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Looking for Sarcopenia Biomarkers

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Sarcopenia, defined as age-associated loss of skeletal muscle mass and function, has emerged as an important public health issue. It is associated with higher mortality, morbidity, physical disability, and health care cost.[1,2] While sarcopenia should be diagnosed with measurements of muscle mass and function, serum biomarkers are needed for screening of sarcopenia in a large population. Serum creatinine is a known biomarker for muscle mass and kidney function because 90% of its precursor, creatine phosphate, is stored in the muscle, its production is mostly constant, and its excretion is completely via the kidney.[3] For patients with normal renal function, serum creatinine is a reasonable biomarker for sarcopenia. In this issue, Thongprayoon et al[4] reported that a low serum creatinine level, most likely due to sarcopenia, is associated with a higher mortality rate.

They found that the association between admission creatinine values and in-hospital and 1-year mortalities is a U-shaped distribution, suggesting that low muscle mass and poor kidney function account for the higher mortality for each end, respectively. Importantly, because males usually have larger muscle mass, the cut-off for low serum creatinine level is sex dependent. From the U curves, the nadir serum creatinine level for males is 0.9-1.0 mg/dL, and for females is 0.7-0.8 mg/dL. Male patients with serum creatinine level <0.6 mg/dL, and females <0.4 mg/dL, had increased in-hospital and 1-year mortality by about two- to threefold. For patients with a low serum creatinine level, the chance to die during the admission is about 1 in 50, and to die within 1 year after discharge would be 1 in 5.[4] These results suggest that we should pay more attention to patients with low serum creatinine levels and follow them more closely after discharge.

In this study, sarcopenia is probably the main cause of low admission serum creatinine levels.[4] However, there are many conditions that may lower serum creatinine level and result in a misdiagnosis of sarcopenia (False positive, **Table**).[3,5,6] Among them, the augmented renal clearance is still not fully understood. It is seen in young intensive care unit patients, probably due to fluid overload, systemic inflammation, and other unknown causes.[6] On the other hand, many sarcopenic patients may not have low serum creatinine levels due to the conditions that raise serum creatinine levels (False negative, **Table**).[3] In this study, 4.6% of male and 2.0% of female hospital patients may have sarcopenia based on low serum creatinine levels.[4] These numbers could be significantly underestimated, most likely due to chronic kidney disease.

To overcome the problems related to chronic kidney disease, Kashani et al[7] proposed using another renal function marker, cystatin,[3] for correction. They found that a sarcopenia index, calculated as (serum creatinine/serum cystatin C) × 100, correlates with the paraspinal muscle surface area at the L4 vertebrae obtained from an abdominal computed tomography scan ($r^2 = 0.27$). This sarcopenia index is an independent predictor of the hospital and 90-day mortality, but not for intensive care unit mortality or long-term physical and mental performance.[7] This relatively low coefficient between the sarcopenia index and muscle surface area suggests that there is room for improvement. As we know that, except in some rare conditions (**Table**), timed urine creatinine value is dependent solely on muscle mass, providing the renal function is in a steady state, estimated glomerular filtration rate (eGFR) based on serum cystatin level ($eGFR_{cystatin}$) is a better way to estimate renal function than creatinine in patients with low muscle

Table False Positive and Negative Conditions for Diagnosing Sarcopenia Based on Low Serum Creatinine Levels

False positive (low serum creatinine level without sarcopenia)
Volume expansion: SIADH, nephrotic syndrome, pregnancy, fluid overload
Advanced liver disease
Augmented renal clearance
Vegetarian diet
Limb amputation
Paraplegia, hemiplegia, and other neuromuscular disorders
False negative (high serum creatinine level with sarcopenia)
Chronic kidney disease
Volume depletion
Inhibitors of creatinine secretion: cimetidine, trimethoprim
Ingestion of cooked meat
Ingestion of creatine supplement

SIADH = syndrome of inappropriate antidiuretic hormone secretion.

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mass.[8] Because timed urine creatinine = serum creatinine × creatinine clearance × time, if we replace creatinine clearance with $eGFR_{cystatin}$, then timed urine creatinine = serum creatinine × $eGFR_{cystatin}$ × time. Therefore, from the physiological point of view, a better sarcopenia index would be calculated as serum creatinine × $eGFR_{cystatin.}$ (Time is a constant and can be removed). This sarcopenia index is expected to be sex dependent; thus, separate normal ranges should be developed for each sex. In addition, this index should not be applied to those who had a loss of muscle mass due to other causes such as limb amputation and hemi- or paraplegia. It would be interesting to see whether future studies based on this proposed sarcopenia index would show a better correlation with sarcopenia, and a stronger predictive power for mortality and morbidity.

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