

Prognostic value of radiologically determined sarcopenia prior to treatment in urologic tumors

A meta-analysis

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Abstract

Objective: Increasing evidence suggests that radiologically determined sarcopenia prior to treatment can serve as a prognostic marker in various tumors. However, there are conflicting conclusions about the prognostic role of sarcopenia in urological tumors. We performed a meta-analysis to assess the association between radiologically determined sarcopenia before treatment and survival outcomes in urological tumors.

Methods: A systematically literature search in PubMed, Cochrane databases, and EMBASE was performed. We estimated hazard ratios (HRs) for overall survival (OS) and cancer-specific survival (CSS). Hazard ratios (HR) with 95% confidence interval (CI) were calculated using STATA 12.0 software.

Results: A total of 16 studies enrolling 2264 patients with urologic tumors were included in our meta-analysis. Among these studies, 13 studies with 1941 patients explored the association between sarcopenia and OS, and 10 studies with 1790 patients investigated the relationship between sarcopenia and OS. The synthesized result suggested that sarcopenia was significantly associated with poor OS (Fixed-effect model, HR 1.73, 95% CI: 1.48–2.01, $P < .05$; heterogeneity: $P = .064$; $I^2 = 40.5\%$), and poor CSS (Fixed-effect model, HR: 1.85, 95% CI: 1.51–2.28, $P < .05$, heterogeneity: $P = .053$; $I^2 = 46.2\%$).

Conclusion: This meta-analysis showed that sarcopenia was associated with poor OS and CSS, suggesting that sarcopenia may serve as a promising prognostic marker in urologic cancer patients. Considering several limitations in our study, in the future more high-quality studies on this topic should be conducted to confirm our findings.

Abbreviations: BMI = body mass index, CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratios, OS = overall survival, PMI = psoas muscle index, SMI = skeletal muscle index.

Keywords: kidney neoplasms, mortality, prognosis, sarcopenia, urinary bladder neoplasms

1. Introduction

Urologic cancers prevail worldwide. There were estimated 108,450 males and 49,770 females newly diagnosed with urologic cancers, and 33,420 patients died in United States in 2019.^[1]

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JL and YD contributed equally to this work.

The authors have no conflicts of interest to disclose.

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Currently, TNM staging system is the most widely recognized method to predict the prognosis and guide therapy in cancer patients. However, in clinical practice, urologists are always confused by the situation that urologic cancer patients with the identical TNM stage, may have diverse oncological outcomes. Hence, it remains imperative to develop additional biomarkers to more accurately predict the prognosis and optimize the individualized treatment in patients with urologic cancers.

Sarcopenia, first introduced by Irwin Rosenberg,^[2] is a common component of geriatric syndrome and is a major challenge to healthy aging.^[3,4] Sarcopenia is featured with muscle mass loss alone or coupled with increased fat mass, and it is defined by loss of muscle, low muscle strength and/or low physical performance according to the European Working Group on Sarcopenia in Older People (EWGSOP).^[5] Aging inversely affects protein synthesis, and skeletal muscle mass reduces progressively year by year in elderly people. This aging-associated sarcopenia is defined as primary sarcopenia, while sarcopenia that does not result from aging is defined as secondary sarcopenia. Several factors are reported to cause secondary sarcopenia, including inflammatory disease, endocrine dysfunction, malnutrition, chronic kidney disease, chronic liver disease, and malignancy.^[6,7] In addition, cachexia is also considered to be a key cause of sarcopenia in oncological patients.^[6] However, a recent review by Cederholm et al pointed out that sarcopenia and cachexia are overlapping syndromes from the perspective of malnutrition in phenotype, but they also have their own distinct

etiologic contribution to cancer progression.^[8] To date, there is no single tool or criteria that is appropriate for both sarcopenia and cachexia.^[8] Therefore, before such a tool or criteria is established, it is necessary to explore the impact of sarcopenia or cachexia alone on survival in cancer patients, which may be used to predict prognosis and conduct individualized treatment in cancer patients. To date, it is widely accepted that pretreatment CT scan is an effective tool to determine whether patients are in the sarcopenic status or not.^[9,10] In this method, 2 imaging parameters are often used to assess the sarcopenic status, one of which is psoas muscle index (PMI) defined as total psoas area (TPA) at the level 3 lumbar divided by height (m²), and the other is skeletal muscle index (SMI) defined as the muscle area at the third lumbar level, controlled by height (m²). Additionally, several parameters that reflect muscle strength and physical function, such as timed up and go test, short physical performance battery, gait speed, chair stand, and grip strength, are also recommended to define sarcopenia.^[5] In recent years, numerous studies reported that cancer patients usually have a high risk of suffering from sarcopenia.^[11–13] Furthermore, a large amount of evidence demonstrated that sarcopenia is an unfavorable prognostic factor in several cancers,^[14–19] including esophageal cancer, lung cancer, gastric cancer, pancreatic cancer, colorectal cancer, and primary liver cancer.

Although the prognostic value of sarcopenia in patients with urologic cancer has also been studied, the conclusions remain conflicting. For instance, some studies^[20–23] indicated that there was no significant correlation between pretreatment sarcopenia and overall survival (OS) or cancer-specific survival (CSS). Inversely, other studies^[24–32] demonstrated that sarcopenia was an unfavorable prognostic parameter in patients with urologic cancers. Therefore, it is very imperative to conduct a systematic review and meta-analysis to comprehensively assess the prognostic value of pretreatment sarcopenia in patients with urologic tumors.

2. Materials and methods

2.1. Literature search and selection

A comprehensive literature search was performed in PubMed, EMBASE, and Cochrane databases for eligible studies that evaluated the prognostic role of sarcopenia in patients with urologic cancers from inception to December, 2018. The detailed search strategy used in PubMed was as following: (((((((("Carcinoma, Transitional Cell"[Mesh]) OR "Ureteral Neoplasms"[Mesh]) OR "Prostatic Neoplasms"[Mesh]) OR "Kidney Neoplasms"[Mesh]) OR "Urinary Bladder Neoplasms"[Mesh]) OR "Urologic Neoplasms"[Mesh])) OR (((((((cancer[Title/Abstract]) OR tumor[Title/Abstract]) OR tumors[Title/Abstract]) OR carcinoma[Title/Abstract]) OR neoplasm[Title/Abstract]) OR neoplasms[Title/Abstract]) OR malignancy[Title/Abstract]) OR cancers[Title/Abstract])) AND (((((((urologic[Title/Abstract]) OR urinary[Title/Abstract]) OR urological[Title/Abstract]) OR renal[Title/Abstract]) OR kidney[Title/Abstract]) OR bladder[Title/Abstract]) OR vesical[Title/Abstract]) OR ureteral[Title/Abstract]) OR upper urinary tract[Title/Abstract]) OR urothelial[Title/Abstract]) OR transitional cell[Title/Abstract]) OR vesical[Title/Abstract]) OR prostate[Title/Abstract])) AND (((((((sarcopenia[Title/Abstract]) OR grip strength[Title/Abstract]) OR chair stand[Title/Abstract]) OR low muscle quantity[Title/Abstract]) OR gait

speed[Title/Abstract]) OR appendicular skeletal muscle mass[Title/Abstract]) OR short physical performance battery[Title/Abstract]) OR (timed up and go test[Title/Abstract]))).

Studies were included if they conformed to the following criteria:

- 1) Diagnosis of urologic cancers was histo-pathologically confirmed;
- 2) The oncological prognosis, including overall survival (OS), or cancer-specific survival (CSS), were compared in urologic cancer patients with sarcopenia versus non-sarcopenia;
- 3) Hazard ratios (HRs) and 95% confidence intervals (CIs) for OS or CSS were available;
- 4) Pretreatment sarcopenia was assessed using image technology; and
- 5) Studies were published in English.

Studies were excluded if they accorded with the following criteria:

- 1) The studies were editorials, letters, reviews, conference abstracts or case reports;
- 2) The studies enrolled overlapped patients;
- 3) The studies focused on investigating the relationship between sarcopenia and non-urological tumors; and
- 4) HRs and CIs could not be obtained.

2.2. Data extraction and quality evaluation

All potentially eligible studies were independently reviewed by 2 investigators (Jialin Li and Yinan Deng) and divergences in data extraction were resolved by the corresponding author. The following datum was extracted: the name of first author, year of publication, cancer type, cancer stage, number of patients, age, follow-up time, methods of assessing sarcopenia, cut-offs of defining sarcopenia, the percentage of patients with sarcopenia, and HRs and CIs for OS and CSS. If hazard ratios from both univariable and multivariable analysis were available in articles, hazard ratios from multivariable analysis were extracted preferentially. If HRs were not directly provided in article, we estimated HRs 95% and their CIs from Kaplan–Meier curves by the Tierney methods. The Newcastle–Ottawa Scale (NOS)^[33] was used to assess the quality of the included studies. In this meta-analysis, we regarded studies obtaining 6 or more scores as high-quality ones. Any divergence was addressed by the corresponding author.

2.3. Statistical analysis

STATA version 12.0 (Stata Corporation, College Station, TX) was used to perform statistical analysis. Random effect model was applied to synthesize data if there was significant heterogeneity among the included studies ($I^2 > 50\%$), otherwise, fixed-effect model was applied.^[34] Subgroup analysis would be conducted to test the stability of our pooled results according to tumor type, country, tumor stage, assessment method, and analysis type. Meta-regression analysis was conducted based on tumor type, country, tumor stage, assessment method, and analysis type to explore the sources of heterogeneity in this meta-analysis. Additionally, sensitivity analysis was also conducted by sequentially omitting single included study to test the stability of our pooled results. Publication bias was assessed by Egger test and Begg test.^[35,36] When there was significant publication bias,

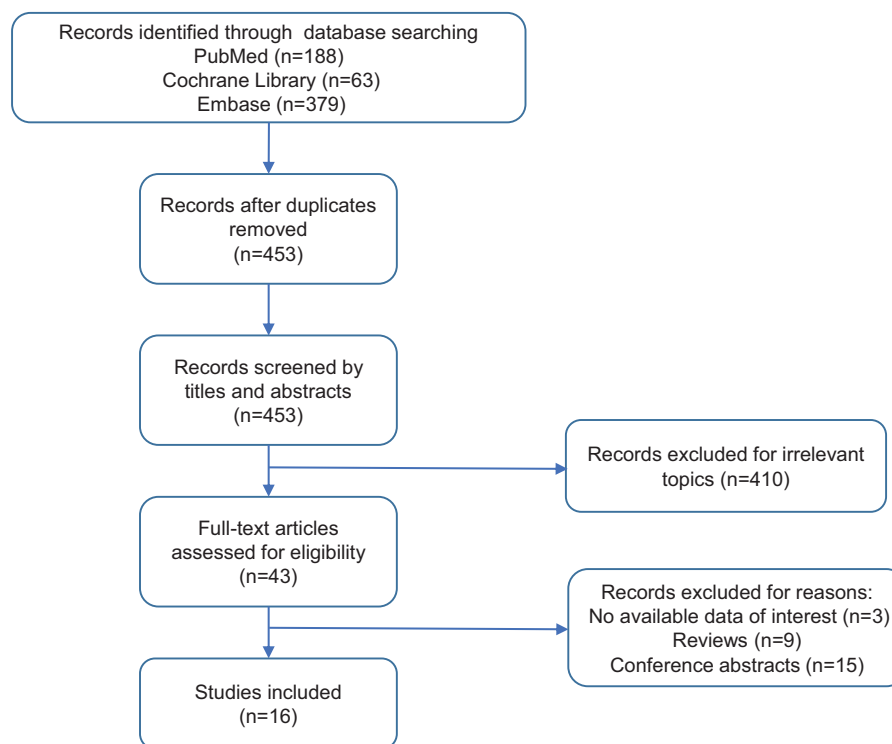


Figure 1. Flow diagram of literature selection.

trim-and-fill method was used to evaluate whether publication bias significantly affected the reliability of our pooled results.^[37] All statistical tests were 2-sided, and P value $< .05$ was considered statistically significant.

2.4. Ethics approval

Although this study did not utilize any human specimen, it has been approved by the Hospital Research Ethics Committee of Peking Union Medical College Hospital.

3. Results

3.1. Literature search and selection

The initial search identified a total of 630 records with 379 from EMBASE, 188 from PubMed, and 63 from Cochrane databases. After excluding 177 duplicated records, a total of 453 studies were further screened by titles and abstracts. In this process, 410 records were excluded due to irrelevant topics. Next, we screened the remained 43 studies by full-text and further excluded 27 studies owing to no available data on survival outcomes ($n=3$), conference abstracts (15), and reviews ($n=9$). Finally, a total of 16 studies were included for this meta-analysis. The Flow diagram of literature selection was displayed in Figure 1.

3.2. Characteristics of included studies

Characteristics of the included studies are presented in Table 1. All 16 studies were retrospective and published between 2014 and 2018. The number of participants ranged from 27 to 500, with a sum of 2264. Twelve studies used the SMI as the indicator of sarcopenia while 4 studies used the PMI. Most studies defined

the patients as sarcopenic and non-sarcopenic using a threshold SMI of $<41 \text{ cm}^2/\text{m}^2$ among women, $<43 \text{ cm}^2/\text{m}^2$ among men with a body mass index (BMI) of $<25 \text{ kg}/\text{m}^2$, and $<53 \text{ cm}^2/\text{m}^2$ among men with a BMI of $>25 \text{ kg}/\text{m}^2$, which was first proposed by Martin et al^[38] Besides, a few of included studies employed a threshold SMI of $<55 \text{ cm}^2/\text{m}^2$ for men and $<39 \text{ cm}^2/\text{m}^2$ for women.^[39] A total of 13 studies evaluated OS, and 10 studies evaluated CSS. The scores of Newcastle–Ottawa scale ranged from 6 to 7, indicating that the quality of the included studies was moderate to high and suitable for synthesized analysis (Table 2).

3.3. Synthesized analysis of the prognostic value of sarcopenia

A total of 13 studies with 1941 patients, which explored the association between sarcopenia and OS in urologic tumors, were included in our meta-analysis. As Figure 2 shown, the synthesized result suggested that sarcopenia was significantly associated with poor OS (Fixed-effect model, HR 1.73, 95% CI: 1.48–2.01, $P < .05$; heterogeneity: $P = .064$; $I^2 = 40.5\%$). Additionally, there were 10 eligible studies with 1790 patients^[23–26,28,29,32,40–42] that evaluated the relationship between sarcopenia and CSS in urologic tumors. Our synthesized analysis of these studies showed that there was also a significant correlation between sarcopenia and poor CSS (Fixed-effect model, HR: 1.85, 95% CI: 1.51–2.28, $P < .05$, heterogeneity: $P = .053$; $I^2 = 46.2\%$) (Fig. 3).

3.4. Subgroup analysis

We performed subgroup analysis, according to tumor type, country, tumor stage, assessment method, and analysis type, to test the stability of our synthesized results. Overall, statistically

Table 1
The main characteristics of the included studies.

Author/year	Country	Tumor type	Tumor stage	No. of patients	Median age (years)	Assessment method	Cut-off of sarcopenia for men	Cut-off of sarcopenia for women	Median follow-up (months)	Survival analysis
Anno/2018	Japan	UTUC	mixed	123	NR	SMI	53/43	41	53.9	CSS ^U
Fukushima/2016a	Japan	RCC	metastatic	92	65 (37–91)	SMI	53/43	41	NR	OS ^M
Fukushima/2016b	Japan	UTUC	mixed	81	71 (41–87)	SMI	53/43	41	41 (4–170)	OS ^M , CSS ^M
Hirasawa/2016	Japan	BC	mixed	136	68.6	SMI	53/43	41	46.7	CSS ^M
Ishihara/2016	Japan	RCC	metastatic	71	NR	SMI	53/43	41	NR	OS ^M
Ishihara/2017	Japan	UTUC	mixed	137	72.8 (39–92)	SMI	53/43	41	43.9 (2.83–140.3)	OS ^M , CSS ^M
Kasahara/2017	Japan	BC	mixed	27	NR	PMI	2.49	2.07	14	OS ^U
Mayr/2018	Germany	BC	mixed	500	72 (65–78)	SMI	53/43	41	22 (10–45)	OS ^M , CSS ^M
Miyake/2017	Japan	BC	non-metastatic	89	71 (48–83)	PMI	53/43	41	29 (10–60)	OS ^M , CSS ^M
Peyton/2016	USA	RCC	mixed	128	63 (31–85)	PMI	4.271	3.804	48.3 (0.1–78.7)	OS ^U
Psutka/2014	USA	BC	non-metastatic	205	71 (63–78)	SMI	55	39	80 (71–122)	OS ^M , CSS ^M
Psutka/2016	USA	RCC	non-metastatic	387	NR	SMI	55	39	86.4	OS ^M , CSS ^M
Saitoh-Maeda/2017	Japan	BC	non-metastatic	63	NR	PMI	NR	NR	24.8	OS ^U
Sharma/2015	USA	RCC	metastatic	93	61 (56–68)	SMI	53/43	41	13 (5–31)	OS ^M
Stangl-Kremser/2018	Austria	BC	non-metastatic	68	82 (75–86)	SMI	53/43	41	12.5 (5.1–23.5)	OS ^U , CSS ^U
Taguchi/2016	Japan	UC	metastatic	64	68 (63.3–73)	SMI	55	39	NR	CSS ^M

BC=bladder cancer, M=multivariable analysis, NR=not reported, PMI=psoas muscle index, RCC=renal cell carcinoma, SMI=skeletal muscle index, U=univariable analysis, UC=urothelial carcinoma, UTUC=upper tract urothelial carcinoma.

significant synthesized HR values for OS (Table 3) and CSS (Table 4) were consistently calculated in each subgroup, indicating the stability of our synthesized results.

3.5. Meta-regression analysis

Our overall combined analyses showed moderate heterogeneity for OS ($I^2=40.5\%$) and CSS ($I^2=46.2\%$). Thus, we conducted meta-regression analysis based on tumor type, country, tumor stage, assessment method, and analysis type to explore the potential sources of the heterogeneity. As shown in Table 3 and

Table 4, none of these factors could explain the heterogeneity for OS and CSS.

3.6. Sensitive analysis

We also performed sensitivity analysis by excluding 1 study in each step to further test the stability of our synthesized results. The results showed that the pooled HR values for OS (Fig. 4A) and CSS (Fig. 4B) did not change significantly when any individual study was excluded, which further indicated that our synthesized results in this meta-analysis were stable.

Table 2
The NOS quality assessment of the enrolled studies.

Study ID	SELECTION			COMPARABILITY		OUTCOME		Total	
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts
Anno/2018	★	★	★	★	★★	☆	☆	★	6
Fukushima/2016a	☆	★	★	★	★★	★	★	☆	6
Fukushima/2016b	★	★	★	★	★★	★	★	☆	7
Hirasawa/2016	☆	★	★	★	★★	★	★	☆	6
Ishihara/2016	★	★	★	☆	★★	★	★	★	7
Ishihara/2017	★	★	☆	★	★★	★	★	☆	6
Kasahara/2017	★	★	★	☆	★★	☆	★	★	6
Mayr/2018	★	★	★	★	★★	★	★	★	8
Miyake/2017	★	★	★	☆	★★	★	★	★	7
Peyton/2016	★	★	☆	★	★★	★	★	☆	6
Psutka/2014	★	★	★	★	★★	★	☆	★	7
Psutka/2016	★	☆	★	★	★★	★	★	★	8
Saitoh-Maeda/2017	★	☆	★	★	★★	★	☆	★	6
Sharma/2015	★	★	☆	★	★★	★	☆	★	6
Stangl-Kremser/2018	★	★	★	☆	★★	★	★	★	7
Taguchi/2016	★	☆	★	★	★★	★	☆	★	6

★ Represents 1 score and; ☆ represents no score in corresponding items. NOS=Newcastle–Ottawa Scale.

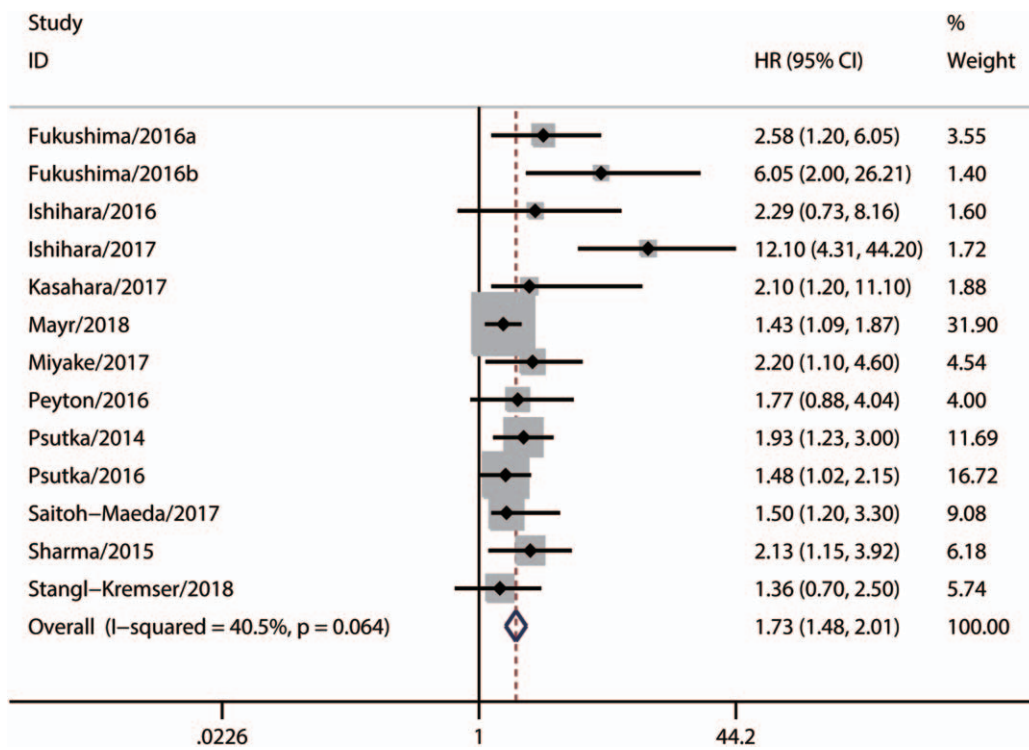


Figure 2. Synthesized analysis of the prognostic value of sarcopenia for OS in urologic tumors. OS=overall survival.

3.7. Publication bias

The publication bias was assessed using Begg and Egger tests. As the Begg tests shown, the funnel plots that assessed the publication bias in the included studies about OS (Fig. 5A) and CSS (Fig. 5B) were asymmetric. Meanwhile, the P values of

Begg and Egger tests were also <.05. These results indicated that there might be significant publication bias in the included studies about OS and CSS. Thus, we performed trim-and-fill analysis to determine whether the publication bias significantly affected the reliability of the pooled results about OS and CSS. The results

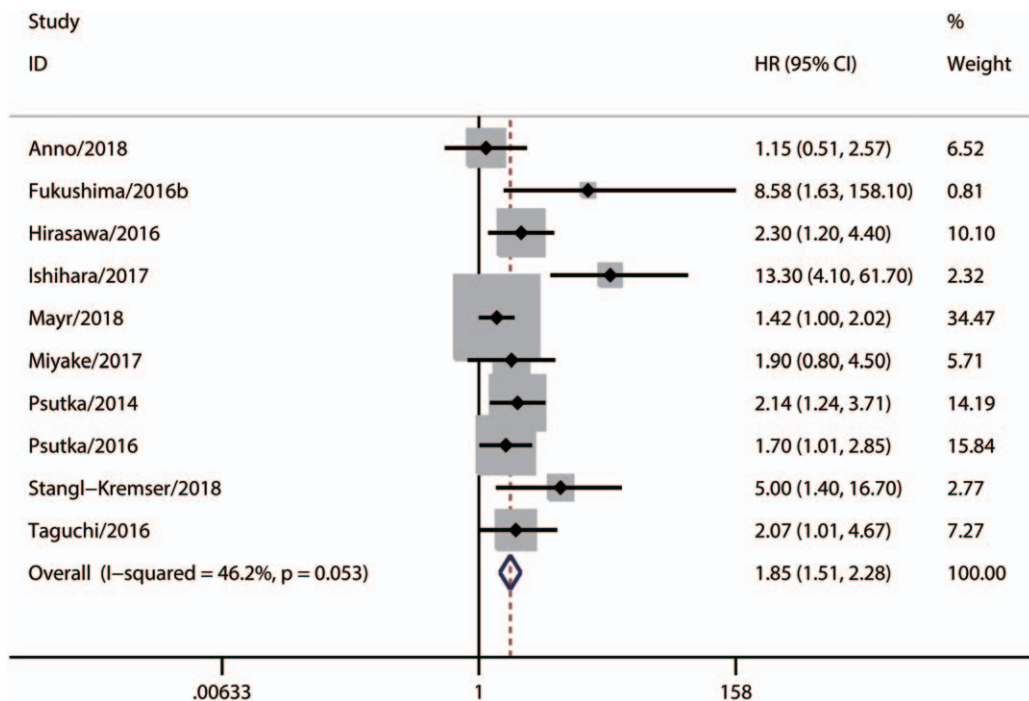


Figure 3. Synthesized analysis of the prognostic value of sarcopenia for CSS in urologic tumors. CSS=cancer-specific cancer.

Table 3
Subgroup analysis of synthesized HRs for OS.

Subgroup analysis	No. of studies	Pooled HR (95% CI)	P value	Meta-regression	
				I ² (%)	P value
^[1] Tumor type				43.16	.54
UTUC	2	8.85 (3.74–21.00)	<.001		
RCC	5	1.77 (1.35–2.31)	<.001		
BC	6	1.58 (1.31–1.91)	<.001		
^[2] Country				41.57	.24
Japan	7	2.33 (1.71–3.19)	<.001		
USA	4	1.73 (1.36–2.21)	<.001		
Austria	1	1.36 (0.7–2.5)	.32		
Germany	1	1.43 (1.09–1.87)	.01		
^[3] Tumor stage				44.13	.97
Mixed	5	2.87 (1.37–6.00)	.005		
Metastatic	3	2.29 (1.45–3.59)	<.001		
Non-metastatic	5	1.63 (1.31–2.03)	<.001		
^[4] Assessment method				45.46	.83
SMI	9	2.04 (1.49–2.79)	<.001		
PMI	4	1.75 (1.24–2.48)	<.001		
^[5] Analysis type				44.19	.4
Univariate	9	2.16 (1.58–2.95)	<.001		
Multivariate	4	1.55 (1.11–2.17)	.01		

BC=bladder cancer, CI=confidence interval, HR=hazard ratio, OS=overall survival, RCC=renal cell carcinoma, UTUC=upper tract urothelial carcinoma.

showed that the adjusted HR values for both OS and CSS were still more than 1 (OS: random-effects model, HR: 1.56, 95% CI: 1.22–2.00, $P < .001$; CSS: random-effects model, HR: 1.66, 95% CI: 1.17–2.37, $P = .005$), suggesting that the publication bias did not significantly affect the reliability of the pooled results about OS and CSS. Furthermore, the adjusted funnel plots that assessed the publication bias in the included studies about OS (Fig. 6A) and CSS (Fig. 6B) became symmetric. In view of the above results, the publication bias determined by Begg and Egger tests did not substantially affect the reliability and stability of our synthesized results.

4. Discussion

Numerous studies have investigated the correlation between sarcopenia and the prognosis of urologic cancers. However, the results were inconsistent. Thus, we conducted this meta-analysis to assess the prognostic significance of sarcopenia in patients with urologic cancers. Our meta-analysis included 16 studies with 2264 patients, which focused on unveiling the predictive value of sarcopenia for the outcome of urologic tumors. From the results of the present study, we found that sarcopenia was significantly correlated with decreased OS and CSS in urologic cancer patients. Furthermore, the results of our subgroup and sensitivity analyses

Table 4
Subgroup analysis of synthesized HRs for CSS.

Subgroup analysis	No. of studies	Pooled HR (95% CI)	P value	Meta-regression	
				I ² (%)	P value
^[1] Tumor type				51.86	.61
UTUC	3	4.51 (0.72–28.18)	.107		
RCC	1	1.70 (1.01–2.86)	.045		
BC	5	1.91 (1.39–2.62)	<.001		
UC	1	2.07 (0.96–4.45)	.107		
^[2] Country				52.17	.97
Japan	6	2.48 (1.40–4.37)	.002		
Germany	1	1.42 (1.00–2.02)	.051		
USA	2	1.90 (1.30–2.76)	.001		
Austria	1	5.00 (1.45–17.27)	.011		
^[3] Tumor stage				50.39	.9
Mixed	5	2.39 (1.21–4.70)	.012		
Metastatic	1	2.07 (0.96–4.45)	.063		
Non-metastatic	4	2.03 (1.46–2.84)	<.001		
^[4] Assessment method				51.27	.91
SMI	9	2.14 (1.51–3.04)	<.001		
PMI	1	1.90 (0.80–4.51)	.145		
^[5] Analysis type				52.13	.88
Univariate	2	2.22 (0.53–9.29)	.28		
Multivariate	8	2.10 (1.50–2.92)	<.001		

BC=bladder cancer, CI=confidence interval, CSS=cancer-specific survival, HR=hazard ratio, RCC=renal cell carcinoma, UC=urothelial carcinoma, UTUC=upper tract urothelial carcinoma.

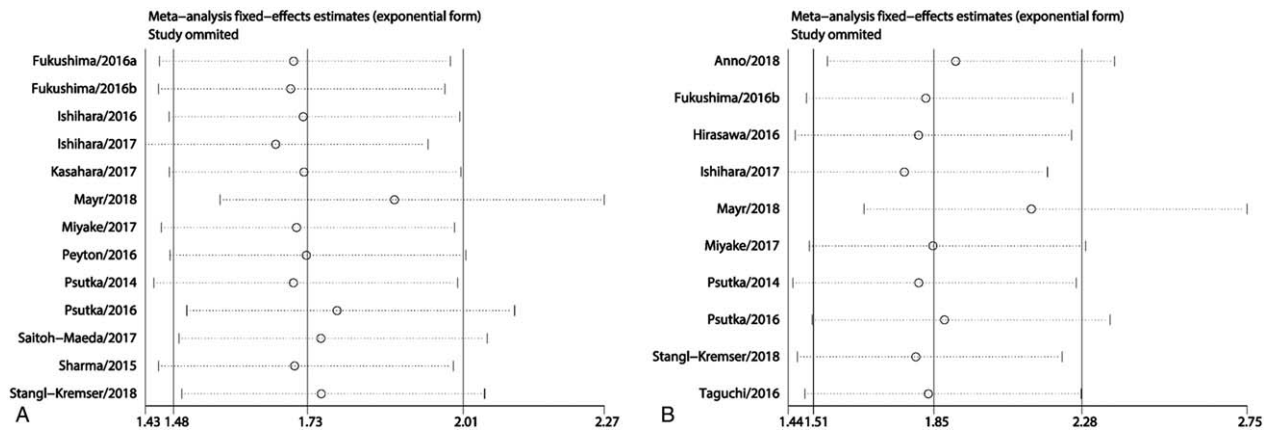


Figure 4. A. The sensitivity analysis for the synthesized HR values assessing the prognostic value of sarcopenia for OS in urologic tumors. B. The sensitivity analysis for the synthesized HR values assessing the prognostic value of sarcopenia for CSS in urologic tumors. CSS = cancer-specific cancer, HR = hazard ratio, OS = overall survival.

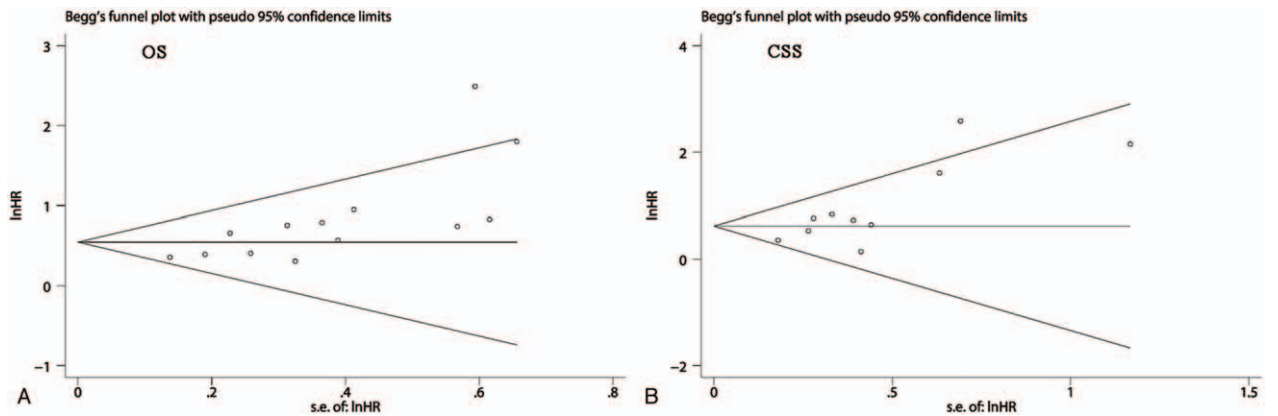


Figure 5. The funnel plots of Begg's test for assessing the publication bias in the included studies about OS (A) and CSS (B). CSS = cancer-specific cancer, OS = overall survival.

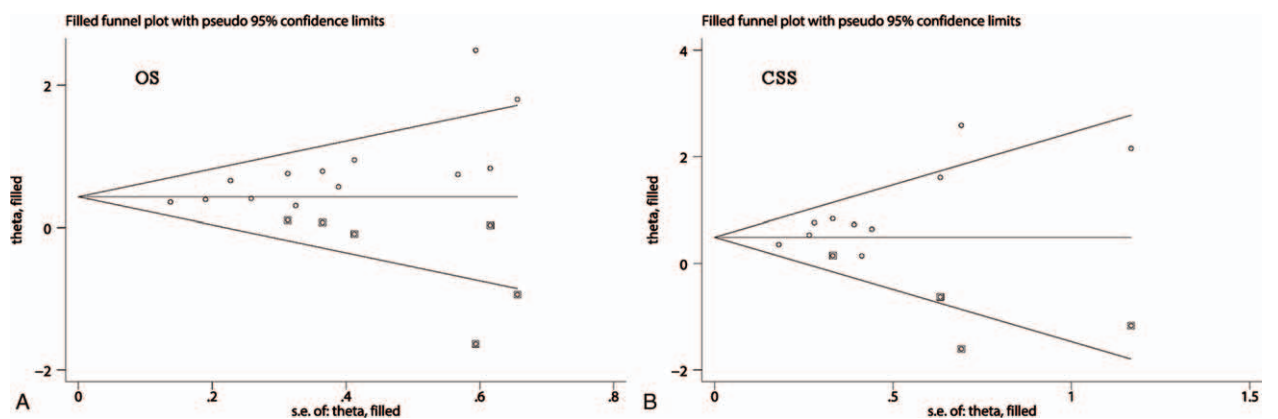


Figure 6. The adjusted funnel plots of Begg's test for assessing the publication bias in the included studies about OS (A) and CSS (B). CSS = cancer-specific cancer, OS = overall survival.

indicated that the pooled HR values in this meta-analysis were stable and reliable. Thus, sarcopenia may serve as a promising marker for assessing the prognosis of urologic cancers.

There are several mechanisms that may underlie the prognostic value of sarcopenia in cancer patients. Some researchers came up with the hypothesis that sarcopenia may be induced by systematic inflammation and malnutrition.^[28,29,43] In the systematic inflammation process, the body tends to decrease the protein synthesis and increase protein degradation,^[44] which may do harm to the discovery of patients. More importantly, a plenty of evidence suggested that the systemic inflammation could promote cancer progression and result in a poor prognosis.^[45,46] Cytokines play a vital role in systemic inflammation associated with cancers and were found to participate in many metabolic pathways responsible for skeletal muscle wasting,^[47] thus probably facilitating the development of sarcopenia. Additionally, it was considered that malnutrition-related to cancer progression and side effects of treatments could lead to anorexia in cancer patients, which subsequently promotes the development of sarcopenia.^[31,48,49] Cachexia is a multisystem syndrome featured with weight loss, loss of muscle mass, systemic inflammation, anorexia, insulin resistance, and functional decline,^[50] and there is a consensus definition of cachexia: weight loss of $\geq 5\%$ of body weight in the past 6 months or $\geq 2\%$ loss in patients with body mass index (BMI) of $< 20 \text{ kg/m}^2$.²³⁹ Numerous studies demonstrated that cachexia could significantly worsen prognosis in cancer patients.^[51–55] Furthermore, cachexia is considered to be important cause of sarcopenia in oncological patients,^[6] which may also partly account for the positive association between sarcopenia and poor survival in patients with urologic tumors. Overall, close relationships of sarcopenia with systematic inflammation, malnutrition and cachexia strongly support our findings in this meta-analysis.

Our findings have some clinical significance. On 1 hand, our meta-analysis demonstrated that pretreatment sarcopenia was associated with inferior OS and CSS in urologic cancer patients, suggesting that sarcopenia may be used to stratify urologic cancer patients with low and high risk, and predict prognosis. On other hand, our study may provide evidence that pretreatment sarcopenia may be used to guide individualized treatments for patients with urologic cancers. Because malnutrition, anorexia, systemic inflammation, and cachexia were considered as important causes of sarcopenia, many therapeutic strategies have been applied to deal with these abnormalities associated with sarcopenia. For example, nutritional intervention and appetite stimulants are commonly used to alleviate skeleton muscle waste. Additionally, various anti-inflammatory drugs and anabolic agents have been tested in clinical trials,^[56,57] including COX-2 inhibitors, immunomodulator, Omega-3 supplements, Ghrelin analogs, and Janus kinase 1 and Janus kinase 2 inhibitor, to treat cancer cachexia.

To our best knowledge, this is the first meta-analysis to comprehensively evaluate the prognostic value of sarcopenia in urological cancers. Compared to individual included studies, our meta-analysis conquered the limitation of small sample size by synthesizing data of 16 eligible studies and thus may provide more strong evidence with larger statistical power. We found no significant heterogeneity in our analysis. Nevertheless, there were still several limitations that should be considered cautiously. First, all the included studies were designed retrospectively and thus could not draw robust conclusions about how plasma sarcopenia affects survival outcomes. Only the relationship

between sarcopenia and poor survival outcome could be deduced. Second, we only estimated OS and CSS, but did not evaluate other survival outcomes, such as disease-free survival and progression-free survival, which was mainly due to a lack of data in the included studies. Third, we only considered studies published in English, which might lead to language bias. Fourth, some of the included studies lacked multivariate analyses, so we could only use HR values from univariate analyses to calculate the synthesized HR value. However, univariate analysis may overestimate effect sizes due to confounder bias. Fifth, the results of Begg and Egger tests suggested that our meta-analysis had significant publication bias. In fact, studies with positive results are usually more easily to be published than those with negative results due to many factors, such as the preference of authors and journal editors and the manipulation of fund provider, which may mainly account for the publication bias. Although there was significant bias in our meta-analysis, our trim-and-fill analysis suggested that the publication bias did not significantly affect the reliability of the pooled results about OS and CSS.

In conclusion, our meta-analysis indicated that sarcopenia was associated with poor OS and CSS in urologic cancer patients, suggesting that sarcopenia may serve as a promising prognostic marker. Considering several limitations in our study, in the future more high-quality studies on this topic should be conducted to confirm our findings.

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