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A Review of the Clinical Significance of Creatinine/Cystatin C

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Abstract. In recent years, the prevalence of sarcopenia has been steadily increasing among the global elderly population, significantly impairing their quality of life and emerging as a critical public health challenge worldwide. The serum creatinine-to-cystatin C ratio (CCR) has gained attention as a promising biomarker for assessing muscle mass and metabolic health. Accumulating evidence suggests its potential utility in predicting the risks and progression of various conditions, including cardiovascular diseases, chronic kidney disease, and non-alcoholic fatty liver disease. This study employs a comprehensive literature review methodology to explore the definition of CCR, elucidate its associations with multiple diseases, and summarize current research trends related to this indicator. Furthermore, this paper reviews the clinical value and recent advances in the application of CCR. In conclusion, this paper highlights that the CCR is an emerging biomarker with significant potential for assessing various conditions, including cardiovascular, renal, and hepatic diseases. It promises to be an effective tool for the screening and management of related diseases in the future.

Keywords: Creatinine, Cystatin C, Creatintine/Cystatin C

1. Introduction

Sarcopenia, characterized by progressive and generalized loss of skeletal muscle mass and function, is a prevalent geriatric syndrome. It not only contributes to declining physical performance and reduced quality of life but also elevates the risk of falls, fractures, and other serious health incidents among the elderly. Moreover, sarcopenia frequently coexists with other chronic conditions such as diabetes, hypertension, and cardiovascular disorders, compounding their adverse effects on health. Age-related decline in muscle mass and strength represents a natural yet accelerable process under certain pathological conditions. Current gold-standard methods for assessing muscle mass, such as dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA), are limited by high costs, operational complexity, and lack of portability, hindering their use in large-scale clinical screenings and long-term monitoring. Hence, there is a pressing need to develop accessible, reliable, and non-invasive biomarkers for muscle mass evaluation. Emerging studies indicate that the creatinine/cystatin C ratio (CCR) may serve as a practical and effective tool for estimating muscle mass and detecting sarcopenia. This review focuses on elucidating the concept of CCR, examining its correlation with various diseases, and synthesizing existing research directions. Through a

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detailed analysis, this paper aims to highlight the predictive value and clinical applicability of CCR across different patient populations.

2. The concept of Creatinine/Cystatin C ratio

2.1. Creatintine

Creatinine is a waste product generated from the metabolism of phosphocreatine in muscle tissue. It is produced at a relatively constant rate proportional to an individual's muscle mass. Under normal physiological conditions, creatinine is freely filtered by the glomeruli and excreted in urine without significant tubular reabsorption or secretion. Therefore, serum creatinine levels are commonly used as a key indicator of renal function, specifically glomerular filtration rate (GFR). However, creatinine levels are influenced by multiple extra-renal factors including age, sex, ethnicity, body mass, and dietary intake. For instance, individuals with greater muscle mass tend to have higher baseline creatinine levels. Pathologically elevated serum creatinine often indicates impaired renal function, particularly when GFR falls below 60 mL/min/1.73m². Conversely, low serum creatinine may result from reduced protein intake, malnutrition, or diminished muscle mass—commonly seen in sarcopenia—though it generally lacks specific diagnostic value in isolation.

Clinically, abnormal levels of creatinine are commonly observed in various disease states. Firstly, it directly reflects the condition of the kidneys. Acute and chronic glomerulonephritis, renal failure and other kidney diseases can lead to a decrease in creatinine clearance capacity, thereby causing an increase in serum creatinine. Secondly, if patients with diabetes and hypertension have poor control of their blood sugar or blood pressure for a long time, it can cause diabetic nephropathy or renal damage due to hypertension, which in turn leads to an increase in creatinine levels. Moreover, muscle damage caused by rhabdomyolysis, severe trauma or excessive exercise will release creatinine into the blood due to the destruction of a large number of muscle cells, resulting in a temporary increase. Therefore, monitoring creatinine levels not only helps in the diagnosis and monitoring of kidney diseases, but also has an important reference value for the assessment of related systemic diseases and muscle damage.

2.2. Cystatin C

Cystatin C is an alkaline secreted non-glycosylated low-molecular-weight protein, belonging to one of the members of the cystatin superfamily of protease inhibitors. It can regulate the activity of extracellular proteases. Cystatin C is encoded by the CST3 gene and is constantly and persistently transcribed and expressed in all nucleated cells, and is almost secreted and expressed in all tissue cells. In addition, cystatin C is recognized as the most active tissue protease B inhibitor. It can regulate the activity of cysteine proteases and thereby affect the migration of neutrophils during the inflammatory response, exerting anti-inflammatory effects, and providing certain protective functions for the body. Cystatin C in the blood can only be cleared by the kidneys. Due to its relatively small molecular weight, it can freely pass through the glomerular filtration membrane and is almost completely reabsorbed and degraded in the proximal tubule, not returning to the circulation again. The renal tubules do not secrete it. Moreover, the concentration of cystatin C in the blood is not affected by age, gender, or smoking habits. Therefore, cystatin C is an ideal endogenous marker for reflecting glomerular filtration rate.

In the clinical environment, cystatin C is usually used as a substitute for serum creatinine in the assessment of renal function. When eGFR is greater than or equal to 60 ml/min/1.73m^2, cystatin C

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outperforms creatinine in identifying renal dysfunction. The clinical reference range is 0.6-1.03 mg/L.

Additionally, Cystatin C can be used to reflect many diseases. Cystatin C (CysC) has extensive application value in clinical disease monitoring. In the field of kidney diseases, CysC can sensitively reflect the glomerular filtration function, especially being suitable for the diagnosis of early kidney damage. Its advantage lies in being less affected by age, gender and muscle mass, and combined detection can further improve the detection rate. For acute severe kidney damage, CysC performs particularly well in disease assessment and prognosis prediction, especially in contrast-induced nephropathy, diabetes combined with kidney damage, and dialysis patients. Moreover, CysC can also be used to identify cystic syndrome (SPS), and its ratio (eGFR CysC/eGFR crea < 0.7) is closely related to the patient's risk of death. In cardiovascular diseases, the level of CysC is positively correlated with the severity of coronary artery lesions and can be used as an auxiliary indicator for predicting the severity of coronary heart disease, and is related to vascular endothelial function damage and cardiovascular event risk. In cerebrovascular and neurological diseases, an elevated CysC level is associated with poor collateral circulation in patients with cerebral infarction and poor prognosis of neurological function, and can also serve as a potential biomarker for acute brain injury and cognitive decline. In endocrine and metabolic diseases, CysC is closely related to the treatment effects of diabetes and its complications (such as diabetic foot), thyroid diseases (such as Hashimoto's thyroiditis), and hyperuricemia. Additionally, in sarcopenia, the ratio of CysC to serum creatinine can be used as an important indicator for evaluating muscle function and osteoporosis risk, while in severe infections, sepsis, liver cirrhosis, and pulmonary arterial hypertension, changes in CysC levels have an important reference value for disease monitoring and prognosis judgment [1].

2.3. Creatinine/Cystatin C ratio (CCR)

As an alternative indicator of muscle mass. A decrease in CCR can be regarded as an alternative indicator of sarcopenia. Since Cr is produced in skeletal muscle, its secretion is affected by the mass of skeletal muscle, but the level of Cr is mainly influenced by renal function. Therefore, it cannot be used as an indicator for evaluating muscle mass. In contrast, CysC is expressed in all nucleated cells and is not affected by the mass of skeletal muscle, but is influenced by renal function. Therefore, its ratio can be used as an indicator for evaluating muscle mass.

This ratio can reflect the risk of frailty, the prediction of the risk of preeclampsia in pregnant diabetic patients, adult non-alcoholic fatty liver disease, the assessment of prognosis (such as HBV-related acute-on-chronic liver failure, peritoneal dialysis patients), the pancreatic B-cell function of elderly female patients with type 2 diabetes; the prediction of adverse outcomes (such as acute kidney injury, coronary artery disease, and chronic obstructive pulmonary disease patients).

3. The clinical applications of Creatinine/Cystatin C

The application of the CCR in clinical practice is becoming increasingly widespread, and its value mainly lies in the risk assessment and prognosis judgment of various diseases. Current research mainly focuses on the following aspects: CCR is closely related to the risk of frailty syndrome [2], and a lower CCR can be regarded as a sensitive indicator of muscle loss and decline in physical function, especially in the elderly population, showing good predictive value; in the cardiovascular field, CCR is significantly related to the severity and prognosis of coronary heart disease. Existing studies are mainly case-control studies, and cohort studies are relatively rare, and most focus on the

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application of CCR in the prognosis assessment of cardiovascular diseases, including the prediction of mortality and all-cause mortality risk for cardiovascular events. In addition, some studies have also begun to explore the clinical significance of CCR in patients with cardiovascular diseases and sarcopenia, and a lower ratio often indicates a higher risk of cardiovascular events and a possibility of adverse outcomes [3]. In obstetrics, CCR is used to predict the risk of preeclampsia in diabetic patients, providing a basis for early intervention [4]; in addition, CCR can also be used to assess the severity and progression of adult non-alcoholic fatty liver disease. At the level of prognosis judgment, CCR shows predictive ability for the outcomes of various diseases, such as the survival situation of patients with hepatitis B-related acute-on-chronic liver failure, the clinical outcome of peritoneal dialysis patients, and the pancreatic β-cell function status of elderly women with type 2 diabetes. At the same time, CCR has also been found to be independently associated with various adverse clinical events, including the occurrence of acute kidney injury, the deterioration of the condition and the risk of death in patients with chronic obstructive pulmonary disease [5], and the pancreatic β-cell function status of elderly women with type 2 diabetes. In recent years, more and more studies have also begun to focus on the application value of CCR in complex clinical scenarios such as tumor-related sarcopenia, comprehensive assessment of the elderly, and coexistence of multiple diseases. It is worth noting that with the deepening of the concept of precision medicine, the combined application of CCR with new biomarkers such as genetic polymorphisms and inflammatory markers is becoming a new research direction. As a composite indicator integrating renal function and muscle metabolism status, CCR not only plays a role in the screening and diagnosis of sarcopenia, but also has significant importance in the prognosis assessment of patients with various diseases and in complex clinical scenarios. Its clinical application prospect will be further expanded with the development of more prospective cohort studies.

In the related research on renal function assessment, estimating the glomerular filtration rate (eGFR) is a core indicator. Existing literature mostly focuses on the validity of eGFR based on Cr, eGFR based on CysC, and the combined eGFR calculated from both (cr-cysc) in evaluating the prognosis and risk of different diseases [6]. It is worth noting that these eGFR estimation formulas are closely related to the physiological basis and clinical significance of the CCR. Since the creatinine level is influenced by both muscle mass and renal function, while cystatin C theoretically depends less on muscle mass, eGFR(cr) may show deviations in muscle-consuming diseases (such as sarcopenia) or individuals with extreme body types; eGFR(cysc) is relatively stable, but it is also affected in inflammatory, thyroid dysfunction, and other conditions; eGFR(cr-cysc) improves the accuracy of estimating renal function in complex clinical situations by combining the two indicators. CCR, as an indicator that simultaneously reflects muscle metabolism and the balance of renal function, its changes not only can assist in interpreting the sources of differences in eGFR results - for example, a lower CCR may indicate that the underestimation of eGFR(cr) is due to muscle loss rather than pure renal function deterioration, but also provides important background supplementation and clinical correction clues for eGFR assessment in patients with multiple diseases such as sarcopenia combined with chronic kidney disease, heart failure, or liver disease, thereby enhancing the comprehensive judgment ability of the patient's overall condition and disease prognosis.

4. Conclusion

In fact, the research direction of this ratio is closely related to the association between sarcopenia and its related diseases. Specifically, scholars analyze the changes of this ratio to reveal the potential pathophysiological connections between sarcopenia and various chronic diseases (such as

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osteoporosis, metabolic syndrome, cardiovascular diseases, and chronic kidney disease). Moreover, the research also focuses on the application value of this indicator in assessing disease prognosis, treatment efficacy, and patient functional status, thereby providing a theoretical basis for early screening, risk stratification, and the formulation of personalized intervention strategies. Therefore, the exploration of this ratio not only deepens the understanding of sarcopenia as a hub role in systemic diseases, but also promotes integrated research on the relationship between muscle health and overall clinical outcomes in a multidisciplinary context.

This article mainly summarizes the clinical significance of creatinine/cystatin C. However, this article does not provide a detailed explanation of the research methods used to determine the ratio in the literature. The serum creatinine/cystatin C ratio has a relatively high predictive value in clinical practice and can provide assistance in understanding the progression of the disease. The serum creatinine/cystatin C ratio represents a promising, economically feasible biomarker with growing applications in geriatrics, nephrology, cardiology, and beyond. Its ability to estimate muscle mass and predict adverse outcomes across various clinical settings underscores its utility. Future research should aim to standardize reference values, validate cutoff points for different populations, and explore its integration into routine clinical practice for improved risk stratification and personalized care.

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