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The Prognostic Value of Body Mass Index in Patients With Urothelial Carcinoma After Surgery: A Systematic Review and Meta-Analysis

Zhiqiang Yang[1,2], Yunjin Bai[1], Xu Hu[2], Xiaoming Wang[2], and Ping Han[1]

Abstract

Background: The clinical evidence of body mass index (BMI) for survival has increased in urothelial carcinoma (UC). This study aimed to investigate the prognostic value of BMI on the oncologic outcomes of patients with UC after surgery.

Methods: The systematic review and meta-analysis was performed using Pubmed, Embase and Cochrane Library. We collected hazard ratio (HR) and 95% confidence interval (CI) on cancer specific survival (CSS), overall survival (OS) and recurrence-free survival (RFS) from the studies including upper tract urothelial carcinoma (UTUC) and urothelial carcinoma of bladder (UCB).

Results: A total of 13 studies comprising over 12,200 patients were enrolled in the quantitative synthesis. Compared with normal weight, overweight was associated with better CSS (HR = 0.87, 95% CI: 0.79-0.95) and RFS (HR = 0.86, 95% CI: 0.78-0.96). Meanwhile, we found that obese patients had worse CSS (HR = 1.14, 95%CI: 1.03-1.26), OS (HR = 1.31, 95% CI: 1.19-1.44) and RFS (HR = 1.24, 95% CI: 1.12-1.37). We observed that underweight was associated with inferior CSS (HR = 1.87, 95% CI: 1.54-2.26) in UTUC patients.

Conclusions: Overweight was a protective factor for patients with UC after surgery, while obesity and underweight predicted unfavorable survival. Individual BMI may be considered for prognostication after surgeries and patient stratification for clinical trials.

Keywords

body mass index, urothelial carcinoma, radical nephroureterectomy, radical cystectomy, meta-analysis

Introduction

Urothelial carcinoma (UC) is one of the most common malignancies, with estimated 85,000 new cases and 19,000 deaths in the United States in 2020.[1] UC is mainly comprised of upper tract urothelial carcinoma (UTUC) and urothelial carcinoma of bladder (UCB). UTUCs account for only 5-10% of UCs, while UCBs account for 90-95% of UCs.[2] Radical nephroureterectomy (RNU) with bladder cuff excision is the standard treatment for high-risk UTUC, despite the high rate of recurrence in the bladder.[2,3] Radical cystectomy (RC) is the recommended therapy for nonmetastatic muscle-invasive bladder cancer (MIBC) and high-risk non-muscle-invasive bladder cancer (NMIBC), but there are still risks of progression.[4,5]

Given the risk of recurrence and progression, it is necessary to predict survival after RNU or RC for UC patients to better select them for subsequent treatments and clinical trials. In fact, several preoperative factors and postoperative factors have been established for prognosis, such as age, tobacco consumption, tumor location, tumor stage, lymph node involvement and surgical margins.[6-11] Among these factors, body mass index

[1] Department of Urology, West China Hospital, Sichuan University, Chengdu, People's Republic of China
[2] West China School of Medicine/West China Hospital, Sichuan University, Chengdu, People's Republic of China

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Corresponding Author:
Ping Han, Department of Urology, West China Hospital, Sichuan University, Chengdu, 610041, People's Republic of China.
Email: hanpingwch@163.com

(BMI) is a simple measurement of body composition and can be easily calculated in clinical settings. Obese (BMI > 30 kg/m^2), overweight (BMI 25.1–30kg/m^2), normal weight (BMI 18.5–25kg/m^2), and underweight (BMI < 18.5 kg/m^2) patients can be identified by globally accepted criteria.[12] Several studies tried to connect abnormal BMI with the prognosis of UC patients after radical surgeries.[13-18] Yeh et al. suggested that obesity was a prognosticator for lower recurrence and mortality in UTUC patients.[19] But Dabi et al. demonstrated that obesity was associated with higher recurrence and CSS.[20] It remained controversial whether patients with abnormal BMI had inferior survival.

Therefore, in this study, we performed a systematic review and meta-analysis to investigate the association between BMI and the oncologic outcomes of patients who underwent RC or RNU for UC.

Methods

Literature Search

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We used PubMed, Embase and Cochrane Library for literature search dated from the inception of each database to July 10th, 2020. The search strategy was based on the following items: ("urothelial" OR "urothelium" OR "bladder" OR "upper tract") AND ("carcinoma" OR "cancer" OR "tumor" OR "tumour") AND ("BMI" OR "body mass index"), as well as their synonyms and medical subject heading terms. Two researchers (ZQ Yang and Xu H) independently screened the titles and abstracts according to the criteria. Final selections were made by full-text reading of the screened studies. Discrepancies between the 2 researchers were discussed and resolved by consensus.

Eligibility Criteria

Studies were included according to the following criteria: (1) observational researches or randomized controlled trials; (2) patients were diagnosed with urothelial carcinoma and underwent radical nephroureterectomy or radical cystectomy; (3) preoperative BMI was evaluated for the prognosis of patients; (4) the data of survival outcomes were available, including overall survival (OS), cancer-specific survival (CSS) or recurrence-free survival (RFS).

Studies were excluded based on the following criteria: (1) studies with metastatic urothelial carcinoma; (2) did not investigate the association between preoperative BMI and survival outcomes; (3) other types of publication such as reviews, case reports or conference abstracts; (4) no available data for analysis.

Data Extraction and Quality Assessment

Two researchers (ZQ Yang and Xu H) independently extracted the following items from eligible studies: the name of the first author and publication year, study design, the time interval of patient enrollment, patient population, number of patients, age of patients, tumor subtype, treatment subtype, cutoff value of BMI, follow-up duration and clinical outcome type. Hazard ratio (HR) and 95% confidence interval (CI) were extracted from the studies to synthesize pooled results. When these 2 parameters were not mentioned in the texts but according Kaplan-Meier curves were available, we digitalized the curves and extracted data using the open-source Engauge Digitizer software (http://digitizer.sourceforge.net/).

We used the Newcastle-Ottawa Quality Assessment Scale (NOS) to evaluate the quality of these studies.[21] Studies rated with 7-9 stars were considered to have low risk of bias and presented superior quality.

Statistical Analysis

HRs and 95% CIs were used for meta-analysis. Heterogeneity among the studies were assessed using Cochrane's Q statistic (P values) and I^2 statistic. When $P < 0.10$ or $I^2 > 50\%$, the random-effect model was used; otherwise, the fixed effect model was adopted. Subgroup analysis was conducted using tumor subtype and population to detect possible source of heterogeneity. Publication bias was assessed by the Begg's funnel plot and Egger's test. Sensitivity analysis was also performed to evaluate the source of publication bias.

All statistical analyses were performed using STATA/SE version 16.0. A 2-sided $P < 0.05$ was considered statistically significant.

Results

Study Selection

The PubMed, Embase and Cochrane Library search identified 1,576 records and yielded 1,476 hits after removing duplicates. By screening titles and abstracts, we kept 67 records. Full text assessment excluded 9 unavailable studies, 10 conference abstracts, 27 mismatched records, 4 reviews and 4 studies without available data. Finally, 13 studies were eligible for further quantitative synthesis.[13-20,22-26] The flow diagram of filtering and selection is presented in Figure 1.

Study Characteristics

Table 1 summarized the characteristics of the included studies. There are 9 studies on UTUC patients who received RNU, and 6 studies investigated UCB patients who received RC. Seven studies enrolled Asian-based population and 6 studies enrolled Western-based population. One study was prospective designed while the rest were retrospective. Inamoto et al. split the patients into 2 groups investigating UTUC. Both Murakami et al. and Bachi et al. included 2 cohorts investigating UTUC and UCB separately. Therefore, although 13 articles were enrolled, the final number of assessable investigations was 16. All studies considered BMI as categorical variable and defined cutoffs according to protocols. The outcome

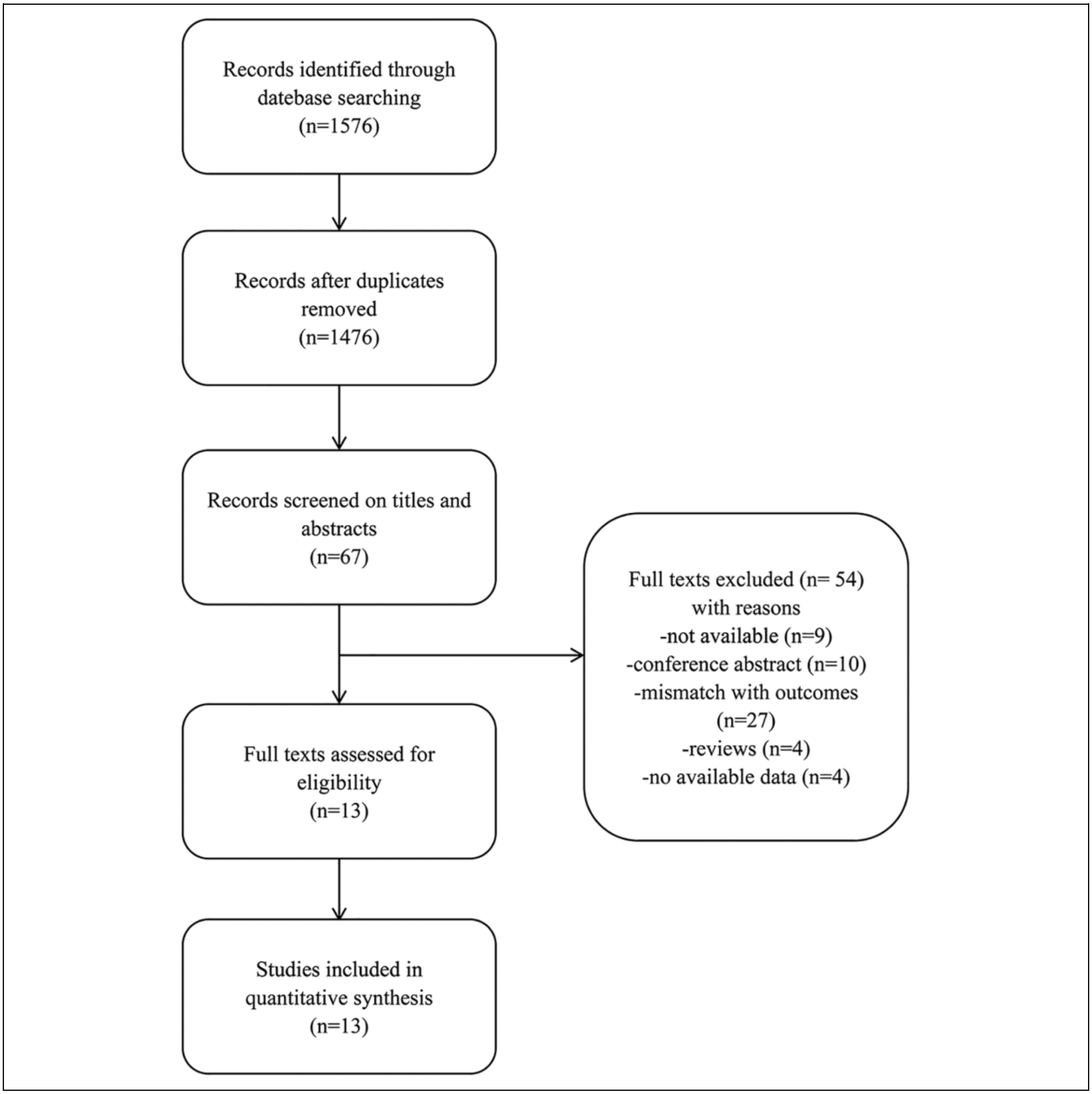

Figure 1. Flow diagram for study selection.

measurements included CSS, OS and RFS. NOS demonstrated that the studies included in our meta-analysis had relatively high quality.

The Prognostic Role of Overweight Compared to Normal Weight

All 16 studies were selected for CSS meta-analysis. The pooled results indicated that overweight was associated with significantly better CSS, with a pooled HR of 0.865 (95% CI: 0.786-0.951, P = 0.003). Significant heterogeneity was detected ($I^2 = 68.1\%$). Subgroup analysis was performed for population and tumor subtype and suggested that overweight was a significant indicator for UCB patients (HR = 0.793, 95% CI: 0.706-0.891, P < 0.001), with no evidence of heterogeneity ($I^2 = 34.2\%$).

The pooled results regarding 7 studies did not show significant relation between overweight and OS (HR = 1.084, 95% CI: 0.922-1.184, P = 0.074). However, subgroup analyses revealed that it was a favorable factor in Western population

Table 1. Characteristics of the Included Studies.

Study (Author/Year)	Design	Enrollment period	Population	Number of patients	Age	Tumor	Treatment	BMI cutoffs and definitions	Follow-up time (months)	Outcomes	NOS
Yeh 2020[19]	Retrospective	1990-2017	Asian	648	Mean (SD) 67.1 (10.8)	UTUC	RNU	Overweight ($\geq$23 kg/m^2) and obesity ($\geq$25 kg/m^2)	Median (IQR) 45.0 (13.2-62.4)	CSS,OS,RFS	8
Inamoto 2019[22]	Retrospective	–	Asian	188	Mean 69	UTUC	RNU	Underweight (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2) and overweight ($\geq$25 kg/m^2)	–	CSS	7
Inamoto 2019[22]	Retrospective	–	Asian	688	Mean 69	UTUC	RNU	Underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2) and overweight ($\geq$25 kg/m^2)	–	CSS	7
Murakami 2018[13]	Retrospective	1990-2015	Asian	441	Median (IQR) 69 (62-75)	UTUC	RNU	Underweight (<18.5 kg/m^2), normal (18.5–25 kg/m^2), overweight (25.1-30 kg/m^2) and obese (>30 kg/m^2)	Median 35.7	CSS	8
Murakami 2018[13]	Retrospective	1990-2015	Asian	286	Median (IQR) 68 (61-74)	UCB	RC	Underweight (<18.5 kg/m^2), normal (18.5–25 kg/m^2), overweight (25.1-30 kg/m^2) and obese (>30 kg/m^2)	Median 30.9	CSS	8
Gierth 2018[14]	Prospective	January-December 2011	Western	460	Median (IQR) 69 (61-75)	UCB	RC	Normal (<25 kg/m^2), overweight (25-29.9 kg/m^2) and obese ($\geq$30 kg/m^2)	Median (IQR) 21 (9-27)	CSS,OS	8
Dabi 2018[20]	Retrospective	1990-2012	Western	237	Mean 69	UTUC	RNU	Normal (18-25 kg/m^2), overweight (25-30 kg/m^2) and obese ($\geq$30 kg/m^2)	Median (IQR) 44 (24-79)	CSS	8
Dabi 2017[23]	Retrospective	1995-2011	Western	701	Mean 66.7	UCB	RC	Normal (18-25 kg/m^2), overweight (25-30 kg/m^2) and obese ($\geq$30 kg/m^2)	Median (IQR) 45 (23-75)	CSS	8
Kim 2015[24]	Retrospective	March 1997-July 2012	Asian	445	Median (IQR) 64.8 (57.5-71.3)	UTUC	RNU	Normal (<23 kg/m^2), overweight (23-24.9 kg/m^2) and obese ($\geq$25 kg/m^2)	Median (IQR) 50.3 (25.1-101.6)	CSS,OS	9
Kwon 2014[15]	Retrospective	August 1990-March 2012	Asian	714	Mean (SD) 62.4 (9.6)	UCB	RC	Normal (<23 kg/m^2), overweight (23-25 kg/m^2) and obese ($\geq$25 kg/m^2)	Median 64.1	CSS,RFS	8
Ishioka 2014[25]	Retrospective	January 1995-December 2010	Asian	1014	Median (IQR) 70 (62-76)	UTUC	RNU	Normal (22.5-25kg/m^2), underweight (<22.5 kg/m^2) and overweight ($\geq$25 kg/m^2)	Median (IQR) 38 (16-73)	CSS	7
Bachi 2014[16]	Retrospective	1990-2010	Western	664	Mean 70.3	UTUC	RNU	Normal (<25 kg/m^2), overweight (25-30 kg/m^2) and obese ($\geq$30 kg/m^2)	Mean (median) 39.2 (24.5)	CSS,OS,RFS	8
Bachi 2014[16]	Retrospective	1998-2008	Western	847	Mean 66.2	UCB	RC	Normal (<25 kg/m^2), overweight (25-30 kg/m^2) and obese ($\geq$30 kg/m^2)	Mean (median) 39 (23.4)	CSS,OS,RFS	8
Liu 2013[29]	Retrospective	August 1998-October 2009	Asian	230	Mean (IQR) 61 (54-69)	UTUC	RNU	Underweight (<18.5 kg/m^2), normal (18.5–25 kg/m^2) and overweight ($\geq$25 kg/m^2)	Mean (median) 72.9 (67.0)	CSS,RFS	8
Chromecki 2013[17]	Retrospective	1979-2008	Western	4118	Median (IQR) 67 (13.86)	UCB	RC	Normal (<25 kg/m^2), overweight (25-29.9 kg/m^2) and obese ($\geq$30 kg/m^2)	Median (IQR) 44 (68.4)	CSS,OS,RFS	8
Ehdaie 2011[18]	Retrospective	1987-2007	Western	520	–	UTUC	RNU	Normal (<25 kg/m^2), overweight (25-29.9 kg/m^2) and obese ($\geq$30 kg/m^2)	Median (IQR) 38 (54)	CSS,OS,RFS	7

UTUC, upper tract urothelial carcinoma; UCB, urothelial carcinoma of bladder; RNU, radical nephroureterectomy; RC, radical cystectomy; BMI, body mass index; IQR, interquartile range; SD, standard deviation; CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; NOS, Newcastle-Ottawa Quality Assessment Scale.

Table 2. Main Results and Subgroup Analysis.

Outcome	Variable	Subgroup	Number of studies	Model	HR (95%CI)	*P* value	I^2(%)
CSS (overweight)	Total		16	Random	0.865 (0.786-0.951)	0.003	68.1
	Population	Asian	9	Random	0.850 (0.719-1.005)	0.057	55.0
		Western	7	Random	0.872 (0.777-0.979)	0.021	79.5
	Tumor	UTUC	10	Random	1.037 (0.877-1.226)	0.674	72.6
		UCB	6	Random	0.793 (0.706-0.891)	<0.001	34.2
CSS (obesity)	Total		12	Random	1.138 (1.028-1.261)	0.013	88.1
	Population	Asian	5	Random	0.592 (0.464-0.755)	<0.001	81.1
		Western	7	Random	1.310 (1.171-1.467)	<0.001	84.0
	Tumor	UTUC	6	Random	1.118 (0.896-1.395)	0.324	86.6
		UCB	6	Random	1.144 (1.020-1.284)	0.022	90.9
CSS (underweight)	Total	UTUC	5	Fixed	1.872 (1.541-2.263)	<0.001	17.6
OS (overweight)	Total		7	Random	1.084 (0.922-1.184)	0.074	86.3
	Population	Asian	2	Random	0.898 (0.675-1.195)	0.459	53.9
		Western	5	Random	1.106 (1.008-1.214)	0.034	90.0
	Tumor	UTUC	4	Random	0.950 (0.787-1.147)	0.595	7.3
		UCB	3	Random	1.125 (1.018-1.244)	0.021	94.8
OS (obesity)	Total		7	Random	1.308 (1.192-1.436)	<0.001	93.4
	Population	Asian	2	Random	0.669 (0.515-0.868)	0.003	68.5
		Western	5	Random	1.443 (1.306-1.594)	<0.001	93.2
	Tumor	UTUC	4	Random	0.999 (0.827-1.207)	0.994	87.5
		UCB	3	Random	1.426 (1.281-1.587)	<0.001	96.5
RFS (overweight)	Total		7	Random	0.864 (0.781-0.957)	0.005	72.6
	Population	Asian	3	Random	0.641 (0.507-0.811)	<0.001	0.0
		Western	4	Random	0.926 (0.827-1.037)	0.183	78.9
	Tumor	UTUC	4	Random	0.970 (0.793-1.187)	0.768	82.2
		UCB	3	Random	0.831 (0.738-0.935)	0.002	40.3
RFS (obesity)	Total		6	Random	1.237 (1.122-1.365)	<0.001	94.7
	Population	Asian	2	Random	0.600 (0.471-0.764)	<0.001	27.7
		Western	4	Random	1.426 (1.281-1.587)	<0.001	94.2
	Tumor	UTUC	3	Random	1.311 (1.057-1.625)	0.014	92.7
		UCB	3	Random	1.219 (1.092-1.361)	<0.001	97.0

CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; UTUC, upper tract urothelial carcinoma; UCB: urothelial carcinoma of bladder; HR, hazard ratio; CI, confidence interval.

(HR = 1.106, 95% CI: 1.008-1.214, P = 0.034) and UCB patients (HR = 1.125, 95% CI: 1.018-1.244, P = 0.021).

As for RFS, the pooled results of 7 studies showed that overweight was associated with significantly better RFS (HR: 0.864, 95% CI: 0.781-0.957, P = 0.005). However, heterogeneity was detected ($I^2 = 72.6\%$). Subgroup analysis revealed that the association was significant in Asian population (HR = 0.641, 95% CI: 0.507-0.811, P < 0.001, $I^2 = 0.0\%$) and UCB patients (HR = 0.831, 95% CI: 0.738-0.935, P = 0.002, $I^2 = 40.3\%$). Detailed information of overweight on CSS, OS and RFS was presented in Table 2 and Figure 2 (A, C, E).

The Prognostic Role of Obesity Compared to Normal Weight

A total of 12 studies were enrolled for CSS meta-analysis. The pooled results indicated that obesity was an unfavorable factor for CSS (HR = 1.138, 95% CI: 1.028-1.261, P = 0.013). However, great heterogeneity was detected ($I^2 = 88.1\%$) and we didn't find the source of heterogeneity through subgroup analysis.

The pooled results of 7 studies showed that obesity was significantly associated with inferior OS (HR = 1.308, 95% CI: 1.192-1.436, P < 0.001). But we also detected heterogeneity ($I^2 = 93.4\%$) and didn't find the source of it through subgroup analysis.

The pooled results of 6 studies revealed that obesity was also significantly associated with worse RFS (HR = 1.237, 95% CI: 1.122-1.365, P < 0.001), despite the evidence of heterogeneity ($I^2 = 94.7\%$). Detailed information of obesity on CSS, OS and RFS was presented in Table 2 and Figure 2 (B, D, F).

The Prognostic Role of Underweight Compared to Normal Weight

There were only 5 studies investigating underweight and its role on CSS of UTUC patients. As presented in Table 2 and Figure 3, the pooled results indicated that underweight was significantly associated with worse CSS (HR = 1.872, 95% CI: 1.541-2.263, P < 0.001). No evidence of heterogeneity was detected ($I^2 = 17.6\%$).

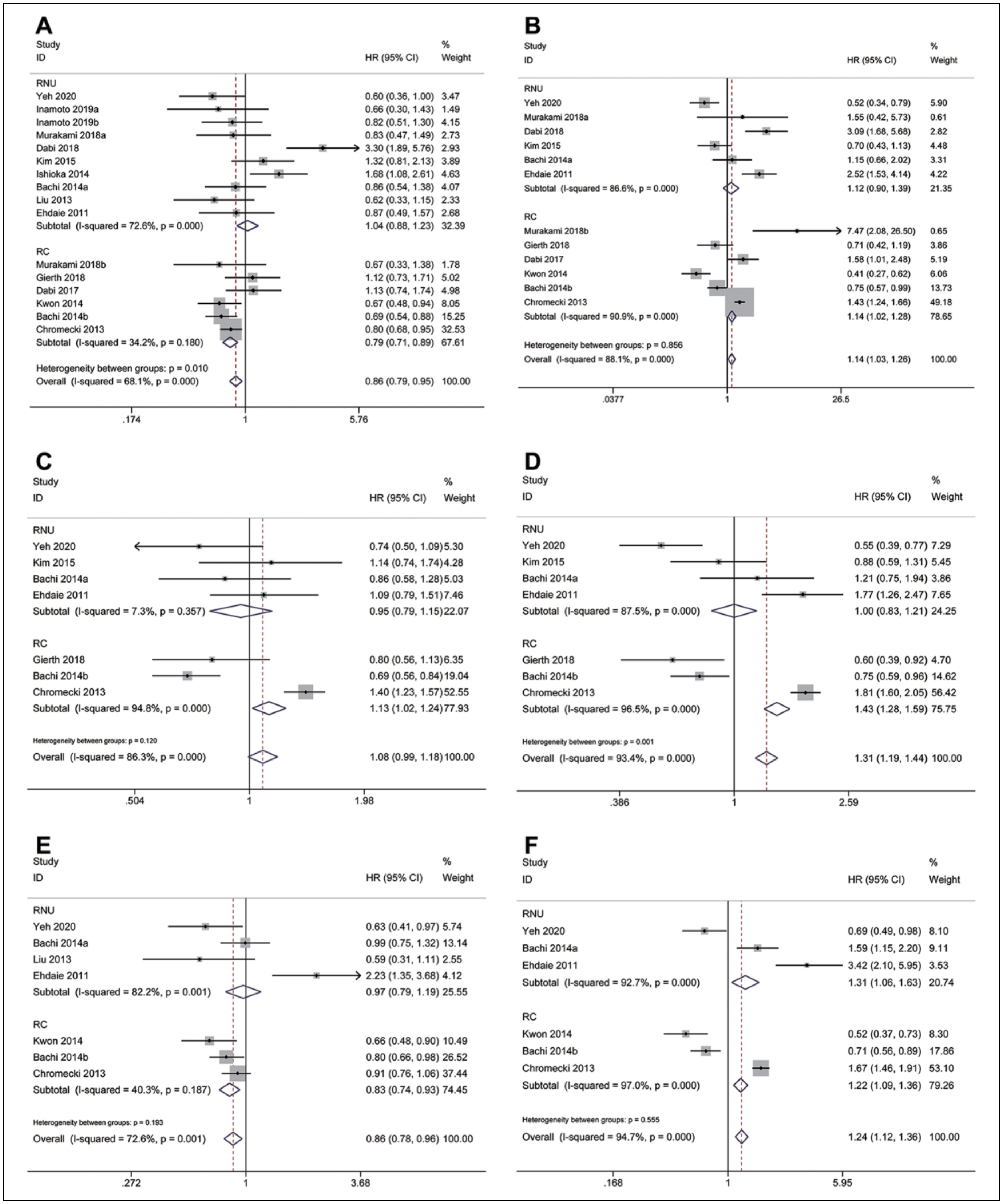

Figure 2. Forest plots showing pooled hazard ratio for (A) CSS of overweight population; (B) CSS of obese population; (C) OS of overweight population; (D) OS of obese population; (E) RFS of overweight population; (F) RFS of obese population. RNU, radical nephroureterectomy; RC, radical cystectomy; CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival.

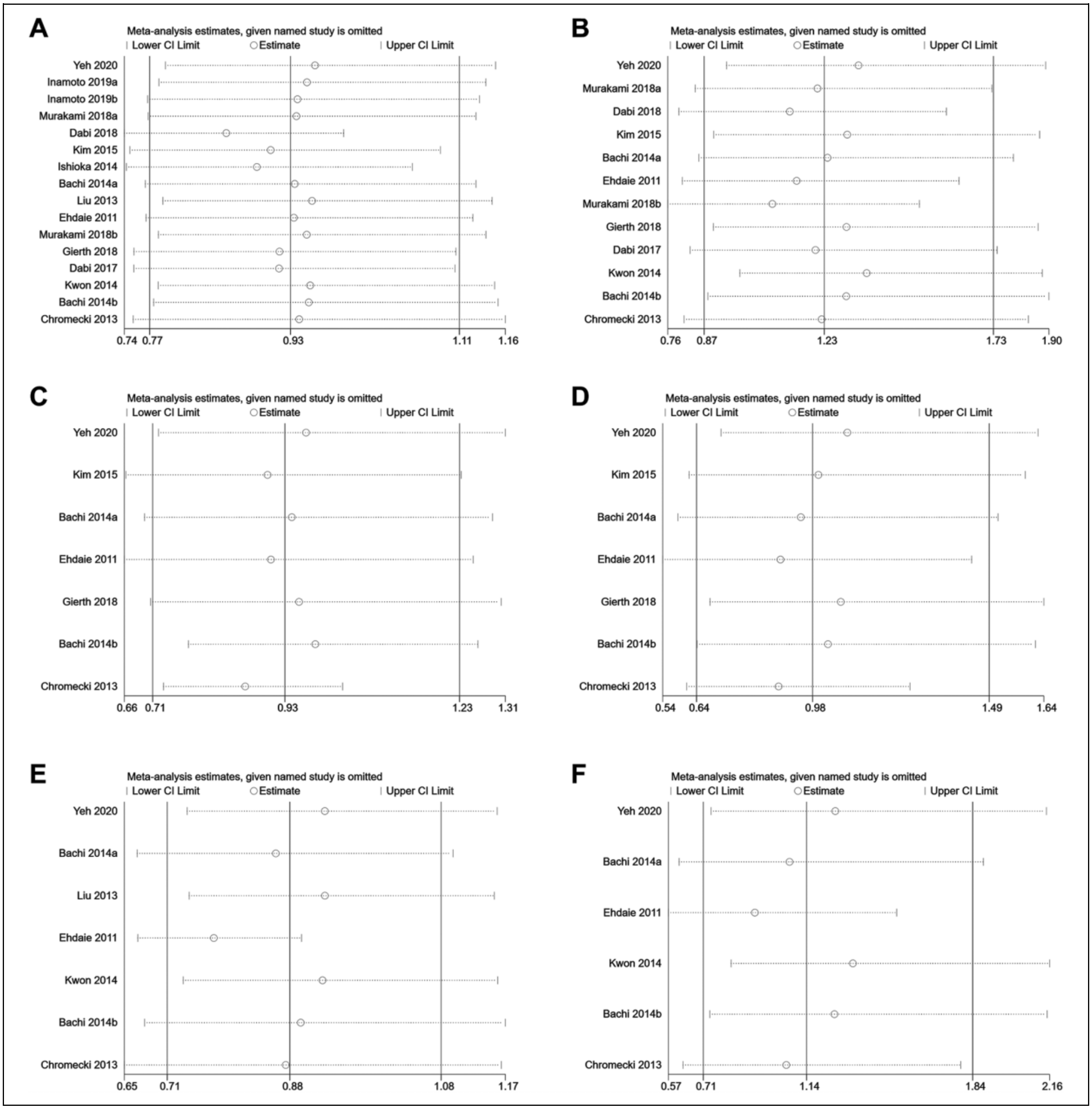

Figure 3. Sensitivity analysis for (A) CSS of overweight population; (B) CSS of obese population; (C) OS of overweight population; (D) OS of obese population; (E) RFS of overweight population; (F) RFS of obese population. CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival.

Publication Bias and Sensitivity Analysis

No evidence of publication bias was present according to Begg's test (overweight-CSS: P = 0.620; overweight-OS: P = 0.881; overweight-RFS: P = 0.881; obesity-CSS: P = 0.244; obesity-OS: P = 0.764; obesity-RFS: P = 0.851; underweight-CSS: P = 0.806) and Egger's test (overweight-CSS: P = 0.290; overweight-OS: P = 0.157; overweight-RFS: P = 0.974; obesity-CSS: P = 0.901; obesity-OS: P = 0.178; obesity-RFS: P = 0.544; underweight-CSS: P = 0.492) (Figures not shown). Sensitivity analyses did not reveal any significant change in the overall estimated effect size after removing studies one by one (Figure 4), which indicated the robustness of our results.

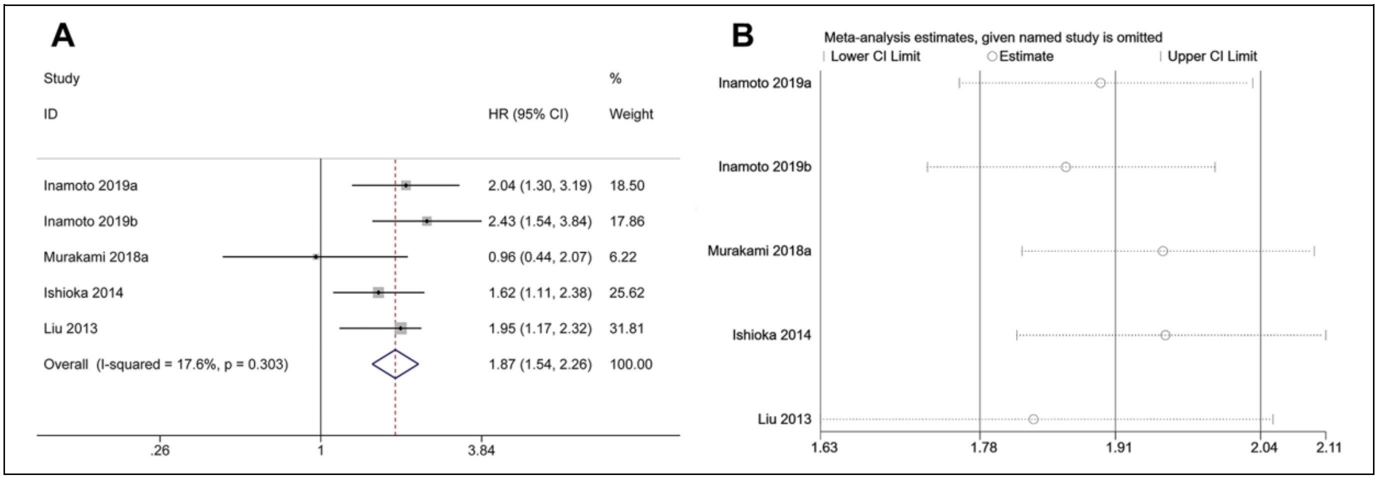

Figure 4. Meta-analysis for underweight population. (A) Forest plot showing pooled hazard ratio; (B) Sensitivity analysis.

Discussion

Our study is in fact the first meta-analysis discussing the prognostic role of BMI in UC patients treated with radical surgeries. After systematic literature search and review, a total of 13 studies comprising over 12,200 patients were included. Different BMIs in these articles were categorized into overweight, obesity, normal weight or underweight, according to guidelines. We found that overweight could predict better CSS and RFS for UC patients after radical surgeries, while underweight could predict worse CSS for UTUC patients after RNU. Besides, we found that obesity was associated with inferior CSS, OS and RFS. Our study confirmed that BMI could serve as a prognostic indicator for UC patients treated with RC or RNU. Since BMI is easy to be measured, it might be utilized to predict survival for this group of patients in clinical settings.

The relationship between BMI and diseases is complex and has been explored since long time ago. Previous studies revealed that BMI was related to various non-cancer diseases, such as orthopedic trauma and chronic obstructive pulmonary disease.[27,28] In recent years, many studies using meta-analytic methods focused on cancer risk, and demonstrated that overweight/obesity increased the risk of kidney cancer, cervical cancer and bladder cancer.[29-31] There are also studies investigating the prognostic value of BMI in other cancers. Krasniqi et al. showed that obesity correlated with worse OS in patients with HER2-positive breast cancer who received pertuzumab.[32] Similarly, Shepshelovich et al. revealed that both underweight and obesity were associated with inferior stage-specific survival in patients with small-cell lung cancer and non-small-cell lung cancer.[33] Notably, in UC patients who underwent radical surgeries, BMI is not only related to long-term oncologic outcomes, but is also associated with perioperative outcomes. For example, Holz et al. found that a higher preoperative BMI was an independent risk factor for perioperative complications after RC.[34] Svatek et al. showed that increasing BMI was significantly associated with the development of postoperative paralytic ileus after RC.[35]

The underlying mechanisms of these results are still unclear. BMI is indeed a surrogate of adiposity, which could indicate the amount of visceral fat and a person's nutritional status. Since thick renal parenchyma acted as a protective barrier against tumor spreading in pT3 UTUC,[36] it was reasonable to imagine that thicker fat barrier could also prevent tumor invasion and decrease residual tumor after RNU. Besides, it was proposed that an appropriate nutritional reserve might improve mortality.[37] However, obesity might be a potential cause of surgical difficulty and insufficient tumor resection,[13] which could partially explain the inferior survival of obese patients. Another hypothesis is that cytokines produced by obese patients' fat tissue could induce chronic inflammation in tumor microenvironment, which may lead to cancer progression.[38] In a review discussing molecular mechanisms linking obesity and cancer, obese patients often have insulin resistance which is associated with activating PI3K/AKT, mTOR/cyclin D1, mTOR/HIF1A/VEGF and Ras pathways that could stimulate tumor growth.[39] As for underweight, it is associated with loss of muscle and fat tissue due to sarcopenia or cachexia, which indicated poor outcomes in previous studies.[40] Future studies are needed to elucidate relevant mechanisms.

The present study has several limitations. Firstly, because we enrolled 12 retrospective studies and 1 prospective study, there might be selection bias. Secondly, there were differences in defining overweight and obesity between Asian-based studies and Westerner-based studies. Hence, we should interpret the results and apply them to clinical settings with caution. Thirdly, important comorbidities such as smoking and physical activity levels were not taken into account during multivariate analyses in these studies, which could induce potential bias. Lastly, there was significant heterogeneity among studies on overweight and obesity. Although subgroup analyses revealed some sources of heterogeneity, there were still some that could not be identified. Therefore, additional large-scale prospective studies using consecutive cohorts and adjusting common comorbidities are needed to confirm our findings.

Conclusions

The results of our meta-analysis showed that overweight was associated with better CSS and RFS in UC patients treated with radical surgeries. Obesity was correlated with worse CSS, OS and RFS in the same population. Underweight predicted inferior CSS in UTUC patients treated with RNU. BMI stratification may help guide UC patients' prognostication and subsequent treatment after radical surgeries.

Authors' Note

Zhiqiang Yang, Yunjin Bai and Xu Hu contributed equally to this work.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ORCID iD

Ping Han https://orcid.org/0000-0003-0537-3829

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