 2023)

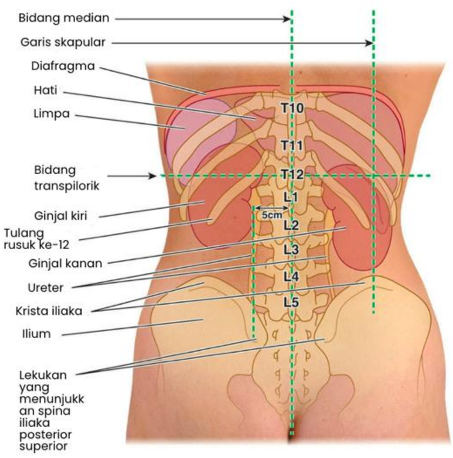
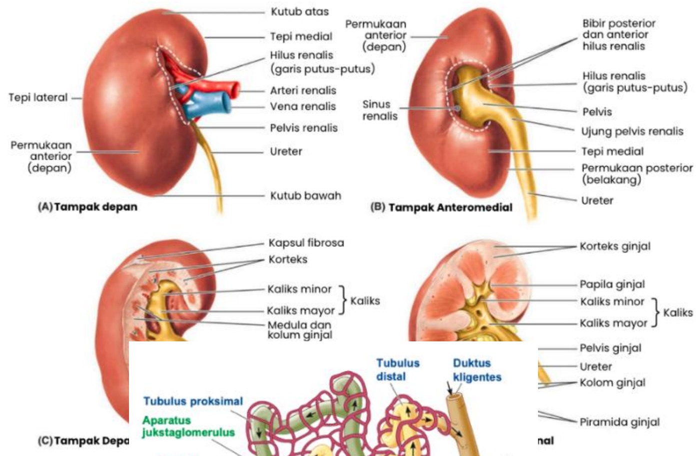


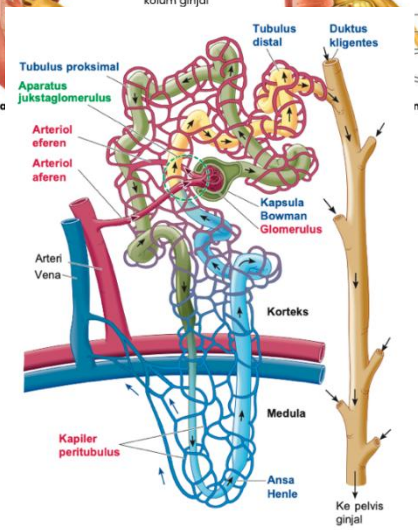
Figure 1. Anatomical location of the kidneys
Source:Moore's, 2023

An adult human kidney weighs about 150 grams and is about the size of a fist. On its medial side is the hilum, a concave area where the renal artery and vein, lymphatic vessels, nerves, and ureter enter and exit, carrying urine from the kidney to the bladder before it is excreted. The kidney is surrounded by a fibrous capsule to protect its internal structures. Anatomically, the kidney consists of an outer cortex and an inner medulla. The medulla is composed of 8 to 10 renal pyramids, the base of which borders the cortex and the tip (the renal papilla) projects into the renal pelvis. This structure can be seen in Figure 2.2. The renal pelvis is funnel-shaped and functions to channel urine to the ureter. This structure branches into major calyces, which then divide into minor calyces that collect urine from the renal papilla. The walls of the calyces, renal pelvis, and ureter contain contractile elements that propel urine toward the bladder, where it is stored until excretion through urination. (Hall, 2021)

Figure 2. Kidney anatomy
Source:Moore's, 2023

The nephron is the smallest functional unit of the kidney, responsible for urine formation through filtration, reabsorption, and excretion. Each adult human kidney has over





one million nephrons spread across the renal cortex and medulla. Structurally, the nephron is composed of vascular and tubular components that work synergistically. The vascular component consists of the afferent arteriole, glomerulus, efferent arteriole, and peritubular capillaries, which supply blood and enable plasma filtration in the glomerulus. The resulting filtrate is then processed by the tubular components, which include Bowman's capsule, proximal tubule, loop of Henle, distal tubule, and collecting duct, to regulate the reabsorption and secretion of substances according to the body's needs until the final urine is formed. Furthermore, the juxtaglomerular apparatus, a connecting structure between the vascular and tubular structures, plays a crucial role in regulating kidney function, including fluid and electrolyte balance, and blood pressure, thus maintaining body homeostasis (Sherwood & Ward, 2019).

Figure 2 Structure of the nephron
Source:Sherwood and Ward, 2019.

B. Kidney physiology

The filtration process in the kidneys occurs when a fluid with plasma-like characteristics passes through the glomerular capillaries and enters the renal tubules. As the glomerular filtrate flows through the renal tubules, its volume decreases and its composition changes through tubular reabsorption and tubular secretion. After undergoing this series of processes, the resulting urine flows to the renal pelvis, then moves to the bladder, before being excreted from the body through urination (Barrett et al., 2019). The kidneys function to regulate fluid balance, osmolarity, electrolyte levels, blood plasma volume, acid-base balance, excrete metabolic wastes and foreign substances, and produce the hormones renin, erythropoietin, and activate vitamin D (Sherwood and Ward, 2019).

C. Chronic kidney disease

Chronic kidney disease (CKD) is a disorder of kidney structure or function that lasts for at least 3 months and impacts health (KDIGO, 2024). Chronic kidney disease (CKD) is a complex, progressive condition that causes long-term kidney damage and carries the risk of progressing to advanced kidney disease if left untreated (Gusev et al., 2021).

Chronic kidney disease (CKD) is diagnosed based on the presence of markers of kidney damage or a decrease in GFR below 60 ml/min per 1.73 m² for at least 3 months. These markers include albuminuria, urinary sediment abnormalities, electrolyte disturbances due to tubular dysfunction, histological abnormalities, structural abnormalities on imaging, or a history of kidney transplantation. CKD is classified using the CGA system, which includes the cause of the disease, the level of kidney function (categories G1–G5), and the level of albuminuria (categories A1–A3) to assess the severity and risk of disease progression (KDIGO, 2024).

Chronic kidney disease is a global public health issue with diverse causes. In developed countries, common risk factors include diabetes, hypertension, high body mass index, and smoking, while in developing countries, glomerulonephritis and interstitial nephritis are often the causes. Risk factors for CKD are divided into non-modifiable factors such as advanced age, race, and family history, and modifiable factors such as diabetes, hypertension, obesity, dyslipidemia, anemia, consumption of nephrotoxic substances, and excessive use of certain medications (Floris et al., 2021; Santos et al., 2025).

In 2017, 697.5 million individuals were living with chronic kidney disease worldwide, with a prevalence of 9.1%, resulting in 1.2 million deaths (Global Burden of Disease, 2020). The prevalence of CKD increases with age and is often accompanied by diabetes, hypertension, and cardiovascular disease (Kovesdy, 2022; Kampmann et al., 2023). In Indonesia, the prevalence of CKD is 0.18%, with the highest rate in the elderly and more common in men. The main causes of stage V CKD are hypertension and diabetic nephropathy, while the leading cause of death in hemodialysis patients is cardiovascular disease (SKI, 2023; Indonesian Renal Registry, 2020).

Chronic kidney disease is characterized by progressive impairment of kidney structure and function due to specific disease-causing mechanisms and a general mechanism involving a reduction in the number of functional nephrons. The remaining nephrons undergo maladaptive hyperfiltration and hypertrophy, leading to glomerulosclerosis and progressive nephron loss. Activation of the renin-angiotensin system, chronic inflammation, podocyte damage, and interstitial fibrosis accelerate the decline in kidney function, ultimately leading to end-stage kidney disease (Loscalzo et al., 2022; Wilson et al., 2021).

Chronic kidney disease can cause a variety of symptoms affecting multiple body systems. Cognitive impairment is common, with a 65% increased risk. In the digestive system, people with advanced CKD may experience anorexia, vomiting, taste disturbances, and uremic breath. Changes in the urinary system include polyuria, oliguria, nocturia, proteinuria characterized by foamy urine, and hematuria. Peripheral edema often occurs due to sodium retention by the kidneys and is exacerbated by hypoalbuminemia. In the cardiovascular system, hypertension is a common condition that can be both a cause and a consequence of CKD, while increased fluid volume can cause shortness of breath due to pulmonary edema and anemia. Structurally, CKD can cause kidney shrinkage with thinning of the cortex or enlargement with numerous cysts. Pruritus and muscle cramps are also common in advanced CKD (Webster et al., 2017).

D. Management of Stage V Chronic Kidney Disease

Conservative renal management is a holistic approach to kidney disease management that focuses on maximizing the patient's quality of life and slowing the progression of CKD without resorting to renal replacement therapy such as dialysis. This approach is a viable treatment option for many patients, particularly those in the elderly with complex comorbidities (Scherer et al., 2023).

Peritoneal dialysis is a renal replacement therapy that uses the peritoneal cavity as an exchange medium by injecting sterile solutions through a catheter. Solutes and fluids are removed from the body using the peritoneal membrane as an exchange medium through diffusion and ultrafiltration. This process can be performed manually through Continuous Ambulatory Peritoneal Dialysis (CAPD) or with the assistance of a machine through Automated Peritoneal Dialysis (APD). PD management and monitoring include evaluating the dialysis dose and identifying and treating infectious and non-infectious complications (Andreoli & Totoli, 2020).

E. Hemodialysis

Hemodialysis is a therapy used to restore the body's electrolyte, fluid, and acid-base balance, as well as to clean metabolic waste through an ultrafiltration process using a semipermeable membrane dialyzer (Niknam et al., 2024).

In hemodialysis, waste and excess fluid are removed through the diffusion of solutes across a semipermeable membrane due to the concentration gradient between the blood and the dialysate. Hemodialysis cannot completely replace all kidney function due to its discontinuous nature, but it plays a crucial role in maintaining body stability and preventing complications from the buildup of metabolic waste (Vadakedath & Kandi, 2017; Mehmood et al., 2019).

Renal replacement therapy planning begins when the GFR is <15–20 ml/minute/1.73 m^2. Hemodialysis is performed on patients with symptoms of kidney failure, fluid imbalance, uncontrolled blood pressure, progressive nutritional decline, or cognitive impairment, which generally occur at a GFR of 5–10 ml/minute/1.73 m^2 (KDIGO, 2024; Ministry of Health, 2023).

An absolute contraindication for chronic hemodialysis is the absence of vascular access. Relative contraindications include severe vascular access problems, heart failure, coagulation disorders, hemodynamic instability, advanced malignancy, advanced organ failure, and advanced AIDS (Ministry of Health, 2023).

Complications of hemodialysis include intradialytic hypotension, nausea, vomiting, hypertension, muscle cramps, headache, infection, cardiovascular disorders, anemia, metabolic bone disease, sleep disturbances, and psychological complications. Long-term complications include amyloidosis, peripheral neuropathy, parathyroid hyperplasia, and acquired cystic kidney disease (Raja & Seyoum, 2020; Habas et al., 2021).

Kidney transplantation is the primary therapy for end-stage renal disease and is considered the best option because it improves quality of life, is more cost-efficient, and provides better life expectancy than long-term dialysis (Novacescu et al., 2024).

F. Chronic Kidney Disease Prevention

CKD prevention encompasses primary and secondary strategies aimed at reducing incidence and slowing disease progression through risk factor control and evidence-based interventions. These strategies include increasing public awareness of CKD, adopting a healthy lifestyle, such as maintaining a body mass index (BMI) <25 kg/m^2, consuming less than 2 grams of salt per day, smoking cessation, and engaging in 30–60 minutes of physical activity 4–7 times per week. Prevention also includes monitoring and treating proteinuria with ACE inhibitors or angiotensin receptor blockers, controlling blood pressure, regulating glycemic control in diabetics, using SGLT2 inhibitors, treating dyslipidemia with statins, and using aspirin and beta-blockers in patients with cardiovascular disease. Various studies have shown that public adherence to these strategies is still low, so the effectiveness of prevention is not optimal and requires systematic intervention to improve its implementation (Luyckx, Cherney, & Bello, 2020).

G. Glomerular Filtration and Glomerular Filtration Rate Measurement

Glomerular filtration is the process of filtering protein-free plasma from the glomerular capillaries into Bowman's capsule, which is the initial stage of urine formation. Approximately 20% of the plasma entering the glomerulus undergoes filtration, producing approximately 125 mL of filtrate per minute or 180 liters per day, with most of the fluid being reabsorbed through the renal tubules and peritubular capillaries (Sherwood and Ward, 2019). The glomerular filtration rate is influenced by the net filtration pressure and the glomerular filtration coefficient (Kf), which is the result of a balance between glomerular hydrostatic pressure, Bowman's capsule hydrostatic pressure, and plasma colloid osmotic pressure. An increase in glomerular hydrostatic pressure will increase GFR, while an increase in pressure within Bowman's capsule or plasma colloid osmotic pressure will decrease it (Hall, 2021).

Glomerular filtration rate reflects the overall excretory function of the kidney and is the combined result of filtration across all nephrons. Decreased GFR can be caused by reduced renal blood flow or a decreased number of functioning nephrons. GFR measurements, either singly or repeatedly, are used to identify the degree of kidney damage, differentiate acute from chronic disorders, and assess the rate of kidney disease progression (Jančič, Močnik, and Marčun Varda, 2022).

Glomerular filtration rate cannot be measured directly but can be assessed through measured GFR using exogenous filtration markers or through estimated GFR (eGFR) based on serum levels of endogenous filtration markers (Levey et al., 2020). The ideal marker for measured GFR should be completely excreted by glomerular filtration, not bound to plasma proteins, and not subject to tubular secretion or reabsorption. Inulin meets these criteria and is considered the gold standard, but is rarely used clinically due to its complex and expensive procedure (Inker and Titan, 2021; Uemura et al., 2022). Therefore, creatinine- or cystatin-C-based eGFR methods are more commonly used, despite their limitations. Because the variables in the estimation equation only reflect population averages and can vary between individuals, interpretation of results requires caution and appropriate additional testing (Inker and Titan, 2021).

H. Kidney Function Biomarkers

Creatinine and cystatin-C are small substances in the blood that serve as markers of kidney function and are filtered through the glomerulus. When kidney function declines and the glomerular filtration rate (GFR) decreases, creatinine and cystatin-C accumulate in the blood, increasing their levels (Pottel, Delanaye, and Cavalier, 2024).

Creatinine is the end product of creatine and phosphocreatine metabolism, formed non-enzymatically in muscle tissue. Approximately 2% of body creatine is converted to creatinine daily and is excreted entirely in the urine without tubular reabsorption. Serum creatinine concentrations are relatively stable and are influenced by muscle mass and the kidney's ability to excrete it, making it widely used as a marker of kidney function and GFR (Kashani, Rosner, and Ostermann, 2020; Narimani et al., 2021). Serum creatinine values are influenced by age, gender, race, muscle mass, protein intake, and certain clinical conditions, so their interpretation needs to take these factors into account (Pernefri, 2023; Rifai et al., 2023; Spencer, Desborough, and Bhandari, 2023).

I. Creatinine-based eGFR equation

a. Cockcroft-Gault

The Cockcroft–Gault equation is one of the earliest equations used to estimate creatinine clearance based on age, weight, sex, and serum creatinine levels. Despite its widespread use for decades, this equation has limitations related to developing populations, sex bias, and changes in current population characteristics (Brunetti et al., 2021; Stehlé and Delanaye, 2024).

b. Modification of Diet in Renal Disease

The MDRD equation calculates eGFR based on age, sex, creatinine level, and race and is considered more practical than the Cockcroft–Gault equation because it does not require weight data. However, its accuracy decreases at GFR above 60 mL/min/1.73 m² (Burballa et al., 2018; Rungkitwattanakul et al., 2022).

c. CKD-EPI 2009 Equation

The 2009 CKD-EPI equation was developed as an improvement on the MDRD and has been shown to be more accurate and have lower bias, especially at GFR >60 mL/min/1.73 m². This equation was developed from a large population and is widely used in clinical practice (Cusumano, Martins, and Diez, 2021).

d. Asian modified CKD-EPI equation

The Asian-modified CKD-EPI equation was developed to improve the accuracy of GFR estimation in Asian populations. Studies have shown that this equation provides more accurate results in patients with chronic kidney disease in Asian populations than the standard CKD-EPI equation (Gao et al., 2021).

e. CKD-EPI 2021 creatinine-based

The 2021 CKD-EPI equation was developed without racial variables to avoid clinical bias. It uses only age, sex, and creatinine levels and is recommended by various international health organizations for a fairer and more equitable assessment of kidney function (Miller et al., 2022; McArthur et al., 2024).

f. Cystatin-C

Cystatin-C is a 13 kDa protein constantly produced by all nucleated cells. It is freely filtered by the glomerulus and almost entirely reabsorbed and metabolized in the proximal tubule. Cystatin-C levels are relatively stable and are not significantly affected by age, gender, muscle mass, or diet, making it a more accurate measure than creatinine in assessing kidney function (Benoit, Ciccia, and Devarajan, 2020; Spencer, Desborough, and Bhandari, 2023). However, cystatin-C levels can be affected by thyroid disorders, chronic inflammation, obesity, smoking, steroid use, and malignancy (Williams and Gerlach, 2025).

g. Cystatin-C based eGFR equation

a) CKD-EPI 2012

The cystatin-C-based CKD-EPI 2012 equation was developed to improve the accuracy of GFR estimation and was considered superior in supporting clinical decision-making and predicting cardiovascular risk and mortality compared to the creatinine-based equation (Cusumano, Martins and Diez, 2021; Zou et al., 2020).

h. Comparison of Cystatin-C and Creatinine-Based eGFR

b) Comparison of creatinine-based eGFR equations in Asia

Several Asian countries have validated creatinine-based eGFR equations, particularly the CKD-EPI 2009 and CKD-EPI 2021. Studies in Korea and Asia-America have shown that use of the CKD-EPI 2021 reduced the prevalence of CKD and resulted in the reclassification of a significant proportion of patients with stage G3–G5 as non-CKD, particularly in the ≥65 age group. Similar findings have also been reported in China, Thailand, and India. However, several studies and statements from the European Renal Association have highlighted the potential for overestimation of GFR, reduced predictive ability of CKD complications, and the risk of underdiagnosis and undertreatment, particularly in older Asian populations (Hwang et al., 2024). A study in Pakistan has shown that the local version of the CKD-EPI equation has the best accuracy compared to the CKD-EPI 2021 and EKFC, which tend to exhibit greater bias and overestimate GFR. These findings emphasize the importance of considering racial and ethnic factors in GFR estimation, and suggest that the 2021 CKD-EPI performs worse than the 2009 CKD-EPI in some Asian populations, including Chinese (Safdar et al., 2024; Wang et al., 2016).

c) Comparison of creatinine-based eGFR equations in Indonesia

Several Asian countries have modified the eGFR equation to suit their respective population characteristics, while in Indonesia, national data on the validation of the eGFR equation is still limited. The CG, MDRD, and CKD-EPI equations are still frequently used in clinical practice. Studies in Indonesia have shown that the 2021 CKD-EPI produces higher eGFR values than the 2009 CKD-EPI and the EKFC, potentially leading to overestimation. Conversely, the EKFC demonstrates better agreement with the 2009 CKD-EPI in classifying kidney function decline (<60 mL/min/1.73 m²) and is considered more appropriate for the Indonesian population (Marpaung et al., 2025).

d) Comparison of accuracy and clinical prognostic value

The National Kidney Foundation and the American Society of Nephrology recommend the use of the latest eGFR equations and the widespread use of cystatin-C to improve the accuracy of kidney function assessments (Delgado et al., 2022). A Swedish study showed that cystatin-C-based eGFR, either alone or in combination with creatinine, was more strongly associated with mortality risk than creatinine-based eGFR, particularly in critically ill patients, due to more stable cystatin-C production and the independence of muscle mass (Karlqvist et al., 2021). A large-scale study in the United Kingdom also showed that cystatin-C-based eGFR was more accurate in predicting mortality and cardiovascular disease risk than creatinine (Spencer et al., 2024). Although there is a strong correlation between cystatin-C-based eGFR and creatinine, differences in estimated results can impact CKD staging, particularly related to age, comorbidities, and race or ethnicity (Chen et al., 2022; Safdar et al., 2023). Research in Indonesia has shown that cystatin-C is more sensitive than creatinine in detecting impaired kidney function (Rachmawati et al., 2023).

e) Comparison of roles in drug pharmacokinetic estimation

Several studies have shown that cystatin-C-based eGFR has equivalent or better accuracy than creatinine in predicting the clearance rate of renally excreted drugs, including antibiotics and cardiovascular drugs (Teaford et al., 2020). Population pharmacokinetic models have also shown that cystatin-C provides more accurate estimates of vancomycin clearance than creatinine-based models (Yun et al., 2023).

f) Comparison in hemodialysis patients

In patients before hemodialysis, serum creatinine levels increased significantly and decreased significantly after dialysis, demonstrating the effectiveness of hemodialysis in clearing creatinine. In contrast, cystatin-C levels tended to remain unchanged or even increase after dialysis, possibly related to the characteristics of the dialyzer membrane and the nature of the cystatin-C molecule. Several studies have shown that cystatin-C levels decrease only during high-flow hemodialysis (Basher et al., 2018).

g) Challenges in clinical implementation

The implementation of cystatin-C testing is still hampered by the high cost of laboratory testing, which can be up to ten times higher than creatinine testing. Although costs have the potential to decrease with increasing global use, this limitation remains a major obstacle, especially in developing countries. The ELISA method is considered a more affordable and sensitive alternative. In Indonesia, the use of cystatin-C is still limited because it is not covered by the National Health Insurance (BPJS Kesehatan), unlike creatinine testing, which is guaranteed under national regulations (Stehlé and Delanaye, 2024; Madise-Wobo et al., 2017).

3. Materials and Method

This study is an observational analytical study with a cross-sectional method conducted to assess the differences and agreement of eGFR values based on creatinine and cystatin-C. The study was conducted from July 1 to August 31, 2025, at Dr. Mohamad Soewandhie General Hospital, Surabaya, and the Ciputra University Laboratory, Surabaya. The study population was patients with stage V chronic kidney disease (CKD) undergoing hemodialysis at Dr. Mohamad Soewandhie General Hospital, Surabaya, with a sample of 53 subjects selected using a total sampling technique according to inclusion and exclusion criteria. The research instruments included examination of serum creatinine levels using the Jaffe method and cystatin-C levels using the ELISA method, which were then used to calculate eGFR using the CKD-EPI 2009 and CKD-EPI 2012 equations. Data collection techniques were carried out by taking venous blood samples before the hemodialysis procedure and recording the subject's clinical data. Data analysis techniques include descriptive statistical analysis, Kolmogorov–Smirnov normality test, paired t-test or Wilcoxon Signed-Rank test according to data distribution, and suitability analysis using the Bland–Altman method, with data processing using Microsoft Excel and Statistical Package for the Social Sciences (SPSS) version 31.

4. Results and Discussion

Research Overview

This is an observational, cross-sectional study that assessed the differences and concordance between creatinine-based eGFR and cystatin-C-based eGFR in patients with Stage V CKD undergoing hemodialysis. A total of 53 subjects were analyzed, with both biomarkers measured simultaneously before the hemodialysis procedure. Creatinine-based eGFR was calculated using the CKD-EPI 2009, while cystatin-C-based eGFR was calculated using the CKD-EPI 2012.

Characteristics Of Research Subjects

Table 1. Characteristics Of Research Subjects

Characteristics	N	Percentage	Median (IQR)	Min-Max
Gender	53			
Man	36	67.9%		
Woman	17	32.1%		
Age			54 (14.50)	32-64

Based on Table 1, the number of study subjects was 53, consisting of 36 men (67.9%) and 17 women (32.1%). The subjects' ages ranged from 32 to 64 years, with a median of 54 years and an IQR of 14.50, indicating that most subjects were in the middle to early elderly age group.

Univariate Analysis

Table 2. Descriptive analysis of eGFR creatinine and eGFR cystatin-C data in male subject

No	Variables	Median	IQR	Intersection	Min Value	Max Value	Range
1	eGFR creatinine	2.00	1.00	1.17	1.00	6.00	5.00
2	eGFR cystatin-C	30.00	57.00	32.84	10.00	121.00	111.00

Table 3. Descriptive analysis of eGFR creatinine and eGFR cystatin-C data in female subjects

No	Variables	Median	IQR	Intersection	Min Value	Max Value	Range
1	eGFR creatinine	3.00	2.00	0.99	1.00	4.00	3.00
2	eGFR cystatin-C	30.00	46.00	32.84	14.00	116.00	102.00

Based on Table 2, descriptive analysis of creatinine- and cystatin-C-based eGFR in male subjects shows clear differences in distribution characteristics between the two methods. The median creatinine-based eGFR in male subjects was 2.00 mL/min/1.73 m² with an IQR of 1.00, a standard deviation of 1.17, a minimum value of 1.00 mL/min/1.73 m², and a maximum value of 6.00 mL/min/1.73 m², resulting in a range of 5.00 mL/min/1.73 m². These values indicate that creatinine-based eGFR in male subjects tends to be very low with relatively narrow variations. In contrast, cystatin-C-based eGFR in male subjects had a much higher median, namely 30.00 mL/min/1.73 m², with an IQR of 57.00 and a standard deviation of 32.84. The minimum value recorded was 10.00 mL/min/1.73 m² and the maximum value reached 121.00 mL/min/1.73 m², with a range of 111.00 mL/min/1.73 m². This indicates that cystati- C-based eGFR in male subjects has a much wider data variation than creatinine-based eGFR.

Based on Table 3, descriptive analysis in female subjects shows a similar pattern. The median creatinine-based eGFR in female subjects was 3.00 mL/min/1.73 m² with an IQR of 2.00, a standard deviation of 0.99, a minimum value of 1.00 mL/min/1.73 m², and a maximum value of 4.00 mL/min/1.73 m², resulting in a range of 3.00 mL/min/1.73 m². This distribution indicates a relatively narrow and consistent variation in creatinine-based eGFR. Meanwhile, the median cystatin-C-based eGFR in female subjects was 30.00 mL/min/1.73 m², with an IQR of 46.00 and a standard deviation of 32.84. The minimum value was recorded at 14.00 mL/min/1.73 m² and the maximum value at 116.00 mL/min/1.73 m², with a range of 102.00 mL/min/1.73 m². These findings indicate that, in both male and female subjects, cystatin-C-based eGFR tends to provide higher values with wider variations than creatinine-based eGFR.

Table 3 Distribution of eGFR creatinine and eGFR cystatin-C stages

eGFR Stadium	eGFR Creatinine Stage	eGFR Cystatin-C Stadium
G1	**0**	**5**
G2	**0**	**10**
G3a	**0**	**5**
G3b	**0**	**7**
G4	**0**	**21**
G5	**53**	**5**
Total	**53**	**53**

Based on Table 4, all subjects were at stage G5 according to eGFR creatinine. Meanwhile, eGFR cystatin-C showed a wider variation in stages, namely G1 (5), G2 (10), G3a

(5), G3b (7), G4 (21), and G5 (5). The most common stage was G4. This distribution indicates that cystatin-C provides a wider range of kidney function estimates than creatinine, which places all subjects at stage G5.

Analysis Bivariate

Table 5. Analysis of differences in eGFR creatinine and eGFR cystatin-C data based on gender

No	Variables	Median	IQR	Intersection	Min Value	Max Value	Range
1	Man	-28.00	56.75	33.00	-119.00	-6.00	113.00
2	Woman	-26.00	47.00	32.07	-112.00	-10.00	102.00

Based on Table 5, in male subjects, the median difference in eGFR values was −28.00 mL/minute/1.73 m² with an IQR of 56.75, a standard deviation of 33.00, a minimum value of −119.00 mL/minute/1.73 m², and a maximum value of −6.00 mL/minute/1.73 m², resulting in a range of 113.00 mL/minute/1.73 m². In female subjects, the median difference in eGFR values was −26.00 mL/min/1.73 m² with an IQR of 47.00, a standard deviation of 32.07, a minimum value of −112.00 mL/min/1.73 m², and a maximum value of −10.00 mL/min/1.73 m², with a range of 102.00 mL/min/1.73 m². The dominantly negative difference values in both groups indicate a difference in eGFR values between the creatinine and cystatin-C methods.

Next, a normality test was performed on the difference in eGFR values using the Kolmogorov–Smirnov test. The results of the normality test showed a p-value <0.05, indicating that the eGFR difference data were not normally distributed. Therefore, the Wilcoxon Signed-Rank test was used to test the difference in eGFR values between the creatinine and cystatin-C methods.

Table 4. Wilcoxon Signed-Rank Test Results

Gender	Z Value	p-value (2-tailed)
Man	-5.233	<0.001
Woman	-3,624	<0.001

The results of the Wilcoxon Signed-Rank test are presented in Table 6. In male subjects, the statistical value $Z = -5.233$ was obtained with $p < 0.001$, while in female subjects the statistical value $Z = -3.624$ was obtained with $p < 0.001$. These results indicate that there is a statistically significant difference between the eGFR values based on creatinine and eGFR based on cystatin-C in male and female subjects.

A concordance analysis between the creatinine-based eGFR and cystatin-C-based eGFR estimation methods was performed using the Bland–Altman method. This analysis aimed to assess the level of agreement between the two kidney function estimation methods by evaluating the difference in eGFR values compared to the average eGFR values of both methods. The results of the Bland–Altman analysis are presented based on gender, namely for male and female subjects.

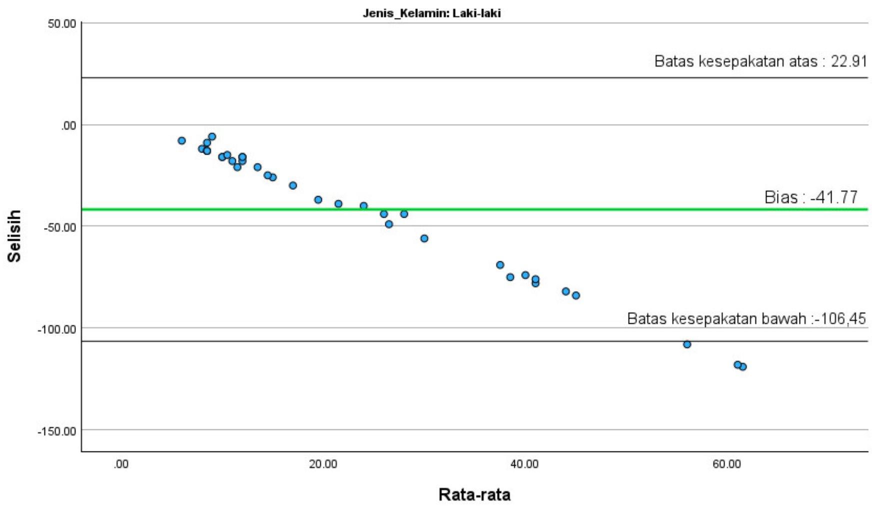


Figure 4. Bland-Altman graph on male subjects

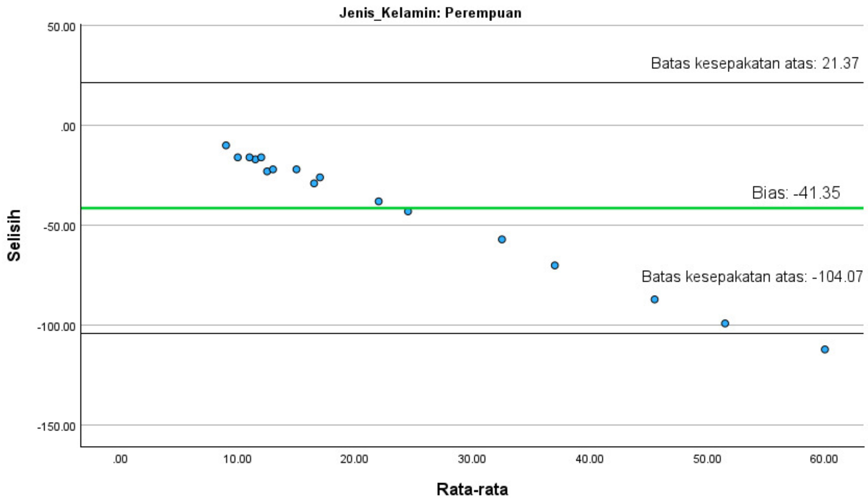


Figure 5. Bland-Altman graph on female subjects

Based on Figure 4, the Bland–Altman graph in male subjects, the Bland–Altman graph shows that the difference in eGFR values between the creatinine and cystatin-C methods is mostly around the bias line of −41.77 mL/min/1.73 m², which indicates that the creatinine-based eGFR value tends to be lower than the cystatin-C-based eGFR. The limits of agreement obtained are in the range of −106.45 to 22.91 mL/min/1.73 m², and most of the observation points are within that range. The distribution of points appears to be spread along the mean eGFR value, with greater variation in the difference at higher mean eGFR values.

Based on Figure 5, the Bland–Altman graph in female subjects shows a relatively similar pattern. The difference in eGFR values is mostly around the bias line of −41.35 mL/min/1.73 m², indicating that the creatinine-based eGFR tends to be lower than the cystatin-C-based eGFR. The limits of agreement are in the range of −104.07 to 21.37 mL/min/1.73 m², with the majority of observation points falling within these limits. The distribution of points appears relatively even along the mean eGFR value, without a clear widening pattern.

Overall, the Bland–Altman analysis results in both male and female subjects showed large and consistent bias values between the two groups. These bias values were well above the clinical threshold of 5 mL/min/1.73 m², indicating that the differences between the creatinine- and cystatin-C-based eGFR methods are clinically significant and cannot be considered interchangeable in assessing kidney function.

Table 5 Proportion of data within the agreed limits

Category	Amount	Presentation
Within the limits of the agreement	-41.64	92.5%
Beyond the limits of the agreement	32.39	7.5%

Discussion

J. Descriptive analysis of eGFR creatinine and eGFR cystatin-C

This study involved 53 patients with Stage V Chronic Kidney Disease undergoing hemodialysis, consisting of 36 men (67.9%) and 17 women (32.1%). The results showed a difference between creatinine-based eGFR and cystatin-C-based eGFR. In general, creatinine-based eGFR yielded lower values than cystatin-C-based eGFR, and this difference was found consistently in both the overall analysis and when the data were stratified by sex.

The difference in eGFR values is related to the differences in the basic biological characteristics of creatinine and cystatin-C as biomarkers of kidney function. Creatinine is a metabolic product eliminated primarily through glomerular filtration, so decreased kidney filtration function will lead to increased serum creatinine levels (Pottel, Delanaye, and Cavalier, 2024). Cystatin-C is an alternative biomarker constantly produced by nucleated cells and eliminated primarily through glomerular filtration, so it is often used as a benchmark in assessing kidney function (Spencer, Desborough, and Bhandari, 2023).

K. Analysis of differences in eGFR creatinine and eGFR cystatin-C values

The Wilcoxon Signed-Rank test results showed a statistically significant difference between creatinine-based eGFR and cystatin-C-based eGFR in both male and female subjects. This finding indicates that the difference between the two estimation methods is consistent and systematic.

Creatinine is not an ideal marker for estimating GFR because creatinine undergoes tubular secretion, and this secretion process increases as kidney disease progresses (Zsom et al., 2022). In low-flux hemodialysis, cystatin-C levels increase from 6.34 ± 1.51 mg/L before dialysis to 6.91 ± 0.93 mg/L after dialysis, because the low-flux membrane is unable to eliminate cystatin-C (Basher et al., 2018).

In advanced CKD, blood cystatin-C levels may not appear to reflect the severity of kidney damage, due to the extrarenal clearance of cystatin-C (Lee et al., 2014). Kinetic studies have shown a non-dialysis nonrenal clearance of cystatin-C of 25 ± 8.2 mL/min (Huang et al., 2015), and at low levels of kidney function this biomarker may not be a good marker of GFR (Mathew et al., 2016).

Biomarker differences between creatinine and cystatin-C can lead to variations in CKD stage classification, including downstages when using cystatin-C-based eGFR (Geißer et al., 2023). A large cohort study reported that discordance between creatinine-based eGFR and cystatin-C-based eGFR was a very common finding, and this discrepancy was found across all stages of CKD, including advanced stages (Carrero et al., 2023).

L. Analysis of the conformity of eGFR creatinine and eGFR cystatin-C values

Bland–Altman analysis revealed a negative bias, with creatinine-based eGFR values tending to be lower than cystatin-C-based eGFR values, and the direction of this bias was consistent across both male and female subjects. Although most differences were within the limits of agreement, the limits of agreement were relatively wide, resulting in limited agreement between the two methods.

Bias exceeding the eGFR difference threshold of 5 mL/min/1.73 m^2 according to KDIGO (2024) indicates that creatinine-based eGFR and cystatin-C-based eGFR are not interchangeable in assessing kidney function. This finding is consistent with a large cohort study showing reclassification of CKD stage after the use of cystatin-C-based eGFR (Shardlow et al., 2017).

The variability of eGFR estimates is significant in patients with very low GFR, and in these conditions, both creatinine- and cystatin-C-based eGFRs experience reduced reliability (Berns, 2015). Therefore, eGFR values do not always reflect the true extent of kidney disease in each individual without considering the overall clinical context (Zsom et al., 2022).

5. Conclusion

There is a difference between creatinine-based eGFR and cystatin-C-based eGFR in assessing kidney function in Stage V CKD patients undergoing hemodialysis at Dr. Mohamad Soewandhie Regional General Hospital, Surabaya. There is no agreement between the results of creatinine-based eGFR and cystatin-C-based eGFR to be used as an alternative to each other in clinical practice in patients with Stage V CKD undergoing hemodialysis at Dr. Mohamad Soewandhie Regional General Hospital, Surabaya.

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