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Advances in sarcopenia and urologic disorders

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Sarcopenia is a loss of muscle strength, muscle mass, and function that can increase a patient's risk of injury, illness, and can even severely impair quality of life and increase a patient's risk of death. A growing body of research suggests that sarcopenia and urinary tract disorders are closely related. In this review, we aimed to emphasize the definition of skeletal sarcopenia, summarize the methods used to diagnose skeletal sarcopenia, discuss the advances in the study of sarcopenia in benign diseases of the urinary system, discuss the advances in the study of sarcopenia in malignant diseases of the urinary system. Sarcopenia and urologic diseases interact with each other; urologic diseases cause sarcopenia, and sarcopenia aggravates the condition of the original disease, thus falling into a vicious circle. This review provides a comprehensive understanding of sarcopenia in urologic diseases, which is very important for the management and prognosis of urologic diseases.

KEYWORDS

sarcopenia, overactive bladder, polycystic kidney, bladder cancer, prostate cancer

1 Introduction

With the aggravation of the aging trend of the national population, sarcopenia has become a global public health problem, and the incidence of sarcopenia is increasing year by year (1). Sarcopenia is a progressive and systemic skeletal muscle disease that involves accelerated loss of muscle mass and function and is associated with increased adverse outcomes such as falls, decreased function, weakness, and mortality (2).

There is an interaction between sarcopenia and urinary tract disorders. Sarcopenia can lead to chronic inflammation, loss of muscle strength and etc. (3). Therefore, patients with sarcopenia have an increased chance of developing urinary tract diseases such as urinary tract inflammation and overactive bladder disease, and even aggravate the progression of diseases such as chronic kidney disease (CKD) and urological malignancies (4–7). Urologic malignancies lead to sarcopenia by causing a decrease in protein intake, an increase in protein catabolism, and a decrease in physical activity, which further affects aspects of surgery, chemotherapy, and prognosis (8, 9). Although studies in recent years have suggested that sarcopenia is associated with urologic disorders, little attention has been paid to the potential role of the urinary system in the etiology of sarcopenia and in interventions. Therefore, in this review, we aimed to (1) emphasize the definition of skeletal sarcopenia, (2) summarize the methods used to diagnose skeletal sarcopenia, (3) discuss the advances in the study of sarcopenia in benign and malignant diseases of the urinary system.

2 Sarcopenia

2.1 Definitions

The term sarcopenia was first coined in 1988 by Rosenberg, who argued that no single feature of age-related decline is more pronounced than weight loss, which affects walking, capacity intake, overall nutritional intake, and more. Thus, initially sarcopenia was considered an age-related loss of skeletal muscle mass (10).

Different definitions of sarcopenia have been proposed by various organizations to date, with the EWGSOP2 definition being the most widely used in clinical practice (11–16). In 2010, EWGSOP published a definition of sarcopenia that is widely used worldwide. Sarcopenia is defined as a disease of old age caused by a decrease in muscle mass, muscle strength and/or physical function (14). In 2018, EWGSOP2 updated and added to the definition of sarcopenia: “sarcopenia is a muscle disease (muscle failure) rooted in adverse muscle changes that accrue across a lifetime; sarcopenia is common among adults of older age but can also occur earlier in life.” In contrast to the 2010 definition, in the updated definition, EWGSOP2 includes low muscle strength as the main indicator of sarcopenia (12). Because an increasing number of scholars believe that muscle number and muscle mass remain problematic as the primary parameters for defining sarcopenia due to technical limitations, muscle strength is preferred over muscle mass in predicting poor outcomes, and muscle strength is currently the most reliable measure of muscle function (17–19). EWGSOP2 diagnostic thresholds are as follows: 1. Low muscle strength: Grip strength <27 kg for men and <16 kg for women or Chair Rise Test: 5 rises in >15 s; 2. Low muscle mass: ASM (appendicular skeletal muscle mass)/height² ≤ 7 kg/m² for men and ≤ 5.5 kg/m² for women; 3. Low physical performance: Step speed ≤ 0.8 m/s or SPPB (Simple Physical Performance Test) score ≤ 8 or TUG (timed up and go walking test) ≥ 20 s or 400 m walk test not completed or completed in ≥ 6 min (12).

Another widely used consensus on sarcopenia is AWGS (Asian Working Group for Sarcopenia), which in 2014 adopted a similar definition to EWGSOP, an age-related geriatric syndrome characterized by decreased muscle mass and low muscle function. The difference is that AWGS requires both low muscle strength and low physical performance to be diagnosed. Additionally, threshold values have been proposed that are compatible with Asian populations based on their anthropometrics (20). In the latest AWGS 2019 consensus, the diagnostic thresholds are as follows: 1. low muscle strength: grip strength <28 kg in men and <18 kg in women; 2. low muscle mass: ASM/height² <7.0 kg/m² for men and <5.4 kg/m² for women as measured by DXA (Dual-energy X-ray bone densitometry); <7.0 kg/m² for men and <5.7 kg/m² for women as measured by BIA (bioelectrical impedance analysis); 3. low physical performance: gait speed <1.0 m/s or chair rise test ≥ 12 s or SPPB ≤ 9. AWGS 2019 also added recommendations for different algorithms to be used in community and hospital settings and introduced the term “possible sarcopenia” to promote early intervention in community settings. Possible sarcopenia is defined as low muscle strength (handgrip strength) or low physical performance (chair rise test) (21).

However, these criteria of weight loss as the main criterion for sarcopenia are not met in certain diseases, such as diabetes (22). In these disorders, the patient’s muscle mass decreases but fat mass remains the same or increases, a condition known as sarcopenic obesity (SO). The European Society for Clinical Nutrition and

Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO), as well as the jointly appointed international expert panel proposes that SO is defined as the co-existence of excess adiposity and low muscle mass/function (23).

2.2 Diagnosis

2.2.1 Screening

Early screening and early intervention for skeletal sarcopenia is important. There are a number of clinical screening tools available to identify sarcopenia (Table 1). SARC-F is currently the most recommended screening tool for sarcopenia, but its sensitivity is low. Researchers have also developed/re-purposed several other screening tools for effective screening. Each of these screening tools has advantages and disadvantages for different clinical use scenarios. Screening tools do not serve as a definitive diagnosis of sarcopenia, and if a screening tool suggests the presence of sarcopenia, a definitive test should be performed.

2.2.2 Physical performance and muscle strength tests

Physical performance is defined as visually measurable whole-body function related to exercise, involving not only muscles but also central and peripheral nerve function. There are several instruments that can be used for fitness testing, including gait speed, the Simple Physical Performance Test (SPPB), timed up and go walking test (TUG), and 400-meter walk test. Gait speed is now widely used in practice, with the commonly used gait speed test being the 4-meter walking speed test, and the EWGSOP2 recommending a speed of ≤ 0.8 m/s as an indicator of severe sarcopenia (24). The SPPB is a comprehensive test that incorporates a gait speed test, a balance test, and a chair stand test, and is scored out of 12, with a score of ≤ 8 indicating poor physical performance (25). In the TUG test, participants were asked to stand up from a standard chair, walk to a marker 3 meters away, turn around and walk back to sit in the chair, taking ≥ 20 s to be considered a poor physical performer. The 400-meter walk test assessed walking ability and endurance, in which participants were asked to complete 20 laps of a 20-meter walk as fast as possible for each lap, with two rest stops permitted during the test, and a final time of ≥ 6 min to be considered a poor performer. Considered to have poor physical performance (26).

Grip strength is easy and inexpensive to measure and can be used as a test tool for arm muscle strength. Grip strength correlates with strength in other parts of the body, so it can be a reliable alternative to more complex measurements of arm and leg strength. Accurate measurement of grip strength requires the use of a calibrated hand-held dynamometer under well-defined test conditions (27).

Seat Stand Test can be used as a test tool for leg muscle strength. It measures the time it takes for a patient to get up in a seated position five times without using their arms. Or it counts the number of times a patient can stand up and sit in a chair in a 30-s period of time (28).

2.2.3 Imaging modalities and body composition measurement tools

Muscle mass can be reported in terms of whole-body skeletal muscle mass (SMM), appendicular skeletal muscle mass (ASM), or muscle cross-sectional area for specific muscle groups. Table 2

TABLE 1 Screening tools for sarcopenia.

Name	Domains measured	Strengths	Limitations	Clinical scenarios
SARC-F	<ul style="list-style-type: none"> Strength Assistance in walking Rise from a chair Climb stairs Falls 	<ul style="list-style-type: none"> Initial diagnosis of sarcopenia Quick and easy to use Suitable for all clinical scenarios High specificity and moderate sensitivity 	<ul style="list-style-type: none"> The first four measures may be biased Muscle function was mainly assessed, and muscle mass was not assessed Low sensitivity 	Suitable for virtually all medical environments
SARC-F Calf	<ul style="list-style-type: none"> Strength Assistance in walking Rise from a chair Climb stairs Falls Calf circumference 	<ul style="list-style-type: none"> Increased sensitivity for SARC-F (45.9%-57.2%) 	<ul style="list-style-type: none"> Calf measurements are susceptible to interference from other factors such as fat and edema 	For community health, specialty clinical settings
Ishii Test	<ul style="list-style-type: none"> Age Grip strength Calf circumference 	<ul style="list-style-type: none"> High sensitivity and specificity (84.9% and 88.2% for men; 75.5% and 92.0% for women) 	<ul style="list-style-type: none"> Not yet validated in multiple populations 	Not commonly used in primary care, generally used in specialty clinical settings
MSRA	<p>MSRA-5 includes:</p> <ul style="list-style-type: none"> Age Protein Physical activity level Number of hospitalizations Weight loss in the last year <p>MSRA-7 includes:</p> <ul style="list-style-type: none"> Age Protein Dairy products consumption Number of meals per day Physical activity level Number of hospitalizations Weight loss in the last year 	<ul style="list-style-type: none"> High sensitivity 	<ul style="list-style-type: none"> Not yet validated in multiple populations 	Generally not used in community hospitals
SarSA-Mod	<ul style="list-style-type: none"> Age Weight Calf circumference 	<ul style="list-style-type: none"> High sensitivity (84.3% in women, 85.4% in men) 	<ul style="list-style-type: none"> Validated in Middle Eastern populations only 	Used in a variety of clinical settings
Grip strength	<p>Low muscle strength was defined as hand grip strength:</p> <ul style="list-style-type: none"> < 30 kg in men < 20 kg in women 	<ul style="list-style-type: none"> Easy to perform in clinic setting with simple, inexpensive tool dynamometer 	<ul style="list-style-type: none"> Requires dynamometer 	Widely used in clinical practice
SarQoL questionnaire	A scale consisting of 55 items in 7 domains in the form of 22 questions	<ul style="list-style-type: none"> Assisting health care providers in assessing patients' perceptions of aspects of their physical, mental and social health 	<ul style="list-style-type: none"> The verification crowd is limited to French-speaking people Participants were mostly community females, and measurements may be biased 	For clinical care and research
Fracture risk assessment tool	<ul style="list-style-type: none"> Age Sex Weight Height Previous fracture Parental hip fracture Glucocorticoid use Rheumatoid arthritis Smoking Alcohol consumption Secondary osteoporosis Bone mineral density with or without bone 	<ul style="list-style-type: none"> The FRAX score without bone density can be calculated using an online calculator High sensitivity (90.9%) 	<ul style="list-style-type: none"> Non-response bias may exist 	

(Continued)

TABLE 1 (Continued)

Name	Domains measured	Strengths	Limitations	Clinical scenarios
Taiwan Risk Score for Sarcopenia	<ul style="list-style-type: none"> Age Sex Underweight Receipt of social assistance pension Lack of exercise Fasting blood glucose Abnormal creatinine levels 	<ul style="list-style-type: none"> High sensitivity (71.8%) High specificity (71.1%) 	Long time for evaluation; Rarely used at present	Be applied cost-effectively in the community for early detection of sarcopenia.
Anthropometric prediction equation (PE)	<p>Anthropometric equations constructed to predict skeletal muscle mass in the limbs based on weight, BMI, age, and sex.</p> <p>"ASM=10.05+0.35×Body weight-0.62×BMI-0.02×age+5.10 (male)"</p>	High specificity (male: 99.5%; female: 94.7%)	Only been used in the community's older population;	Screening for sarcopenia in primary and aged care
Chair rise	<ul style="list-style-type: none"> Strength Cut-off points >15 s for 5 chair rises 	<ul style="list-style-type: none"> Easy to perform in clinic setting Requires no specialized tools 		

SARC-F, Strength, Assistance Walking, Rise from a Chair, Climb Stairs, and Falls; MRSA, Mini Sarcopenia Risk Assessment Questionnaire; SarSA-Mod, Sarcopenia Scoring Assessment Models; SarQoL, Sarcopenia Quality of Life; FRAX, Fracture Risk Assessment Tool; BMI, Body Mass Index.

summarizes imaging measurement tools as well as body composition measurement tools.

Magnetic resonance imaging (MRI) and computed tomography (CT) are considered the gold standard for noninvasive assessment of muscle mass (28). However these tools are not commonly used in primary care due to the high cost of the equipment, lack of convenience, and the need for a trained professional to use them. In addition, the cut-off point for measuring low muscle mass is not well defined. Studies have shown that CT images of specific lumbar spine markers correlate significantly with whole-body muscle. L3-CT imaging of the third lumbar spine is not limited to patients with cancer; this parameter has also been used as a predictor of mortality and other prognostic indicators in intensive care units and in patients affected by liver disease (29). Mid-thigh imaging (MRI or CT) is a good predictor of skeletal muscle mass throughout the body, and its correlation is stronger than the correlation between L1-L5 psoas muscle area and total body muscle (29).

Dual-energy X-ray bone densitometry (DXA) is a more widely available instrument for non-invasive determination of muscle mass. The advantage of the DXA is that it provides a reproducible estimation of ASM within a few minutes when using the same instrument and cut-off points. However, DXA instruments are not yet portable for use in the community, which is a disadvantage (30).

Bioelectrical impedance analysis (BIA) has been used to estimate SMM or ASM, BIA devices do not measure muscle mass directly but estimate muscle mass based on whole body conductivity. BIA requires specific conversion equations for calibration. For example, the Sergi equation is based on older European populations, and other relevant differences such as age and ethnicity of these populations and patients should be considered in clinical work, in addition to the fact that BIA measurements are affected by the hydration status of the patient. However, BIA needs more studies to validate population-specific prediction equations (31).

Muscle ultrasound assessment of pterygoid muscles such as the quadriceps can detect reductions in muscle thickness and cross-sectional area in a relatively short period of time, and therefore the

technique has great potential for clinical application. The EuGMS Myasthenia Gravis Group has recently proposed a consensus protocol for muscle assessment using ultrasound, which involves the measurement of muscle thickness, cross-sectional area, fascicle length, droop angle, and echogenicity. Echogenicity reflects muscle mass because the non-contractile tissue associated with myasthenia gravis is highly echogenic (32). Therefore, ultrasound has the advantage of being able to assess muscle quantity and quality. Echo intensity is shown to be more useful than traditional sarcopenia-related parameters in predicting hospital-related complications in older acutely hospitalized patients (33).

Skeletal Muscle mass Index (SMI) is an indicator for assessing muscle mass, which is calculated by the formula $ASM/height^2$ (34), so the measurement of SMI usually relies on the aforementioned imaging techniques, such as dual-energy x-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI). As a superior index of sarcopenia, SMI not only predicts long-term survival in patients with urologic cancers, but also provides guidance on discharge management after surgery (35, 36). In addition, with advances in imaging technology, automated muscle segmentation and analysis methods are being developed to improve the accuracy and reproducibility of SMI measurements (37, 38). These studies contribute to a better understanding and application of SMI to improve the diagnosis and management of sarcopenia.

2.2.4 Laboratory biomarkers

Creatine is produced by the liver and kidneys and taken up by myocytes, a portion of which is irreversibly converted to creatinine phosphate on a daily basis, and excess creatine in the circulation is converted to creatinine and excreted in the urine (39). Creatinine excretion rate is a promising metabolic index for assessing whole-body muscle mass. Fasting patients were orally administered an appropriate dose of deuterium-labeled creatine, followed by determination of labeled and unlabeled creatine and creatinine in urine by liquid chromatography and tandem mass spectrometry (40). Study Shows Creatine Dilution Test Results Correlate Well with MRI-Based Measures of Muscle Mass and Moderately with BIA and

TABLE 2 Imaging modalities and body composition measurement tools for sarcopenia.

Name	Strengths	Limitations	Clinical scenarios
L3-CT	<ul style="list-style-type: none"> L3 levels are strongly correlated with whole body muscle mass and fat mass 	<ul style="list-style-type: none"> Not universally used Cannot control bias due to height error Limited availability Lack of portability High cost and radiation exposure 	Suitable for cancer patients, seriously ill patients, liver disease patients
Mid-thigh imaging (MR/CT)	<ul style="list-style-type: none"> Considered the gold standard noninvasive tool for assessing muscle mass 	<ul style="list-style-type: none"> Higher equipment costs Lack of portability Higher operator requirements 	Not commonly used in primary care, generally used in specialist clinical settings
Muscle ultrasound	<ul style="list-style-type: none"> Portable Inexpensive Non-invasive No ionizing radiation Highly reproducible 	<ul style="list-style-type: none"> Lack of harmonized diagnostic criteria 	Clinical pilot studies
DXA	<ul style="list-style-type: none"> Provides ASM reproducibility estimates in minutes 	<ul style="list-style-type: none"> Inconsistent results from different brands of machines Affected by patient hydration status 	Generally not used in community hospitals
BIA	<ul style="list-style-type: none"> Low cost Portable 	<ul style="list-style-type: none"> Lack of standardization limits its accuracy 	Used in a variety of clinical environments

CT, Computed Tomography; MR, Magnetic Resonance; DXA, Dual-energy X-ray Absorptiometry; BIA, Bioelectric Impedance Analysis; ASM, Appendicular Skeletal Muscle Mass.

DXA Measures (41, 42). The test currently requires a significant amount of research to provide further improvements.

Potential biomarkers may also include markers of neuromuscular junctions, muscle protein transitions, behaviorally mediated pathways, inflammation-mediated pathways, redox-related factors and hormones or other anabolic factors (43). However, due to the complex pathophysiology of sarcopenia, there is still no single biomarker to recognize this condition in heterogeneous populations of young and old.

3 Sarcopenia and benign diseases of the urinary system

3.1 Inflammation of the urinary system

Inflammatory cytokines have been shown to promote muscle wasting, stimulate protein metabolism and inhibit protein synthesis (44, 45). Among many inflammatory cytokines, the main ones are tumor necrosis factor- α (TNF- α), C-reactive protein (CRP), interleukin (IL)-6. TNF- α is a key stimulator of chronic inflammation that triggers skeletal muscle contractile dysfunction. TNF- α inhibits protein synthesis via the IGF1/AKT pathway, thereby triggering muscle atrophy (46, 47). Sarcopenia was strongly associated with serum CRP levels, an indicator of infection ($p < 0.0001$) (48). Sustained elevation of IL-6 aggravates muscle atrophy by reducing muscle anabolism and damaging energy homeostasis, and it also directly mediates muscle catabolism (49). Increased IL-6 stimulates muscle protein degradation by interfering with insulin/PI3K/AKT signaling (50, 51).

Urinary tract infections are a common infectious disease that can occur anywhere in the urinary tract. In addition to simple urinary tract infections that can resolve on their own or be treated with

antibiotics, there are more complex forms such as catheter-associated urinary tract infections. Catheter-associated urinary tract infections are also a common complication in trauma hospitalized patients, and a study by James DeAndrade et al. showed that myasthenia gravis was an independent risk factor for catheter-associated urinary tract infections ($p = 0.011$) (52).

3.2 Overactive bladder

Overactive bladder (OAB) is a syndrome characterized by symptoms of urinary urgency, typically accompanied by urinary frequency and nocturia, and may or may not involve urge incontinence. It is not associated with urinary tract infections or other definitive pathological changes. Recent studies have explored the relationship between sarcopenia and OAB, with promising findings.

A retrospective study conducted by Song et al. demonstrated a positive association between sarcopenia and the risk of OAB in adults in the United States (53). The study also suggested that sarcopenia could serve as a predictor for OAB. Similarly, Ida S et al. conducted a cross-sectional study which revealed a significant association between sarcopenia and OAB in elderly male patients with diabetes (5). Furthermore, Hashimoto et al. identified sarcopenia and visceral fat accumulation as potential risk factors for severe storage symptoms in female patients aged 65 years and older (54). While these studies suggest a possible link between sarcopenia and OAB, there is a need for further research and validation using multi-center data and larger sample sizes. Additionally, the underlying mechanism by which sarcopenia contributes to the development of OAB remains unknown.

In conclusion, sarcopenia may be a risk factor for developing OAB, but more research is needed to establish a definitive relationship. Further studies should aim to explore the mechanisms underlying this association and confirm the findings using larger and more diverse study populations.

3.3 Polycystic kidney

Polycystic kidney disease (PKD) is a benign urologic disorder of genetic origin. While generally non-malignant, it can still harm kidney function and necessitate dialysis treatment in extreme circumstances. PKD patients typically have numerous cysts, and their body mass index (BMI) may conceal underlying underweight issues. Consequently, Chih-Horng Wu and his team employed total abdominal muscle area (TAM) at the third lumbar vertebrae as a diagnostic standard for sarcopenia. Their research concluded that sarcopenia can be accurately diagnosed in PKD patients using CT and MRI scans (55). However, the disease may be hidden by the cysts. There was a negative correlation between kidney volume and abdominal muscle mass, but not with adipose tissue. Additionally, factors such as age, BMI, serum creatinine levels, and kidney volume play a crucial role in muscle loss in PKD patients.

A study by Lee et al. indicated that good nutritional status helps preserve renal function in PKD patients (56). Analysis from a two-year randomized controlled trial, CRAD001ADE12, suggests that the accelerated growth of cysts in patients with autosomal dominant polycystic kidney disease (ADPKD) can be slowed down with the use of everolimus, a mammalian target of rapamycin (mTOR) inhibitor (57). However, this substance is also associated with weight loss, particularly in women. This impact is possibly due to a decrease in food intake, including fat and protein, induced by the central nervous system, along with an increase in fat oxidation and mobilization. In skeletal muscles, glucose uptake and oxidation might be decreased, potentially leading to cachexia and muscle atrophy. Such findings are of significant importance for PKD patients undergoing immunosuppressive mTOR inhibitory therapy.

Ryu et al. demonstrated in a cross-sectional study that adopting the Dietary Approaches to Stop Hypertension (DASH) dietary pattern can help protect muscle strength in PKD patients. Therefore, a DASH diet might be effective in maintaining muscle strength and preventing sarcopenia among patients with ADPKD (58).

3.4 Kidney stone

Kidney stone disease is one of the most common benign diseases of the urinary system. A recent study points to a strong correlation between kidney stones and sarcopenia and that sarcopenia is an independent risk factor for kidney stones (59). Another study also noted that the risk of developing kidney stones decreased with an increase in the muscle-fat ratio (60). However, more research is needed to confirm these studies as they were all cross-sectional studies from the same database and did not look more closely at the relationship between stone composition, stone location, stone size and sarcopenia.

4 Sarcopenia and malignant diseases of the urinary system

4.1 Bladder cancer

Bladder cancer is one of the most common malignant tumors of the urinary system. Worldwide, the incidence of bladder cancer ranks 10th among malignant tumors, and the incidence in men is four times higher than that in women (61). Bladder cancer is categorized into

non-muscle-invasive (NMIBC) and muscle-invasive (MIBC) (62). These two subtypes are treated differently and have different prognoses. Treatment of NMIBC includes transurethral cystectomy of the bladder tumor and postoperative intravesical instillation of chemotherapeutic agents or immunotherapy (63). Radical cystectomy and pelvic lymphadenectomy are considered the gold standard for the treatment of MIBC and high-grade NMIBC, which may be followed by chemotherapy or neoadjuvant chemotherapy (64).

Mechanistically, BCa has been shown to induce an inflammatory microenvironment through the release of cytokines including TNF- α (65, 66). Up-regulation of the ATP-ubiquitin-protein pathway may also promote protein degradation and tissue wasting. In addition, animal models have demonstrated that BCa also affects mitochondrial phospholipid dynamics and overall mitochondrial function that influences skeletal muscle activity (8, 67). PI3K/Akt signaling plays a key role as a general regulator of skeletal muscle homeostasis (including protein synthesis and degradation) in skeletal muscle tissues. Multiple factors (e.g., TNF- α and IL-6) can promote skeletal muscle depletion by inhibiting the PI3K/Akt signaling pathway in cancer cachexia. In addition, oxidative stress promotes skeletal muscle depletion by increasing protein degradation and inducing myofiber apoptosis through damage to mitochondrial DNA (68, 69). Therefore, decreasing the secretion of associated factors and reducing inflammation are possible therapeutic ideas.

From a therapeutic aspect, sarcopenia is a strong adverse prognostic factor in patients with a variety of cancers including uroepithelial carcinoma (68). Chemotherapy regimens for BCa may further accelerate muscle wasting and lead to weight loss, e.g., cisplatin may cause muscle dysfunction by altering a variety of mechanisms including the ubiquitin-protein pathway, calcium homeostasis, mitochondrial damage, and cytokine upregulation (70). For patients treated with neoadjuvant chemotherapy, Tobias Tuse Dunk Hansen et al. observed a higher prevalence of skeletal sarcopenia in patients receiving NAC compared with patients undergoing surgery alone or in combination with NAC (71). Timothy D. Lyon et al. demonstrated that patients with sarcopenia who received neoadjuvant chemotherapy prior to radical cystectomy were associated with poorer CSS, suggesting that that sarcopenia is associated with NAC prognosis, but this does not suggest that skeletal muscle reduction is significantly associated with pathologic response to chemotherapy. Pierre Regnier et al. showed that skeletal muscle reduction was an independent predictor associated with risk of renal damage during NAC and early postoperative complications after RC (72).

Triple therapy (TMT) is a well-established alternative to radical cystectomy (RC) for patients with muscle-invasive bladder cancer (MIBC) seeking to preserve their native bladder or who are inoperable due to comorbidities. Fukushima et al. demonstrated through a literature response that sarcopenia does not affect the response and prognosis of triple therapy in patients with MIBC on bladder-preserving therapy. However, the effect of sarcopenia on the complication rate of bladder preserving therapy is uncertain due to limited evidence (73, 125). Liu et al. showed that both sarcopenia and a high systemic immunoinflammatory index (SII) were useful predictors of response to intravesical BCG in intermediate- and high-risk NMIBC patients (74). Intermediate- and high-risk NMIBC patients with sarcopenia or high SII at diagnosis are associated with poorer RFS, and the combination of sarcopenia and SII may be a better predictor of RFS. Ferini et al. demonstrated that sarcopenia could not be considered a negative prognostic factor for elderly patients with MIBC receiving radiotherapy (75). Stangl-Kremser et al. also concluded that that sarcopenia has no prognostic effect on

survival in patients with high-risk urothelial carcinoma of the bladder undergoing radiotherapy (76). Thus, radiotherapy is a viable and effective option for these patients, especially if surgery is not indicated.

Not only that, but there is a potential impact of sarcopenia on the surgical management of bladder cancer patients. Several studies have reported the prognostic role of skeletal muscle reduction in patients undergoing radical cystectomy for bladder cancer. Studies have shown that skeletal muscle reduction is a significant predictor of cancer-specific survival (CSS) and overall survival (OS). Psutka et al. demonstrated, for the first time, that skeletal muscle reduction was an independent predictor of poor CSS and OS in bladder cancer. Patients with skeletal muscle reduction had lower 5-year CSS and OS rates than non-skeletal muscle reduction patients (49% vs. 72% for CSS and 39% vs. 70% for OS) (77). Similar results were reported in the studies by Shimpei Yamashita and Roman Mayr et al. (78, 79). In conclusion, it has been shown through most studies that skeletal sarcopenia is an important factor in the poor prognosis of patients undergoing radical cystectomy for bladder cancer (80, 81).

4.2 Prostate cancer

Prostate cancer is one of the most common malignant tumors of the male reproductive system, the second most common cancer in men and the fifth leading cause of cancer death (82). The prognostic value of sarcopenia in advanced prostate cancer has been evaluated, and the study showed that sarcopenia was significantly associated with progression-free survival in advanced prostate cancer (HR = 1.61, 95% CI: 1.26, 2.06, $p < 0.01$), but sarcopenia did not have a significant effect on overall survival and cancer-specific survival, suggesting that sarcopenia is an important prognostic factor for progression-free survival in patients with advanced PCa (81).

Androgen deprivation therapy (ADT) stands as the current treatment modality for metastatic prostate cancer; however, the majority of cases ultimately advance toward desmoplasia-resistant prostate cancer typified by the escalation of prostate-specific antigen levels and the progression of both primary and metastatic sites. Given the chronic nature of prostate cancer, these therapies tend to be administered over an extended duration, thereby establishing a strong association between long-term chemotherapy and the development of sarcopenia. Consequently, the urgent need to investigate the relationship between chemotherapy for prostate cancer and sarcopenia emerges as a paramount clinical concern that significantly impacts the prognosis of patients undergoing chemotherapy for prostate cancer. ADT therapies significantly impact the human body, inducing side effects such as skeletal sarcopenia and bone loss, notably among the elderly demographic (83). Active intervention can successfully mitigate these adverse effects posed by ADT therapy. On a mechanistic level, sarcopenia accelerated by hormone deprivation therapy is a result of prostate tumor-derived growth differentiation factor 11 (GDF11) signaling from the tumor to the muscle tissue (84). Liver-targeted testosterone therapy (LTTT) presents a promising, simplistic approach to prevent sarcopenia and bone loss during ADT (85). Furthermore, Zhang and his team proposed the potential of eldecalcitol to counteract sarcopenia caused by ADT treatment, utilizing the PI3K/AKT/FOXOs signaling pathway in a constructed mouse model (86). Also, a resistance-focused exercise regimen proves effective in ameliorating sarcopenia in men with prostate cancer undergoing ADT (87, 88).

The impact of sarcopenia, a negative prognostic factor, on prostate cancer treated with docetaxel or abiraterone acetate has been confirmed

through a series of clinical trials (89–92). Additional research implies that sarcopenia may interact with excessive visceral fat accumulation, thereby adversely affecting early urinary function following I-125 low-dose brachytherapy against prostate cancer (93). However, it is important to note that such acceleration in sarcopenia was not observed in men with metastatic castration-resistant prostate cancer (mCRPC) undergoing Ra-223 treatment (94). Furthermore, a related study that explored the correlation between sarcopenia in castration-resistant prostate cancer (CRPC) and treatment outcomes with androgen receptor axial therapy (ARATs) revealed that the latter could potentially offer enhanced efficacy among CRPC patients with sarcopenia, compared to those devoid of it (95).

Furthermore, the prognosis of prostate cancer patients who are undergoing surgical intervention varies significantly between those with sarcopenia and those sans sarcopenia. According to research conducted by Mitsui Y et al., patients diagnosed with sarcopenia have reportedly expressed greater clinical dissatisfaction concerning postoperative urinary function than their counterparts lacking this condition, in the context of robot-assisted radical prostatectomy (96). It is plausible that sarcopenia might serve as a predictive factor for postoperative erectile dysfunction following robot-assisted radical prostatectomy (97). Mason et al. showed that sarcopenia did not predict biochemical recurrence in patients undergoing radical prostatectomy (98). In contrast, Pak et al. showed that preoperative sarcopenia led to a higher risk of biochemical recurrence in patients undergoing radical prostatectomy (99). More clinical samples are needed to demonstrate the link between sarcopenia and biochemical recurrence of prostate cancer.

4.3 Renal cell cancer

Globally, Renal Cell Carcinoma (RCC) is ranked as the sixth and tenth most prevalent forms of cancer in males and females, respectively (100). A meta-analysis highlighted a significant correlation between reductions in skeletal muscle (sarcopenia) and Overall Survival (OS), Cancer-Specific Survival (CSS), and Progression-Free Survival (PFS) of RCC patients regardless of variables like age, tumor location, and stage (101). Notably, the study also suggested a persistent and potentially intensifying implication of skeletal muscle reduction on all-cause mortality and cancer-specific mortality throughout prolonged follow-ups in RCC. Nonetheless, this inference may be skewed, as the researchers could not unequivocally attribute the survival outcomes to tumor development or skeletal muscle reduction, a challenge that has baffled previous studies as well. Another meta-analysis reiterated these inconclusive results, showing no significant difference in PFS between sarcopenic and non-sarcopenic RCC patients. Consequently, supplemental data-oriented studies are necessitated (102).

Sarcopenia is a significant prognostic factor in metastatic renal cell carcinoma (103). In patients diagnosed with metastatic renal cell carcinoma undergoing chemotherapy, the presence of skeletal sarcopenia could potentially heighten the risk of treatment-related toxicity while simultaneously shortening survival rates. This finding originates from a retrospective analysis conducted by Hideto Ueki et al., utilizing the Skeletal Muscle Minority Index (SMI) as a predictor for the therapeutic efficacy of nivolumab in the treatment of this disease. Concurrently, the study draws parallels between sarcopenia - diagnosed via the Psoas Muscle Index (PMI) - and an unfavorable prognosis in patients diagnosed with RCC. It is important to underscore, however, the considerable variation in diagnosis rates of sarcopenia and the lack

of a demonstrable association between sarcopenia, as identified by SMI, and prognosis (104, 105). During the course of cabozantinib therapy, it has been observed that a considerable proportion of patients manifested significant early skeletal muscle deterioration correlating to an unfavorable progression-free survival (PFS) (106, 107). Furthermore, myasthenia gravis emerged as a crucial prognostic indicator in metastatic renal cell carcinoma (mRCC) patients undergoing primary treatment with sunitinib (108). Additionally, a study by S. Antoun et al., demonstrated that patients displaying sarcopenia were prone to encounter dose-limiting adverse events during targeted therapy regimens, as indicated by clinical data presenting skeletal muscle loss as a predictor of such therapies' toxicity. Notably, a body mass index (BMI) less than 25 kg/m² coupled with diminished muscle mass emerged as a significant predictor of targeted agents' toxicity (109–111). Intriguingly, sarcopenia was found to predict the response to Interleukin-2 (IL-2) treatment in metastatic RCC scenarios (112).

Jongpil Lee and collaborators explored the correlation between the decrement in skeletal muscle mass and the overall survival rate in patients undergoing radical surgery for localized renal cell carcinoma (113). The study implicates that sarcopenia in conjunction with a modified Glasgow scale could serve as a more robust prognostic marker following the surgical procedures for localized renal cell carcinoma (114). Additionally, limited mobility, when coupled with serum albumin levels, could also prefigure the prognosis after surgery (115, 116). A separate study by Pranav Sharma et al. postulated that hypokinesia might act as a potential prognostic indicator for overall survival subsequent to a nephrectomy for metastatic renal cell carcinoma (117, 118). Moreover, a study conducted on a Chinese cohort further substantiated that sarcopenia post nephrectomy is indicative of a poor prognosis (119). Additionally, a significant correlation has been found between sarcopenia and an increased risk of recurrence of clear cell renal cell carcinoma in male patients (120). Consequently, emergent prognostic tools, including the novel index derived from the integration of albumin-globulin score and sarcopenia, known as the CAS, have been developed to forecast the progression of renal cancer subsequent to a surgical intervention (121). Furthermore, the low ratio of creatinine to cystatin-C (Cr/Cys-C) could potentially function as a serum biomarker indicating the development of sarcopenia in patients undergoing nephrectomy treatment for RCC (122).

4.4 Germ cell carcinoma of the testis (GCT)

GCT is a common solid tumor among young men that is sensitive to chemotherapy and has a high cure rate. Patients with GCT are characterized by their general youth and are therefore unlikely to have aging-related muscle loss at the time of diagnosis. Phuong et al. showed that in patients with testicular germ cell carcinoma (GCT) receiving cytotoxic chemotherapy, decreased skeletal muscle mass during chemotherapy was independently associated with a higher incidence of chemotherapy-related adverse events (123). Therefore, intervening in GCT patients with decreased skeletal muscle mass during chemotherapy may be able to reduce the incidence of adverse events. In addition, a prospective study found that reduced muscle mass was significantly associated with poor postoperative prognosis in patients with metastatic germ cell tumors (mGCTs) receiving postoperative chemotherapy who underwent post-chemotherapy retroperitoneal lymphadenectomy (PC-RPLND) after oncolytic chemotherapy, and that further evaluation of the preoperative nutritional status of this population may be helpful in reducing morbidity after PC-RPLND (124).

5 Conclusion

In recent years, there has been an increasing amount of research on skeletal sarcopenia and urologic diseases, and the importance of sarcopenia in urologic diseases has received increasing attention. Sarcopenia and urologic diseases interact with each other; urologic diseases cause sarcopenia, and sarcopenia aggravates the condition of the original disease, thus falling into a vicious circle. This review systematically analyzes the relationship between sarcopenia and urological diseases and reveals the potential role of sarcopenia in the development and progression of urological diseases. Our analysis suggests that sarcopenia is not only a common complication of urologic diseases, but may also be an important predictor of disease progression and poor prognosis. And this review highlights potential interventions for sarcopenia, such as nutritional support and physical activity, which may help improve the prognosis of patients with urologic diseases. Although our review provides valuable insights, we also recognize that limitations exist. First, the included studies were diverse in design, which may have contributed to the heterogeneity of results. Second, most of the studies were cross-sectional, and future studies need to be further validated using more uniform study designs and methods, as well as prospective studies with large samples. Early screening, diagnosis, and intervention of sarcopenia in urologic diseases is important. Therefore, we suggest that recommendations for screening and management of sarcopenia be included in clinical guidelines for urologic diseases. In conclusion, this review provides new perspectives for understanding the role of sarcopenia in urologic diseases and provides valuable information for future research and clinical practice.

Author contributions

TZ: Data curation, Writing – original draft. WM: Conceptualization, Data curation, Methodology, Writing – review & editing. MH: Data curation, Methodology, Writing – review & editing. QY: Writing – review & editing. XP: Writing – review & editing. JJ: Writing – review & editing. JQ: Conceptualization, Supervision, Writing – review & editing. JW: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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