

# Serum creatinine level, a surrogate of muscle mass, predicts mortality in critically ill patients

Charat Thongprayoon<sup>1</sup>, Wisit Cheungpasitporn<sup>1</sup>, Kianoush Kashani<sup>1,2</sup>

<sup>1</sup>Division of Nephrology and Hypertension, <sup>2</sup>Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

Correspondence to: Kianoush Kashani, MD. Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Email: kashani.kianoush@mayo.edu.

**Abstract:** Serum creatinine (SCr) has been widely used to estimate glomerular filtration rate (GFR). Creatinine generation could be reduced in the setting of low skeletal muscle mass. Thus, SCr has also been used as a surrogate of muscle mass. Low muscle mass is associated with reduced survival in hospitalized patients, especially in the intensive care unit (ICU) settings. Recently, studies have demonstrated high mortality in ICU patients with low admission SCr levels, reflecting that low muscle mass or malnutrition, are associated with increased mortality. However, SCr levels can also be influenced by multiple GFR- and non-GFR-related factors including age, diet, exercise, stress, pregnancy, and kidney disease. Imaging techniques, such as computed tomography (CT) and ultrasound, have recently been studied for muscle mass assessment and demonstrated promising data. This article aims to present the perspectives of the uses of SCr and other methods for prediction of muscle mass and outcomes of ICU patients.

**Keywords:** Creatinine; cystatin; intensive care unit (ICU); malnutrition; mortality; muscle mass

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## Introduction

Creatinine is an endogenous substance generated from the nonenzymatic conversion of creatine and creatine phosphate, 95% of which is found in muscle (1). Creatinine is an uncharged, small molecular weight substance (113 Da) that is not bound to serum proteins. It is filtered freely by the glomerulus without tubular reabsorption. Creatinine is also secreted by the renal tubules only in small amounts (1).

The serum creatinine (SCr) level is ubiquitously used to estimate glomerular filtration rate (GFR) during a steady state of renal function. Although elevated SCr could be due to changes in its secretion (impact of medications: probenecid, cimetidine, trimethoprim) or production (due to increased muscle mass or meat consumption), its rise usually indicates either acute kidney injury (AKI) or chronic kidney disease. SCr-based AKI definitions have demonstrated consistent power in predicting mortality and other outcomes among the hospitalized patients (2-8). Due to the correlation between SCr levels and muscle mass, SCr

in the steady state has been used as a surrogate of muscle mass measurements (9). Creatinine generation is low among individuals who have more diminutive muscle mass, either constitutionally or disease-related. Therefore, low SCr level could be considered as a proxy of protein-energy wasting in some clinical situations (10). This article discusses the perspectives of the utility of SCr and other methods as predictors of muscle mass and outcomes of intensive care unit (ICU) patients.

## Mechanism of low serum creatinine (SCr) level

Low SCr levels are associated with multiple factors as shown in *Table 1* (10-15). As previously stated, creatinine generation could be reduced in the setting of low muscle mass. In the other words, malnourished individuals with smaller muscle mass have lower SCr levels. Muscle mass is related to gender (females may have less muscle mass), age (advancing age may be associated with decreasing muscle mass), and ethnic background (African Americans tend to

**Table 1** Factors associated with low serum creatinine levels

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Low muscle mass (female gender, elderly, chronic illness)
Malnutrition
Vegetarian diet
Pregnancy
Advanced liver disease
Fluid overload
Augmented renal clearance

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have higher muscle mass) (10). Individuals' SCr levels can also be affected by diet. Arginine and glycine are creatine precursors. Therefore, low dietary protein intake can limit creatinine generation. Also, cooked meat contains a significant amount of creatinine, which is absorbed in the intestinal tract. Thus, protein malnutrition could result in low SCr levels (11). A high GFR, as in pregnancy, could also lower SCr levels (10-12).

Patients with advanced liver diseases can have low SCr due to diminished creatinine production from decreased hepatic creatine synthesis, enhanced tubular creatinine secretion, and reduced skeletal muscle mass (12). Creatinine is distributed in total body water, and large fluid volume resuscitation, as is often required in the sickest ICU patients, could increase the volume of distribution of creatinine, resulting in lowered SCr values (13). Chronic illness, age, malnutrition, and pathologic conditions such as protein-losing disorders like enteropathies and nephrotic syndrome, also impact muscle mass and creatinine production (11).

Augmented renal clearance (ARC), an enhanced elimination of solutes by the kidneys at a rate significantly higher than normal, is a phenomenon whereby patients experience marked increase in functional creatinine clearance and GFR in acute illness; thus, leading to low SCr levels (14). With reported incidence rates ranging from 16% to 100%, ARC is commonly observed among ICU patients (15). Systemic inflammatory response syndrome (SIRS) is a common cause of ARC in critically ill patients (14).

### Low serum creatinine (SCr) levels and mortality

Cartin-Ceba *et al.* (16) have previously reported the results of a large retrospective cohort study of 11,291 patients admitted to Mayo Clinic Hospital—Rochester ICUs between 2003 and 2006, evaluating the association between

baseline SCr concentration at admission to ICU and in-hospital mortality. Both low and high baseline SCr levels were associated with increased in-hospital mortality. Multivariable regression analysis was used to adjust for various relevant variables including body mass index (BMI). The noted low baseline SCr was independently associated with increased mortality in a dose-response fashion. The investigators postulated that the association was due to diminished muscle mass and malnutrition.

Recently, Udy *et al.* (17) reported a large retrospective study of 1,045,718 patients across 172 ICUs by exploring data from the prospective Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation adult patient database. To mitigate the impact of volume resuscitation on SCr levels during ICU admission, the investigators stratified patients based on the peak recorded SCr concentration during the first 24 h of ICU admission, rather than the lowest SCr levels. Using a reference SCr value of 0.79–0.89 mg/dL, the investigators reported a progressively increased risk of ICU mortality at peak admission SCr levels <0.68 mg/dL and SCr levels <0.34 mg/dL [odds ratio (OR) for in-hospital mortality =2.03; 95% CI, 1.86–2.21]. The study of SCr levels as a predictor of ICU or hospital outcomes is associated with limitations, as mentioned earlier. Fluid resuscitation is very prevalent in the ICU, especially within 24 h of ICU admission, so using peak SCr levels cannot completely eliminate this potential confounder. Also, low SCr levels may represent ARC; this would potentially interfere with maintaining therapeutic antimicrobial concentrations, which could be potentially associated with increased ICU mortality (14). Despite these limitations, it could be reasonably postulated that low SCr level on ICU admission reflects low muscle mass or malnutrition, which are associated with increased mortality.

Previous studies have demonstrated that high SCr levels in hemodialysis patients are associated with greater survival, whereas low SCr levels are associated with increased mortality (18,19). In the Alberta Kidney Disease Network (AKDN) study among >900,000 Canadians, Tonelli *et al.* (20) found low SCr levels with eGFR  $\geq 105$  mL/min/1.73 m<sup>2</sup> were associated with increased mortality. Also, low SCr levels have been correlated with cardiovascular diseases (21,22). Recently, Choi *et al.* (23) conducted a cross-sectional study of 6,986 middle-aged Korean men, which showed a U-shaped association between eGFR and advanced coronary artery calcification, as measured by computed tomography (CT). Compared with study individuals who

had eGFRs between 75 and 89 mL/min/1.73 m<sup>2</sup>, those with either lower or higher eGFRs were at increased risk for coronary artery calcium scores above 100. Even after adjustment for confounders, individuals with low SCr levels and eGFRs  $\geq 105$  mL/min/1.73 m<sup>2</sup> had an OR of 2.53 for advanced coronary artery calcification, compared with subjects with eGFRs between 75 and 89 mL/min/1.73 m<sup>2</sup>. However, the data on proteinuria, an important marker of kidney damage, was not available in this study (23). Proteinuria, particularly albuminuria, has been shown to be associated with higher mortality and acute myocardial infarction (20). In addition, a SCr-based GFR equation is affected by non-GFR determinants of SCr including diet, muscle metabolism, and metabolic disorders. Combined analysis revealed that higher mortality in non-critically ill patients with low SCr levels likely results from malnutrition and illness, not from enhanced kidney function. Although future studies are required to assess the impact of changes in the GFR of the outcomes, in studies used cystatin C (CysC), which is independent of muscle metabolism and diet, there is a linear, not a U-shaped, association between eGFR and adverse events (24).

### Muscle mass, nutritional status, and mortality

Skeletal muscle, accounting for 40% of body weight and 50% of body protein, plays a vital role in regulating immune function, glucose disposal, protein synthesis and mobility (25). Muscle provides a massive dynamic reservoir of proteins, minerals, and other intermediate metabolites that can be cannibalized to meet the need of other tissues involved in the inflammatory response. Loss of skeletal muscle and the reduced protein reservoir may predispose impaired tissue healing and poor immune function (26). As more than 75% of glucose metabolism is handled by skeletal muscle, its atrophy can impair insulin signaling, and glucose tolerance (27).

Studies have shown the reduced survival rates and the increased hospital lengths of stay of patients who have a poor nutrition status and low muscle mass (26,28,29). In patients with low muscle mass and malnutrition, cardiovascular outcomes are generally poor (30), life expectancy in cancer is reduced (31), and outcomes following liver transplantation are unfavorable (32). In elderly patients, sarcopenia, the age-associated loss of skeletal muscle mass and function, is associated with higher morbidities and mortalities (33).

Malnutrition and wasted muscles are common features

in ICU patients, due to a protracted catabolic condition, correlated with high morbidity and mortality. The critical illness-related hypercatabolic state does not improve by just providing adequate nutritional support (34). Inflammatory cytokines in the setting of SIRS/sepsis have an established role in regulating muscle mass. TNF- $\alpha$ , IL-1, IL-6, and endotoxin infusions result in muscle wasting syndrome due to increased protein catabolism, inhibition of protein synthesis, inhibition of muscle cell differentiation, or reduced amino acid uptake (35). ICU-related respiratory muscle wasting leads to difficulties in weaning patients from mechanical ventilation (36).

### Assessment of muscle mass and nutritional status in ICU

Critically ill patients require special considerations during muscle mass assessment. *Table 2* shows the typical methods used for nutritional status and muscle mass assessment in ICUs (37-48). Several studies have indicated the tools typically used to assess nutritional status are poor indicators of malnutrition in the critically ill population (37,49-51). Skeletal muscle wasting in the ICU is frequently masked by excess fat (sarcopenic obesity) (52), or by fluid retention that can amount to 10–20% of the patient's body weight (53). As discussed earlier, SCr levels are influenced by age, diet, exercise, stress, and renal disease and require cautious interpretations. Having low BMI and weight are also identified risk factors for death in ICU patients (38). Unfortunately, many ICU patients are edematous, and the measured weight and BMI may not reflect the real body muscle mass (39). Interpretation of results of other anthropometric measurements such as mid-upper arm circumference and triceps skinfold thickness also remains uncertain and of limited value to the ICU setting, as the techniques all assume a normal state of hydration (54). In addition, since ICU patients are frequently sedated, voluntary muscle strength tests cannot be performed because of impaired patient cooperation.

Albumin is also a poor marker of nutritional status, especially in the ICU setting, due to changes in intravascular volume, as well as other factors, including the impact of acute infection, inflammation, hepatic function, and protein-losing states (40). The use of tools that assess muscle mass and nutrition, such as subjective global assessment (SGA) and Nutrition Risk in Critically Ill Score (NUTRIC) (37) has been proposed. However, screening and evaluation tools often have components that are difficult to obtain in

**Table 2** Assessment of muscle mass and nutritional status in intensive care unit (ICU)

Characteristics	Tools for muscle mass assessment in ICU	Tools for nutritional status in ICU
Body mass index (BMI)	X	X
Imaging studies including CT scan, MRI and ultrasonography	X	
Muscle biopsies	X	
Muscle strength tests		X
Neutron activation analysis (IVNAA)	X	
Nutrition Risk in Critically Ill Score (NUTRIC)		X
Nutrition-focused physical assessment (NFPA)		X
Physical assessment and anthropometric measurements (mid-upper arm circumference and triceps skinfold thickness)	X	X
Serum alanine aminotransferase (ALT)	X	
Serum albumin	X	X
Serum and urine creatinine	X	
Serum prealbumin		X
Subjective global assessment (SGA)		X

X, assessment tool.

the ICU due to the severity of illness and hence cannot uniformly identify patients at risk of malnutrition (37,55). Also, performing a nutrition-focused physical assessment (NFPA) in ICU patients might not be accurate, since they frequently are intubated, sedated, and volume overloaded (55).

To date, the only two validated methods for measuring the loss of lean tissue in critically ill patients with severe edema have been *in vitro* neutron activation analysis (IVNAA) (41) and assessing differences in muscle fiber area using repeated muscle biopsies (42). The former requires radiation and is not commonly available, and the latter is time-consuming and invasive. Both methods are only used in research settings.

Imaging techniques, such as CT, magnetic resonance imaging (MRI) or ultrasound have recently been studied for muscle mass assessment (43,44). Commonly performed on ICU patients, CT scans provide a more reliable measure of muscle mass in comparison with externally measured muscle circumferences (43), in these medically ill populations. The CT images can be combined with mathematical reconstruction algorithms to estimate the mass of individual muscle groups or the total-body skeletal muscle mass. Single-slice CT images in the L3 region can predict whole-body muscle and adipose tissue volume in healthy individuals and ICU populations (44). However, CT scans are not performed on every critically ill patient, as it is costly

and involves radiation exposure for prospective evaluation of body composition (44). Ultrasonography is a new and promising non-volitional measure that enables identification of changes in muscle structure and morphology (56). It is noninvasive, inexpensive, and can be performed at the bedside. Studies have also shown good inter- and intra-observer reliability (45,46). Campbell *et al.* (47) suggested that ultrasound could identify and possibly quantify muscle wasting in edematous patients with multiple organ failures. Other studies have also demonstrated that loss of muscle mass, determined by ultrasound, correlated negatively with the ICU length of stay (29,57). Also, this measurement correlates well with CT scan evaluations. While the findings are promising, further studying of assessing muscle mass by using ultrasonography to predict mortality and poor outcomes of ICU patients is needed.

## Conclusions

Low muscle mass is a strong predictor of poor outcomes in ICU patients. Studies have shown high mortality in ICU patients with low admission SCr levels. Although SCr levels can be used as a surrogate of muscle mass, it is influenced by other GFR- and non-GFR-related factors. Further studies are needed to implement insights of underlying mechanisms of an association between low SCr

and mortality in the ICU patients as well as to evaluate if aggressive nutritional support in critically ill patients with low SCr levels can improve their mortality. Studies have demonstrated promising data on the uses of CT scans and ultrasonography for muscle mass measurement in ICU patients.

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