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The prognostic value of sarcopenia in patients with surgically treated urothelial carcinoma: A systematic review and meta-analysis

Xu Hu [a,1], Wei-Chao Dou [a,1], Yan-Xiang Shao [a], Jian-Bang Liu [a], San-Chao Xiong [a], Wei-Xiao Yang [a], Xiang Li [b,*]

[a] West China School of Medicine/West China Hospital, Sichuan University, Chengdu, 610041, PR China
[b] Department of Urology, West China Hospital, West China Medical School, Sichuan University, 37 Guoxue Street, Chengdu, 610041, PR China

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ABSTRACT

Objective: Sarcopenia is associated with unfavorable prognosis in patients undergoing surgical treatments of the respiratory tract, gastrointestinal tract and urinary tracts. We summarized all available evidence to investigate the prognostic value of sarcopenia in patients with surgically treated urothelial carcinoma (UC).

Methods: We conducted a comprehensive study search up to January 2019, searching the online database Embase, PubMed and Cochrane Library. The hazard ratio (HR) and 95% confidence interval (CI) were extracted from the studies.

Results: A total of 12 research consisting of 2075 patients were enrolled in the quantitative synthesis. We observed that UC patients with sarcopenia had a worse OS (HR = 1.87; 95%CI 1.43–2.45; P < 0.001) and CSS (HR = 1.98; 95%CI 1.43–2.75; P < 0.001). Stratified by tumor, sarcopenia is also an unfavorable factor for OS and CSS in patients with upper tract urothelial carcinoma (UTUC) or urothelial carcinoma of bladder (UCB).

Conclusion: Sarcopenia is an unfavorable factor for OS and CSS in patients with surgically treated UC. Besides, stratified by tumor, the results of patients with UTUC or UCB are consistent with previous results. More prospective studies are required to validate our findings.

1. Introduction

Urothelial carcinoma (UC) remains to be one of the most causes of cancer-related death, with an estimated 0.55 million new cases and 0.2 million deaths worldwide in 2018 [1]. UC mainly consists of bladder cancer (BC) and upper tract urothelial carcinoma (UTUC), locating in the lower and upper urinary tract, respectively [2]. BC occupies 90%–95% of UC and is the most common urinary tract cancer, while UTUC is rare and takes up 5%–10% of UC [2–4]. Although radical cystectomy (RC) is the standard treatment for muscle-invasive bladder cancer (MIBC) and high-risk non-muscle-invasive bladder cancer (NMIBC) with curative intent, RC only provides 5-year overall survival (OS) rate of approximately 60% [3–5]. Similarly, radical nephroureterectomy (RNU) remains the standard management for non-metastatic UTUC, but the prognosis of patients undergoing RUN is relatively poor, 20%–30% would have distant metastasis and eventually die of cancer [2,6,7].

Therefore, the identification of high-risk patients as adjuvant therapies is necessary to improve survival. Currently, an increasing number of studies investigated various prognostic factors of UC to stratify the risk of patients, such as pathological T stage, tumor grade, lymphovascular invasion (LVI), performance status, body mass index (BMI), nutritional status, systemic inflammation and others [2–4,7–10].

Involuntary weight loss and cachexia have long been associated with poor survival [11]. Sarcopenia, a concept reflecting the scarcity of skeletal muscle mass, develops as a physiological change during the development of cancer cachexia [11–13]. Reportedly, sarcopenia is associated with unfavorable prognosis in patients undergoing surgical treatments of the respiratory tract, gastrointestinal tract and urinary tracts [14–16]. However, in patients with UC treated surgically, the prognostic value of sarcopenia remains controversial. Some studies found that sarcopenia is not associated with survival of patients with UC [17–19], while other studies revealed the

* Corresponding author.
E-mail address: xiangli.87@163.com (X. Li).
[1] These authors contributed equally to this article.

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prognostic value of sarcopenia in patients with UC [20–22]. Therefore, in order to explore the prognostic value of sarcopenia in patients with UC, we carried out this systematic review and meta-analysis. We summarized all available evidence to investigate the prognostic value of sarcopenia in patients with surgically treated UC.

2. Method

2.1. Literature search strategy

We performed this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [23]. We conducted a comprehensive study search up to January 2019, searching the online database Embase, PubMed and Cochrane Library. We used the following items: urothelial carcinoma (bladder, urothelial, cancer, carcinoma or tumor) and sarcopenia (skeletal muscle index, muscle mass, muscle strength, muscle depletion or muscle insufficiency) as keywords or Mesh. We also reviewed the reference lists of all available studies in case of missing records. Two investigators screened the literature independently, any conflicts were resolved by discussing or consulting another one.

2.1. Study selection

We enrolled studies according to the following inclusion criteria: 1) population-based studies; 2) patients were diagnosed urothelial carcinoma and treated surgically; 3) sarcopenia was identified based on skeletal muscle mass or psoas muscle mass using images; 4) evaluated the prognostic value of preoperative sarcopenia, 5) reported available data of survival such as overall survival (OS) or cancer-specific survival (CSS). The following studies were excluded: 1) non-English language; 2) patients were not treated surgically; 3) did not define sarcopenia accurately, 4) did not evaluate the prognostic value of sarcopenia, 5) no available data for analysis. We also excluded conference abstracts because of the lack of detailed information. As for duplicated records, we only included the most recent and informative study.

2.3. Data extraction and quality assessment

Two authors extracted the following items from all eligible studies independently: the name of the author, study design, sample size, diseases, treatments, age, the definition of sarcopenia, duration of follow-up. As for the outcome, we extracted hazard ratio (HR) and 95% confidence interval (CI) from the studies. If the HRs and 95%CI were not reported, we could estimate the HR and 95%CI according to the method by Tierney [24]. We used the Cochrane Collaboration Risk of Bias Tool to evaluate the quality of randomized-control studies [25]. Concerning the observational studies, we applied the Newcastle-Ottawa Quality Assessment Scale (NOS). And studies with a score of no less than 7 were regarded as good quality.

2.4. Statistical analysis

All statistical analyses were performed using STATA version 12 (StataCorp, College Station, TX, USA). The endpoints of OS and CSS were characterized by HR and 95%CI. We used Q and I^2 statistics to identify the heterogeneity among studies. A fixed-effect model was applied when no apparent heterogeneity was observed ($P < 0.10$ or $I^2 > 50\%$); otherwise, a random-effect model was applied [26]. We also performed subgroup analyses based on available data. Furthermore, we conducted sensitivity analyses to check the stability of the pooled results. Regarding the publication bias, we used Egger's test and Begg's test. A two-sided P-value <0.05 was defined as a statistical difference. When no meta-analysis could be conducted, we only described the study results.

3. Results

3.1. Literature search

The literature search strategy yield 394 literature, 30 of which were duplicated records. After screening titles and abstracts of the remaining 364 research, 55 research was accepted for further review. Finally, a total of 12 research consisting of 2075 patients were enrolled in the quantitative synthesis [17–22,27–32]. A flow diagram of the literature search and selection is shown in Fig. 1.

3.2. Clinical characteristic of enrolled studies

All studies were retrospective and published in the recent five years. Five studies involved patients with non-metastatic UTUC, which were treated by RUN [17,18,21,27,29]. The remaining 7 studies enrolled patients with non-metastatic urothelial carcinoma of the bladder (UCB), which underwent RC [19,20,22,28,30–32]. The sample sizes of eligible studies are relatively small, and only 4 studies enrolled more than 200 patients. The patients' age of included studies was relatively large, and the median age ranged from 66.6 to 73. All studies identified sarcopenia by measuring skeletal muscle and psoas muscle at the level of the L3 using computed tomography (CT) images. One study did not report the number of patients with sarcopenia [17]. To sum up, 51.9% (1012/1950) patients had sarcopenia. Ten studies evaluated the association between OS and sarcopenia, and 9 studies investigated the actual impact of sarcopenia on CSS, only one study reported the recurrence-free survival (RFS). Nearly all studies except one had a relatively long follow-up [19]. All studies were evaluated based on NOS and considered as high quality. The detailed information was summarized in Table 1.

3.2. Overall survival

Regarding 10 studies comprising 1816 patients, the incidence of sarcopenia was found to be 897 cases out of 1816 (49.4%). We observed that patients with sarcopenia had a worse OS compared with those without sarcopenia, the pooled HR was 1.87 (95%CI, 1.43–2.45; $P < 0.001$; Fig. 2A). Moderate heterogeneity was revealed ($I^2 = 54.3\%$; $P = 0.016$), so we used the random-effect model. Stratified by tumors, sarcopenia is also associated with inferior OS in patients with UTUC and UCB, the HRs were 2.53 (95% CI, 1.09–5.85; $P = 0.03$) and 1.63 (95%CI, 1.37–1.94; $P < 0.001$), respectively.

3.4. Cancer-specific survival

Nine studies incorporating 1513 patients investigated the actual impact of sarcopenia on CSS. As present in Fig. 2B, we demonstrated that sarcopenia is associated with poor CSS, the pooled HR is 1.98 (95%CI, 1.43–2.75; $P < 0.001$). Because of heterogeneity among studies ($I^2 = 39.4\%$; $P = 0.095$), we applied the random-effect model. Stratified by tumors, sarcopenia is also associated with poor CSS in patients with UTUC and UCB, the HRs were 2.61 (95%CI, 1.03–6.64; $P = 0.044$) and 1.73 (95%CI, 1.35–2.21; $P < 0.001$), respectively.

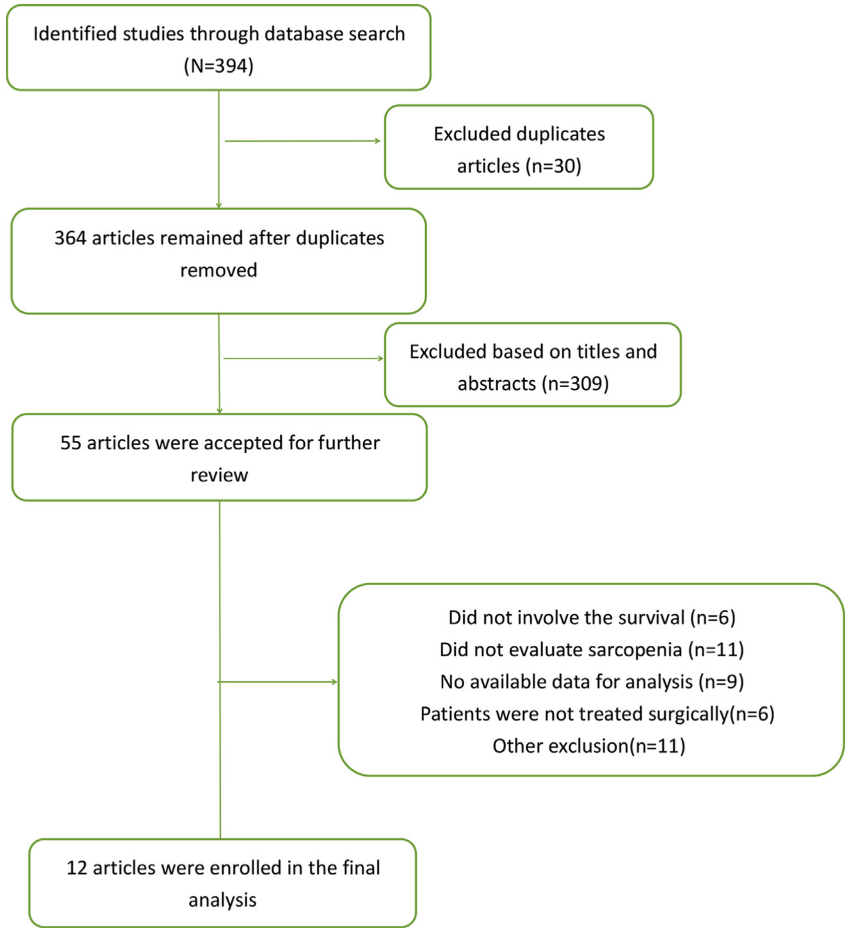

Fig. 1. Flow diagram of literature search.

3.5. Sensitivity analyses and publication bias

We conducted sensitivity analyses by omitting each study sequentially. After removing each study sequentially, we did not detect relatively change, which indicated the robustness of our results (Fig. 3). Concerning publication bias, we did not observe significant publication bias of OS and CSS based on the Egger's test (OS: P = 0.081; CSS: P = 0.152) and Begg's test (OS: P = 0.119; CSS: P = 0.721; Fig. 4).

3.6. Subgroup analyses

We carried out subgroup analyses stratified by tumor, measurement of sarcopenia and regions. Stratified by tumor, sarcopenia is associated with inferior OS and CSS in patients with UTUC, the pooled HRs were 2.53 (95%CI 1.09–5.85) and 2.61 (95%CI 1.03–6.64). And for patients with UCB, the sarcopenia is also an unfavorable factor for OS (HR = 1.63; 95%CI 1.37–1.94) and CSS (HR = 1.73; 95%CI 1.35–2.21). The subgroup analyses stratified by geographical regions showed that Asian patients with sarcopenia had a decreased OS and CSS (HR = 2.63; 95%CI 1.37–5.07, HR = 2.21; 95%CI 1.40–3.48, respectively). Similarly, as for the non-Asia regions, the sarcopenia was associated with inferior OS (HR = 1.63; 95%CI 1.37–1.94) and CSS (HR = 1.65; 95%CI 1.12–2.43). The sarcopenia was identified by different measurements. Measured by skeletal muscle, the patients with sarcopenia had a worse OS (HR = 1.85; 95%CI 1.30–2.64) and CSS (H = 2.14; 95%CI 1.24–3.70) compared with those without sarcopenia. For sarcopenia identified by skeletal muscle and adjusted for body mass index (BMI), sarcopenia is also regarded as an unfavorable factor for OS (HR = 2.31; 95%CI 1.44–3.70) and CSS (HR = 2.22; 95% CI 1.42–3.47). However, when measured by psoas muscle, the pooled results suggested that there was no significant association between sarcopenia and OS (HR = 1.46; 95%CI 0.79–2.68), CSS (HR = 1.26; 95%CI 0.47–3.38). We summarized relevant information in Table 2.

4. Discussion

The term “sarcopenia” was firstly described by Irwin Rosenberg in 1989 and means “sarx for flesh and penia for loss” in Greek, describing the age-related decrease of muscle mass [33]. According to the recommend of European Working Group on Sarcopenia in older people (EWGSOP), the diagnosis of sarcopenia should be based on the co-occurrence of low muscle mass and low muscle function (strength or performance) [34]. In cancer cachexia, sarcopenia is defined as low skeletal muscle mass at the level of L3 [13]. More and more studies evaluated the relationship between sarcopenia and outcome of various malignancies [14–16].

In this study, we focused on the prognostic value of sarcopenia in patients with UC. We demonstrated that sarcopenia is correlated with poor OS and CSS in patients with UC. Stratified by tumor, for patients with UTUC or UCB, there was also a significant association between sarcopenia and survival. Concerning the difference of regions, we divided patients into Asia and non-Asia, and sarcopenia is regarded as an unfavorable factor in both subgroups. While for

Table 1
Clinical characteristics of included studies.

Study/ Published year	Enrollment date/Location	Study type	Treatment	Tumor	Number of patients	Age Median (IQR)	Sarcopenia definition	sarcopenia	Outcomes	Follow-up Median IQR (months)	NOS
Itami 2019	October 1995 and December 2016/Japan	Retrospective	RUN	non-metastatic UCUT	125	Median (Range) 72 (38–90)	The cross-sectional area of the skeletal muscle and psoas major muscle at the level of the L3. SMI of <43 cm^2/m^2 among men with a BMI of <25 kg/m^2, <53 cm^2/m^2 for men with a BMI of >25 kg/m^2, and <41 cm^2/m^2 for women. PMI <6.36 cm^2/m^2 for men and <3.92 cm^2/m^2	NA	OS CSS	51 (6–227)	7
Mayr 2018	2004 and 2014/ Germany	Retrospective	RC	non-metastatic UCB	500	72 (65.00 –78.00)	The cross-sectional skeletal muscle surface (cm^2) at the level of the L3. SMI of <43 cm^2/m^2 for men with BMI <25 kg/m^2, SMI <53 cm^2/m^2 for men with BMI≥25 kg/m^2, and SMI <41 cm^2/m^2 for women.	189 (37.8%)	OS CSS	35 (20–58)	8
Kocher 2018	2002 and 2016/ US	Retrospective	RUN	non-metastatic UTUC	100	Mean (SD) 67.5 (10.2)	The cross-sectional skeletal muscle area at the L3 level. SMI <55 cm^2/m^2 for men and <39 cm^2/m^2 for women	42 (42%)	OS	Mean (Range) 31.2 (5.0–122.0)	8
Anno 2018	2003 and 2014/ Japan	Retrospective	RUN	non-metastatic UTUC	123	<70 years 44 (35.8%)	The area of skeletal muscle at L3. SMI<43 cm^2/m^2 among men with a BMI <25, SMI <53 cm^2/m^2 among men with a BMI ≥25, and SMI <41 cm^2/m^2 among women	50 (40.7%)	CSS	4.49 years	7
Miyake 2017	January 2006 and July 2016/ Japan	Retrospective	RC	MIBC	117	72 (61–77)	The cross-sectional area of the psoas major muscle at the level of L3. PMIs <6.36 cm^2/m^2 for men and <3.92 cm^2/m^2 for women	23 (20%)	OS CSS	22 (10–64)	7
Ishihara 2017	October 2003 and December 2013/Japan	Retrospective	RUN	non -metastatic UCUT	137	Median (Range) 73.0 (39 –92)	The cross-sectional area of skeletal muscle at L3. SMI of <43 cm^2/m^2 among men with a BMI of <25 kg/m^2, <53 cm^2/m^2 among men with a BMI of >25 kg/m^2, and<41 cm^2/m^2 among women	90 (65.7%)	OS CSS RFS	Median (range) 34.7 (2.83–140.3)	7
Miyake 2017	January 2006 and October 2014/Japan	Retrospective	RC	non-metastatic UCB	89	71 (48–83)	The cross-sectional area of skeletal muscle at the level of L3. SMIs of <43 cm^2/m^2 for males with a BMI <25 kg/m^2; <53 cm^2/m^2 for males with a BMI ≥25 kg/m^2; and <41 cm^2/m^2 for females.	67 (75%)	OS CSS	29 (10–60)	7
Hirasawa 2016	March 2003 and January 2015/Japan	Retrospective	RC	non-metastatic UCB	136	Mean 68.6	The cross-sectional skeletal muscle area at the L3 level. SMI of <43 cm^2/m^2 for men with BMI<25 kg/m^2, SMI <53 cm^2/m^2 for men with BMI ≥25 kg/m^2, and SMI<41 cm^2/m^2 for women	65 (47.8%)	CSS	Mean 46.7	8
Fukushima 2016	November 2001 and February 2015/Japan	Retrospective	RUN	non-metastatic UTUC	81	Median (Range) 71 (41–87)	The cross-sectional areas of skeletal muscle at L3. SMI <43 cm^2/m^2 for males with BMI <25 kg/m^2, <53 cm^2/m^2 for males with BMI≥25 kg/m^2, and <41 cm^2/m^2 for females	47 (58%)	OS CSS	Median (Range) 41 (4 –170)	7
Psutka 2015	2000 and 2008/ US	Retrospective	RC	non-metastatic UCB	262	71 (63–78)	The cross-sectional skeletal muscle and adipose areas at L3. Male: SMI less than 55 cm^2/m [2], female: SMI less than 39 cm^2/m^2	177 (67.6%)	OS	6.3 (5.7–9.5)	8
Smith 2014	2008 and 2011/ US	Retrospective	RC	MIBC	200	Median 66.6	The cross-sectional area of the right and left psoas muscles at L3. 653 cm^2/m^2 for men, 523 cm^2/m^2 for women	121 (61%)	OS	Median 1.4 years	8
Psutka 2014	2000 and 2007/ US	Retrospective	RC	non-metastatic UCB	205	71 (63–78)	The cross-sectional area of all skeletal muscle at L3. SMI of <55 cm^2/m^2 for men and <39 cm^2/m^2 for women.	141 (68.8%)	OS CSS	6.7 (5.9 –10.2) years	8

RUN: radical nephroureterectomy; RC: radical cystectomy; UTUC: upper tract urothelial carcinoma; UCB: urothelial carcinoma of bladder; MIBC: muscle-invasive bladder cancer; IQR: interquartile range; SMI: skeletal muscle index; PMI: psoas muscle index; BMI: body mass index; NA: not available; OS: overall survival; CSS: cancer-specific survival; RFS: recurrence-free survival; NOS: Newcastle-Ottawa Quality Assessment Scale.

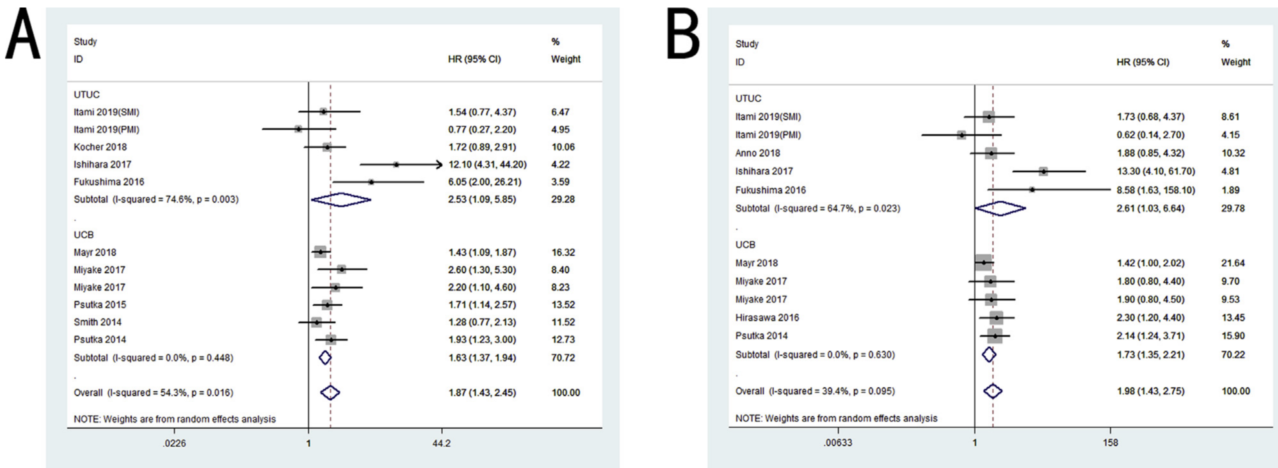

Fig. 2. The association between sarcopenia and A): OS; B): CSS in patients with UC.

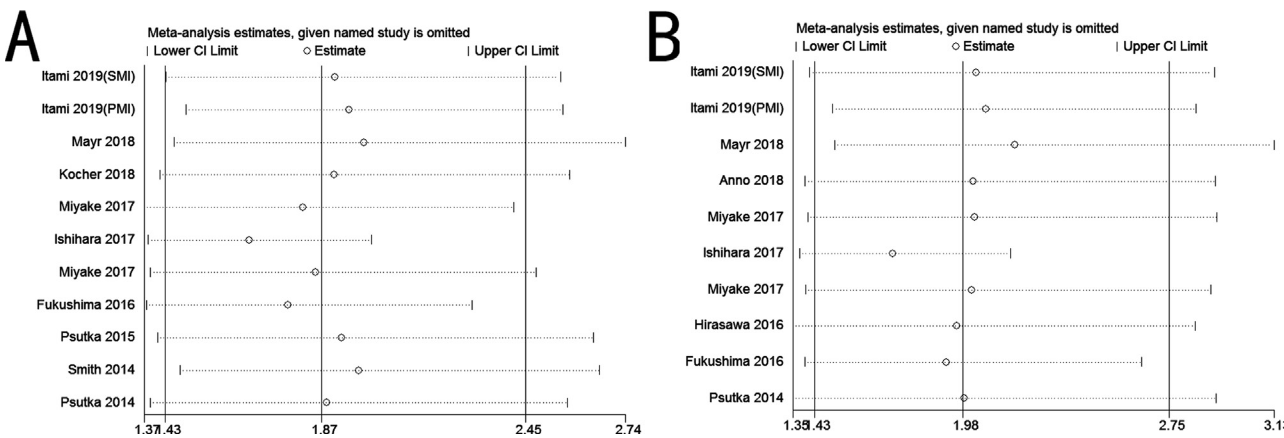

Fig. 3. Sensitivity analyses for A): OS; B): CSS.

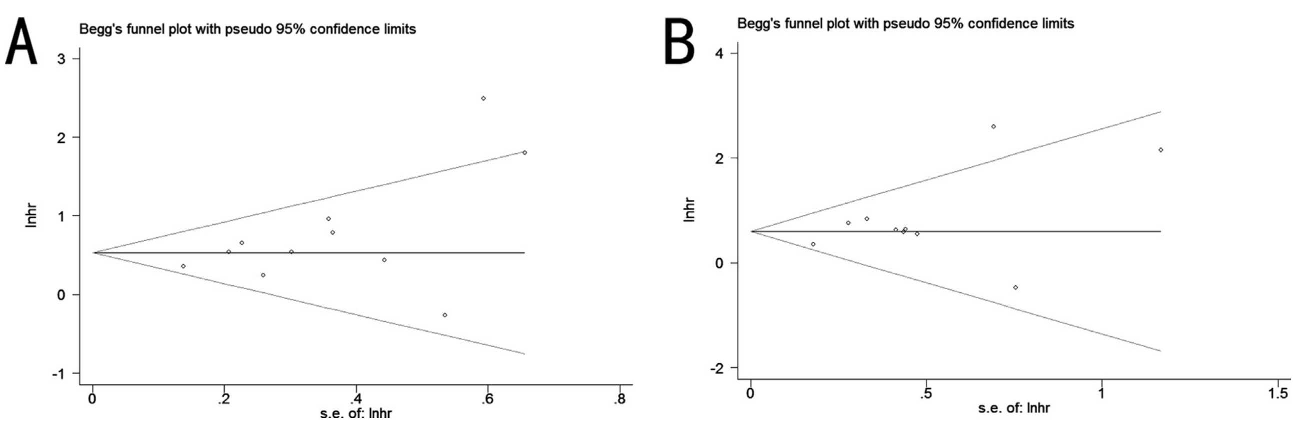

Fig. 4. Begg's funnel plot for A): OS; B): CSS.

different measurements of sarcopenia, sarcopenia is associated with inferior OS and CSS except for the psoas muscle subgroup. Furthermore, we conducted sensitivity analyses, and the adjusted results did not tend to alter. No publication bias was observed, which indicated the robustness of final results.

Our study suggested that sarcopenia is an unfavorable factor of survival in UC patients undergoing surgical resection. Our findings are consistent with previous studies. Deng et al. conducted a meta-analysis and found that sarcopenia was an independent predictor of poor OS in patients with surgically treated non-small cell lung cancer (HR = 2.85; 95%CI 1.67–4.86; P < 0.001) [15]. Besides, Psutka et al. included 389 patients with localized renal cell carcinoma, which were treated by radical nephrectomy, and demonstrated that sarcopenia was associated with poor CSS (HR 1.70; 95%CI

Table 2
Subgroup analyses of OS and CSS.

Outcome	Variable	Number of studies	Model	HR (95%CI)	I^2	P value of heterogeneity
OS	All	10	Random	1.87 (1.43–2.45)	54.3%	P = 0.016
tumor	UTUC	4	Random	2.53 (1.09–5.85)	74.6%	P = 0.003
	UCB	6	Random	1.63 (1.37–1.94)	0%	P = 0.448
measurement	Skeletal muscle	2	Random	1.85 (1.30–2.64)	0%	P = 0.761
	Skeletal muscle-adj	6	Random	2.31 (1.44–3.70)	70.2%	P = 0.005
	Psoas muscle	3	Random	1.46 (0.79–2.68)	53.2%	P = 0.118
regions	Asia	5	Random	2.63 (1.37–5.07)	66.7%	P = 0.01
	Non-Asia	5	Random	1.56 (1.30–1.86)	0%	P = 0.707
CSS	All	9	Random	1.98 (1.43–2.75)	39.4%	P = 0.095
disease	UTUC	4	Random	2.61 (1.03–6.64)	64.7%	P = 0.023
	UCB	5	Random	1.73 (1.35–2.21)	0%	P = 0.63
measurement	Skeletal muscle	1	Random	2.14 (1.24–3.70)	–	–
	Skeletal muscle-adj	7	Random	2.22 (1.42–3.47)	51.9%	P = 0.052
	Psoas muscle	2	Random	1.26 (0.47–3.38)	33.2%	P = 0.221
regions	Asia	7	Random	2.21 (1.40–3.48)	40.0%	P = 0.112
	Non-Asia	2	Random	1.65 (1.12–2.43)	34.4%	P = 0.217

Skeletal muscle-adj: adjust for body mass index; UTUC: upper tract urothelial carcinoma; UCB: urothelial carcinoma of bladder; OS: overall survival; CSS: cancer-specific survival; HR: hazard ratio; CI: confidence interval; -: Not available.

1.01–2.85; P = 0.047) and OS (HR 1.48; 95%CI 1.02–2.15; P = 0.039) [35]. Mayr et al. enrolled 500 patients undergoing RC and observed that sarcopenia was an independent predictor of OS (HR = 1.43; 95%CI 1.09–1.87; P = 0.01) and CSS (HR = 1.42; 95%CI, 1.00–2.02; P = 0.048) [20]. Pustka et al. revealed that sarcopenia was an unfavorable factor of OS (HR = 1.71; 95%CI 1.14–2.57; P = 0.01) in a single-institution cohort of 262 patients with RC treated UCB [30]. Ishihara et al. involved 137 UTUC patients undergoing RUN, and the results suggested that sarcopenia was correlated with OS (HR = 12.1; 95%CI 4.31–44.2; P < 0.001) and CSS (HR = 13.3; 95%CI 4.10–61.7; P < 0.001) [21]. Except for the mortality outcomes, sarcopenia is also associated with tumor relapse including recurrence-free survival (RFS) or progression-free survival (PFS). Studies which focused on RFS or PRS were few. Ishihara et al. observed that sarcopenia negatively affected RFS (HR = 5.18; 95%CI 2.36–12.7; P < 0.001) among patients who were undergoing RUN for UTUC [21]. Besides, they also found that sarcopenia was associated with decreased PFS in patients with metastatic renal cell carcinoma [36]. Furthermore, sarcopenia may have an effect on survival in patients with inoperable tumors. Taguchi et al. reported that sarcopenia was associated with CSS in patients with metastatic UC (HR = 2.07; 95% CI 1.01–4.67; P = 0.045) [37]. And Fukushima et al. found that sarcopenia is an unfavorable factor for OS in patients with advanced UC (HR = 3.36; 95%CI 1.90–6.08; P < 0.001) [38].

The relationship between sarcopenia and poor survival in patients with malignancies remains unclear. Hirasawa et al. found that more patients with sarcopenia were elderly (P < 0.001) and had decreased serum albumin (P < 0.001), hemoglobin (P = 0.002) and relatively higher serum levels of CRP than those without sarcopenia. These factors might be related to cachexia, and they have been established as potential factors for patients with UC. Muscle wasting is the result of a combination of decreased protein synthesis and increased protein degradation [39]. And recent studies have shown a role of skeletal muscle as a secretory organ of cytokines and other peptides (interleukin (IL)-6, IL-8, IL-15, Brain-Derived Neurotrophic Factor (BDNF), and Leukemia Inhibitory Factor), which were associated with inflammation [40]. These results suggested that systematic inflammatory response or nutritional disorder exists in the patients with sarcopenia, which may directly promote progression of tumor and affect the response to treatments. As results, further studies are needed to explore the relationship between sarcopenia and reduced survival.

The definition of sarcopenia is still controversial and slightly different definitions were used in studies. Some studies used skeletal muscle area, and some studies measured skeletal muscle are and adjusted for BMI, while others total psoas muscle area. In general, people with higher skeletal muscle mass present higher BMI. However, some people with high BMI may have low skeletal muscle mass because of excessive fat, which is regarded as "sarcopenia obesity" [16]. Thus, it is necessary to take obesity into consideration when identify sarcopenia. With the prevalence of obesity increasing, skeletal muscle mass adjusted for BMI may be more accurate and appropriate.

We conducted subgroup analyses based on measurements. We found that except for the psoas muscle subgroup, sarcopenia is associated with inferior OS and CSS in the other two subgroups. While in the psoas muscle subgroup, only two studies were enrolled. Japanese investigators have set psoas muscle index (PMI) cutoff value as 36 cm^2/m^2 for males and 3.92 cm^2/m^2 for females based on healthy young adult undergoing living donor liver transplantation [41]. In this study, the PMI cutoff values were established at the mean PMIs minus 2 standard deviations of the younger donors (<50 years). However, this definition and cutoff value need validation for application. Some studies evaluated the prognostic value of skeletal muscle density. Skeletal muscle density not only reflect the skeletal muscle mass but also others such as fat. A low skeletal muscle density reflects more fat infiltration in the skeletal muscle, which is thought to be associated with skeletal quality [13,16]. Therefore, we did not include relevant studies in our analysis. And the cut-off values of sarcopenia were also different. Obesity is defined with different cutoff values of BMI based on ethnicity. We should also consider the ethnicity difference when evaluated the sarcopenia. In different regions, the body composition is also different. Recently, some studies found that skeletal muscle index (SMI) cutoff values determined by Western populations are unfit for Asian, because Asians have lower SMI compared with Westerners [38,42]. Besides, Asians are known to have higher visceral adipose tissue, higher subcutaneous adipose tissue but lower skeletal compared with Caucasians for the same BMI [43]. Considering this respect, Martin used a relatively lower SMI cutoff value for non-obese men, which might be fit for Asian males than the International Consensus of Cancer Cachexia definition [11,13]. For Asian populations, more relevant studies are need to establish the optimal SMI cutoff values. Furthermore, according to EWGSOP recommendation, the identification of sarcopenia is based on not only skeletal muscle mass but also skeletal muscle strength and physical performance. But most of the studies only evaluate the sarcopenia based on skeletal muscle mass. Skeletal muscle strength and physical performance are not be evaluated easily. Besides, they are evaluated by physicians, thus their evaluation may be subjective and inconsistent. Although skeletal muscle mass is related to strength, their trajectories of decline during progress do not overlap. Furthermore, muscle strength is also a stronger predictor of adverse outcomes [44]. In my opinion, skeletal muscle strength and physical performance should also be evaluated. Methods for evaluation include upper-limb hand-grip dynamometry and lower-limb extension strength testing for the skeletal muscle strength and walking speed for physical performance, respectively [34]. Hence, a more accurate consensus should be presented.

Sarcopenia has important implications for clinical practice. The patients with sarcopenia experience an inferior survival. So these patients might be candidates for adjuvant therapies. Sarcopenia may be beneficial to suggest patients on their personalized risk to determine therapeutic strategies including adjuvant therapies and clinical trials. Close postoperative follow-up should be emphasized for these patients. In addition to prognostic value, the identification of sarcopenia offers a potential opportunity to improve outcomes in patients. Physical exercise, vitamin D or omega-3 fatty acid dietary supplementation and others could improve or decrease the incidence of sarcopenia, which is also beneficial to survival [45]. Furthermore, sarcopenia is accessible to evaluate, without additional cost. Because the computed tomography (CT) images CT scans are commonly used for diagnosis, staging, and follow-up of patients. Besides, sarcopenia is a relatively objective measure because it is likely to evaluate the body composition using CT with a precision error of 1.4% [46].

However, our study is not free of limitations. Firstly, a total of 12 research consisting of 2075 patients were enrolled, which is a relatively small number and may limit the power of the final results. So more studies are needed to confirm our findings. Next, all studies were retrospective and may increase the risk of bias, which may partially explain the heterogeneity among studies. Thirdly, the discrepancies among studies exist, including the regions, tumor, and definition of sarcopenia. Therefore, based on relevant information, we carried out subgroup analyses. And further prospective studies are needed to validate the prognostic value of sarcopenia.

5. Conclusion

We conducted this meta-analysis evaluate the actual impact of sarcopenia on the survival of patients with surgically treated UC. We demonstrated that sarcopenia is an unfavorable factor for OS and CSS in patients with UC. Furthermore, stratified by tumor, the results of patients with UTUC or UCB are consistent with previous results. More studies are required to confirm our findings.

Authorship

Xu Hu, Wei-Chao Dou, and Xiang Li drafted the manuscript. Yan-Xiang Shao, Jian-Bang Liu and Xu Hu collected those medical data. Xu Hu, San-Chao Xiong and Wei-Xiao Yang performed statistical analyses. Xu Hu, Wei-Chao Dou, and Xiang Li revised the manuscript. Xu Hu and Xiang Li designed the study.

Conflict of interest

We declare that we have no conflict of interest.

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