Prognostic impact of preoperative anemia on upper tract urothelial carcinoma

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Abstract

The aim of this study was to investigate the effect of preoperative anemia on the prognosis of patients who underwent radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC).

A total of 620 patients with UTUC were retrospectively analyzed. Anemia was decided by preoperatively measured hemoglobin values based on the World Health Organization (WHO) classification. Kaplan–Meier method and Cox proportional hazards regression models were used to analyze the relationship between anemia and survival outcomes. The meta-analysis part was performed according to PRISMA guidelines.

The median follow-up was 51 (range: 1–168) months. A total of 246 patients had preoperative anemia in our cohort. Anemia was found to be related to high-grade ($P < .001$), sessile architecture ($P = .001$), advanced T stage ($P < .001$), lymphovascular invasion (LVI) ($P = .006$), and worse chronic kidney disease (CKD) stage ($P = .012$). Kaplan–Meier curves revealed that patients with preoperative anemia had worse overall survival (OS), cancer-specific survival (CSS), and disease recurrence-free survival (RFS) (all $P < .001$). Multivariable Cox analyses found that anemia was an independent predictor of CSS [hazard ratio (HR) 1.719, 95% confidence interval (95% CI): 1.285–2.300], RFS (HR 1.427, 95% CI: 1.114–1.829) and OS (HR 1.756, 95% CI: 1.353–2.279). Among patients without end-stage renal disease (ESRD, n = 614), the anemia was also proved to be associated with worse outcomes in multivariable Cox analysis (OS, HR 1.759, 95% CI: 1.353–2.287; CSS, HR 1.726, 95% CI: 1.289–2.311, and RFS, HR 1.431, 95% CI: 1.117–1.837). Seven studies were included in the meta-analysis, and the pooled results showed that anemia was also related to worse CSS (HR 2.05, 95% CI: 1.73–2.44), RFS (HR 1.57, 95% CI: 1.30–1.90), and OS (HR 1.53, 95% CI: 1.10–2.13), but not related to intravesical recurrence (HR 1.17, 95% CI: 0.75–1.82).

Preoperative anemia was proved to be significantly associated with worse oncologic outcomes in patients with UTUC following RNU.

Abbreviations: CKD = chronic kidney disease, CSS = cancer-specific survival, ESAs = erythropoiesis-stimulating agents, ESRD = end-stage renal disease, IVR = intravesical recurrence, MFS = metastasis-free survival, OS = overall survival, RFS = recurrence-free survival, RNU = radical nephroureterectomy, UTUC = upper tract urothelial carcinoma.

Keywords: anemia, nephroureterectomy, prognosis, upper urinary tract, urothelial carcinoma

1. Introduction

Upper tract urothelial carcinomas (UTUCs) are tumors derived from urothelium along the pyelocaliceal cavities and ureter, accounting for approximately 5% to 10% of urinary tract carcinomas.[1] While, its incidence rate is higher in China, especially in Taiwan district, due to the use of traditional herbs which contain aristolochic acid.[2] Radical nephroureterectomy (RNU) with bladder cuff excision is the gold standard treatment for UTUC and has provided durable local tumor control and

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better long-term survival.[1,3] Although surgical and medical management has improved, the 5-year cancer-specific mortality rates remain relatively high, ranging from 20% to 30%.[4]

Studies have reported some traditional prognostic predictors for UTUC after RNU, such as pathological tumor stage and grade, tumor location and architecture, lymphovascular invasion status, concomitant carcinoma in situ, and age.[5] Recently, an increasing interest in biomolecular predictors for UTUC has been noted, including impaired renal function,[6] and elevated C-reactive protein,[7] which have been investigated as prognostic factors for urothelial carcinoma.[8] Although several studies have reported that preoperative anemia may also have a potential to be an independent predictor of oncologic outcomes for UTUC after RNU, its role has not been fully investigated and their results are still controversial.[2,9–15] As it is easily available from preoperative routine examinations in clinical practice, a better understanding of preoperative hemoglobin level may improve prognostication for urothelial carcinoma after RNU.

Therefore, in this study, we aimed to further investigate the effect of preoperative anemia on oncologic outcomes of patients who underwent RNU for UTUC in our center and perform a literature review.

2. Patients and methods

2.1. Patients

The data of 688 patients with UTUC received RNU treatment between October 2003 and December 2015 were collected from our center with approval from the institutional review board. Six patients with the previous cystectomy for invasive bladder cancer and 5 patients underwent RNU and radical cystectomy were excluded; Fifty-seven patients were excluded due to missing data on clinicopathological variables or follow-up, and preoperative hemoglobin. No single patient received neoadjuvant chemotherapy before surgery. Therefore, a total of 620 patients were retrospectively reviewed. Lymph node dissection was not routinely performed.

All RNU specimens were respectively processed according to standard procedures. Tumor stage and grade were evaluated according to the 2002 American Joint Committee of Cancer TNM classification and the WHO International Society of Urological Pathology consensus classification, respectively. The preoperatively hemoglobin values of all patients were used for analysis and obtained from blood tests within 30 days before surgery. Anemia is defined as 13 mg/dL or less in males and 12 mg/dL or less in females according to the WHO guideline.[16] Patients were categorized into 2 groups (normal or anemia group) based on hemoglobin levels. The clinicopathological data, including patients' age, gender, smoking history, surgical approach and renal function, preoperative hydronephrosis, and tumor side as well as tumor size were also collected. End-stage renal disease (ESRD) was defined as patients with stage 5 chronic kidney disease (CKD).

2.2. Follow-up

Patients were followed every 3 to 4 months for the first year after surgery according to the guideline, semiannually for the second and third year, and annually thereafter, or as clinically indicated with urinary cytology and excretory urography of the contralateral upper urinary tract, and routine check-ups that included history, physical examination, blood laboratory tests, and chest

radiography. If clinically indicated, selective bone scan and chest/abdomen computed tomography (CT)/magnetic resonance imaging (MRI) were elevated.[17] Disease recurrence was defined as local recurrence in the operating field, lymph node spread, and/or distant metastasis that had not been found in the preoperative examination. Specifically, the tumor found in the urinary bladder or contralateral upper urinary tract after surgery was not regarded as tumor relapse.

2.3. Systematic review

The systematic literature review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart and followed the PRISMA guidelines for meta-analysis.

2.4. Statistical analysis

Continuous variables were analyzed using Student t test and categorical variables were elevated using the Chi-squared test or Fisher exact test. Univariable and multivariable logistic regression analysis were used to evaluate the anemia with clinicopathological features. The Kaplan–Meier method was used to calculate survival outcomes, including overall survival (OS), cancer-specific survival (CSS), and disease recurrence-free survival (RFS), and the log-rank test was used to assess differences. Univariable and multivariable Cox proportional hazards regression models were used to evaluate the relationship between variables and OS, CSS and RFS. Risk factors with a P value <.1 in the univariable analysis were included in the multivariable analysis model. Especially, CKD stage was also included in multivariable models due to its potential covariant effect with anemia. Hazard ratios (HRs) with their 95% confidence intervals (95% CIs) were used to assess the strength of the individual variables. All reported P values were 2-sided with statistical significance set at $P < .05$. Statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY).

In terms of meta-analysis, Stata v. 12.0 (StataCorp, College Station, TX) was used to perform all statistical analyses. Statistic heterogeneity scores were assessed by using both the standard Cochrane Q test and I^2 statistic to quantify inconsistency across studies and to assess the impact of meta-analysis heterogeneity. A value of $P < .05$ for Cochrane Q test or an I^2 statistic > 50% indicates a considerable level of heterogeneity, resulting in the use of the random-effects model. Publication bias was investigated by visual inspection of Begg funnel plots.

3. Results

The baselines of patients included in the present study are summarized in Table 1. The median follow-up duration was 51 (range: 1–168) months. The mean age of the whole cohort was 65.70 ± 11.35 years. Only 6 patients had ESRD in this cohort. Four hundred sixty-two patients had high-grade tumors and 310 patients were diagnosed with the ≥T3 stage. A total of 246 patients had preoperative anemia. Among them, 188 patients had slight level anemia, 53 patients had moderate anemia, and only 5 cases had severe anemia. Anemia was found to be related to high-grade ($P < .001$), sessile architecture ($P = .001$), advanced T stage ($P < .001$), lymphovascular invasion (LVI; $P = .006$), and worse CKD stage ($P = .012$). No relationship was found between anemia and tumor size or CVH.

Table 1

Baseline characteristics of 620 patients with upper tract urothelial carcinoma included in the present study.

Variables	Total (n=620)	Anemia (-) (n=374)	Anemia (+) (n=246)	P
Age, y (Mean±SD)	65.70±11.35	64.71±11.57	67.21±10.85	.007
Male/Female, n	355/265	218/156	137/109	.522
CVH (with/without), n	143/477	82/292	61/185	.406
LVI (present/absent)	100/520	48/326	52/194	.006
Size (>3/≤3 cm), n	433/187	258/116	175/71	.567
Margin status (positive/negative), n	50/570	30/344	20/226	.961
Multifocality (with/without), n	103/517	73/301	30/216	.017
Tumor side (left/right), n	315/305	188/186	127/119	.741
Tumor grade (high/low)	462/158	260/114	202/44	<.001
Tumor site, n (%)				<.001
Pelvicalyceal	350 (56.5)	196 (52.4)	154 (62.6)	
Ureteric	161 (26.0)	119 (31.8)	42 (17.1)	
Both	109 (17.6)	59 (15.8)	50 (20.3)	
Tumor stage, n (%)				<.001
pTa, pTis, pT1	187 (30.2)	124 (33.2)	63 (25.6)	
pT2	123 (19.8)	90 (24.1)	33 (13.4)	
pT3	218 (35.2)	119 (31.8)	99 (45.4)	
pT4	92 (14.8)	41 (11.0)	51 (20.7)	
Lymph node status, n (%)				.058
pN0	82 (13.2)	49 (13.1)	33 (13.4)	
pNx	472 (76.1)	294 (78.6)	178 (72.4)	
pN+	66 (10.6)	31 (8.3)	35 (14.2)	
Tumor architecture (sessile/papillary), n	427/193	238/136	189/57	.001
CKD stage				.012
CKD 1 (>90 mL/min/1.73 m^2)	88 (14.2)	53 (14.2)	35 (14.2)	
CKD 2 (60–89 mL/min/1.73 m^2)	273 (44.0)	176 (47.1)	97 (39.4)	
CKD 3 (30–59 mL/min/1.73 m^2)	239 (38.5)	140 (37.4)	99 (40.2)	
CKD 4 (15–30 mL/min/1.73 m^2)	14 (2.3)	4 (1.1)	10 (4.1)	
CKD 5 (<15 mL/min/1.73 m^2)	6 (1.0)	1 (0.3)	5 (2.0)	
Surgical approach (laparoscopy/open), n	178/442	126/248	52/194	.001
Hydronephrosis (yes/no), n	376/244	235/139	141/105	.169
Bladder cancer, n (%)				.461
Without	537 (86.6)	325 (86.9)	212 (86.2)	
With history	9 (1.5)	7 (1.9)	2 (0.8)	
Concomitant	74 (11.9)	42 (11.2)	32 (13.0)	
Adjuvant therapy (yes/no), n	255/365	171/203	84/162	.004
Slight anemia, n	188 (30.3)	–	188 (76.4)	
Moderate anemia, n	53 (8.5)	–	53 (21.5)	
Severe anemia, n	5 (0.8)	–	5 (2.1)	

CKD = chronic kidney disease, CVH = concomitant variant histology, LVI = lymphovascular invasion.

The receiver operating characteristic (ROC) curve showed that the area under the curve (AUC) of anemia was 0.598. Kaplan–Meier curves revealed that patients with preoperative anemia had worse OS, CSS, and RFS (all $P < .001$) (Fig. 1A–C). Univariable Cox analysis found that anemia was related to poor survival outcomes of patients with UTUC (CSS: HR 2.112, 95% CI: 1.597–2.794; RFS: HR 1.724, 95% CI: 1.361–2.185; and OS: HR 2.088, 95% CI: 1.627–2.681, respectively) (Table 2).
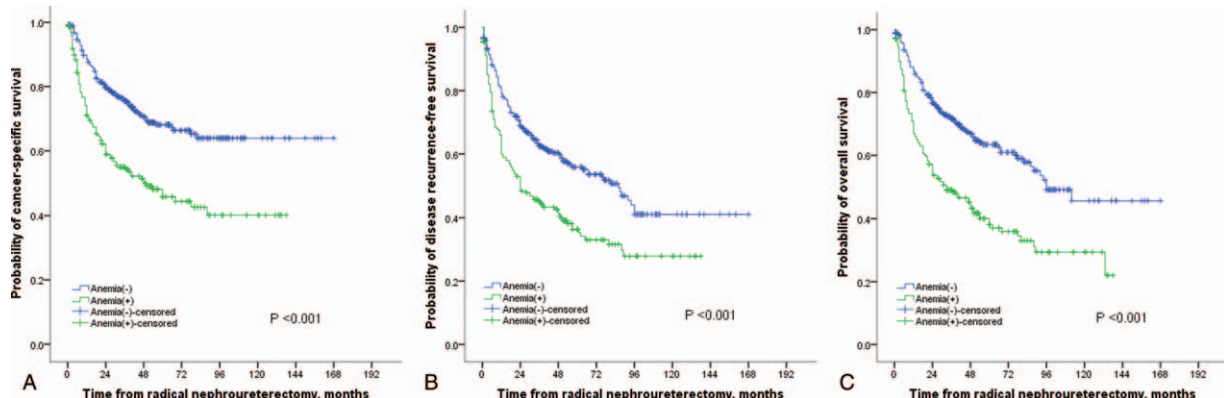

Figure 1. Kaplan–Meier curves for CSS (A), RFS (B), and OS (C) stratified according to preoperative hemoglobin values in patients undergoing RNU of UTUC.

Table 2

Cox proportional hazard univariate analysis to predict survival outcomes of patients with upper tract urothelial carcinoma.

Variable	Cancer-specific survival		Recurrence-free survival		Overall survival	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age, y (continuous)	0.992 (0.980–1.005)	.230	0.995 (0.985–1.006)	.373	1.000 (0.989–1.012)	.963
Sex (male vs female)	0.842 (0.636–1.114)	.229	0.893 (0.704–1.132)	.350	0.902 (0.701–1.159)	.418
Tumor grade (high vs low)	3.219 (2.099–4.935)	<.001	2.268 (1.652–3.115)	<.001	2.736 (1.912–3.914)	<.001
Margin status (positive vs negative)	2.221 (1.459–3.381)	<.001	1.870 (1.279–2.734)	.001	2.030 (1.377–2.993)	<.001
LVI (positive vs negative)	2.707 (1.969–3.723)	<.001	2.215 (1.670–2.938)	<.001	2.474 (1.850–3.309)	<.001
CVH (with vs without)	2.340 (1.741–3.145)	<.001	1.980 (1.531–2.561)	<.001	2.139 (1.680–2.863)	<.001
Tumor size (≥3 vs <3 cm)	2.019 (1.447–2.818)	<.001	1.923 (1.457–2.537)	<.001	1.957 (1.458–2.627)	<.001
Tumor architecture (sessile vs papillary)	3.555 (2.396–5.275)	<.001	2.523 (1.876–3.392)	<.001	2.954 (2.125–4.108)	<.001
Hydronephrosis (yes vs no)	1.283 (0.956–1.721)	.097	1.404 (1.092–1.805)	.008	1.375 (1.055–1.792)	.018
Tumor site		.624		.667		.777
Ureteric vs pelvicalyceal	1.023 (0.736–1.422)	.893	0.971 (0.733–1.287)	.837	0.961 (0.713–1.294)	.792
Both vs pelvicalyceal	1.203 (0.825–1.755)	.337	1.139 (0.824–1.575)	.432	1.104 (0.782–1.560)	.573
Surgical approach (laparoscopic vs open)	0.706 (0.504–0.990)	.043	0.897 (0.682–1.178)	.433	0.752 (0.555–1.018)	.065
Tumor stage		<.001		<.001		<.001
pT2 vs pTis, Ta, T1	1.538 (0.902–2.622)	.114	1.395 (0.927–2.100)	.111	1.536 (0.973–2.423)	.065
pT3 vs pTis, Ta, T1	3.422 (2.215–5.286)	<.001	2.655 (1.894–3.723)	<.001	3.130 (2.149–4.558)	<.001
pT4 vs pTis, Ta, T1	9.153 (5.794–14.459)	<.001	6.737 (4.645–9.771)	<.001	7.836 (5.239–11.720)	<.001
Lymph node status		<.001		<.001		<.001
pNx vs pN0	1.457 (0.889–2.386)	.135	1.525 (1.018–2.282)	.040	1.481 (0.965–2.273)	.073
pN+ vs pN0	6.259 (3.613–10.843)	<.001	5.477 (3.419–8.773)	<.001	5.549 (3.390–9.084)	<.001
Stage 3–5 vs stage 1–2 CKD	1.009 (0.761–1.337)	.953	1.128 (0.890–1.430)	.317	1.095 (0.853–1.407)	.476
Anemia (yes vs no)	2.112 (1.597–2.794)	<.001	1.724 (1.361–2.185)	<.001	2.088 (1.627–2.681)	<.001
Adjuvant therapy (yes vs no)	0.989 (0.748–1.309)	.940	1.106 (0.873–1.401)	.402	0.911 (0.709–1.171)	.466

CKD = chronic kidney disease, CVH = concomitant variant histology, LVI = lymphovascular invasion.

Multivariable Cox analysis further confirmed that anemia was an independent predictor of worse CSS (HR 1.719, 95% CI: 1.285–2.300; P < .001), RFS (HR 1.427, 95% CI: 1.114–1.829; P = .005), and OS (HR 1.756, 95% CI: 1.353–2.279; P < .001) (Table 3). But anemia was not associated with intravesical recurrence (IVR) (HR 1.086, 95% CI: 0.755–1.564; P = .656). The study also confirmed that tumor stage, tumor grade, LNM, CVH, tumor size, and tumor architecture were independent predictors of survival outcomes in UTUC patients (Table 3).

Subgroup analysis based on the level of anemia was performed and the results found that both slight and moderate anemia

contributed to worse OS (HR 1.689, 95% CI: 1.278–2.233 and HR 2.101, 95% CI: 1.379–3.200, respectively), CSS (HR 1.595, 95% CI: 1.163–2.188 and HR 2.331, 95% CI: 1.491–3.644, respectively), and RFS (HR 1.339, 95% CI: 1.024–1.751 and HR 1.842, 95% CI: 1.229–2.761, respectively) in multivariable model, but severe anemia was not related to survival outcomes (OS, HR 1.206, 95% CI: 0.292–4.988; CSS, HR 1.316, 95% CI: 0.316–5.482, and RFS, HR 0.831, 95% CI: 0.197–3.360, respectively).

Among patients without ESRD (n=614), the anemia was proved to be associated with worse outcomes in both univariable and multivariable Cox analysis (OS, HR 1.759, 95% CI

Table 3

Cox proportional hazard multivariate analysis to predict survival outcomes of patients with upper tract urothelial carcinoma.

Variable	Cancer-specific survival		Recurrence-free survival		Overall survival	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Tumor grade (high vs low)	1.881 (1.183–2.991)	.008	1.492 (1.053–2.115)	.025	1.710 (1.156–2.530)	.007
Margin status (positive vs negative)	1.102 (0.708–1.714)	.667	0.989 (0.662–1.477)	.957	1.040 (0.692–1.564)	.850
LVI (positive vs negative)	1.139 (0.797–1.628)	.475	1.021 (0.741–1.408)	.898	1.113 (0.803–1.542)	.519
CVH (with vs without)	1.609 (1.178–2.198)	.003	1.388 (1.058–1.822)	.018	1.574 (1.188–2.085)	.002
Tumor size (≥3 vs <3 cm)	1.667 (1.176–2.363)	.004	1.660 (1.243–2.218)	.001	1.693 (1.242–2.308)	.001
Tumor architecture (sessile vs papillary)	1.678 (1.070–2.631)	.024	1.430 (1.014–2.017)	.041	1.488 (1.017–2.175)	.041
Hydronephrosis (yes vs no)	0.929 (0.682–1.265)	.639	1.045 (0.801–1.364)	.744	1.005 (0.760–1.329)	.972
Surgical approach (laparoscopic vs open)	0.949 (0.668–1.348)	.768	1.112 (0.838–1.477)	.461	0.970 (0.709–1.328)	.851
Tumor stage		.002		<.001		<.001
pT2 vs pTis, Ta, T1	1.243 (0.714–2.163)	.442	1.169 (0.763–1.790)	.473	1.287 (0.801–2.068)	.297
pT3 vs pTis, Ta, T1	1.767 (1.080–2.889)	.023	1.682 (1.145–2.470)	.008	1.741 (1.135–2.671)	.011
pT4 vs pTis, Ta, T1	2.892 (1.617–5.173)	<.001	2.878 (1.782–4.646)	<.001	2.855 (1.712–4.762)	<.001
Lymph node status		.001		<.001		.001
pNx vs pN0	1.765 (1.064–2.926)	.028	1.841 (1.216–2.786)	.004	1.817 (1.169–2.824)	.008
pN+ vs pN0	2.972 (1.644–5.375)	<.001	2.928 (1.758–4.875)	<.001	2.761 (1.621–4.703)	<.001
Anemia (yes vs no)	1.731 (1.293–2.317)	<.001	1.420 (1.107–1.821)	.006	1.758 (1.353–2.282)	<.001
Stage 3–5 vs stage 1–2 CKD	0.888 (0.662–1.192)	.430	1.063 (0.828–1.365)	.632	0.984 (0.756–1.279)	.901

CKD = chronic kidney disease, CVH = concomitant variant histology, LVI = lymphovascular invasion.

Table 4

Overall characteristics of studies included in meta-analysis.

Study	Duration	Follow-up mo (mean ± SD)	No. of patients	No. of anemic patients	Age [y, (mean ± SD)]	Tumor location (pelvis/ureter/both)	Type of operation (open/laparoscopic)	Tumor stage (<3/≥3)	History of bladder cancer (yes/no)	No. of adjuvant chemotherapy	Anemia criteria	NOS
Gunay et al[10]	1987–2009	56.2 ± 5.3	101	32	60.5 ± 1.1	70/26/0	86/15	50/46	18/78	NR	WHO*	7
Morizane et al[14]	1995–2011	37.9 ± 27.5	99	68	73.0 ± 7.0	35/53/11	64/35	59/38	15/84	33	<12 vs ≥12 mg/dL	6
Rink et al[12]	1992–2012	30 ± 27.3	282	112	69.0 ± 9.6	159/74/49	220/62	111/171	NR	47	WHO*	7
Milojevic al[11]	1999–2013	34.5 ± 25.5	238	97	66.5 ± 8.9	142/96/0	NR	119/119	58/180	48	Adjusted for age†	7
Xing et al[2]	2003–2013	65.0	686	422	68.0 ± 11.7	366/320/0	234/452	386/300	0/686	NR	WHO*	8
Yeh et al[13]	2000–2013	NR	370	242	65.5 ± 10.3	143/161/66	227/143	83/287	NR	38	WHO*	7
Tan et al (present)	2003–2015	56.3	620	246	65.7 ± 11.4	350/161/109	178/442	310/310	9/611	182	WHO*	8

IQR = interquartile range, NOS = Newcastle–Ottawa Scale, NR = not reported, SD = standard deviation, WHO = World Health Organization.

* Anemia in WHO criteria is defined as hemoglobin less than 130 and 120 g/L in males and females, respectively.

† Anemia is defined as in male patients younger than 60 years as 13.7 g/dL or less and in those 60 years old or older as 13.2 g/dL or less. In female patients of all ages, the corresponding threshold for anemia was 12.2 g/dL or less.

CI: 1.353–2.287; CSS, HR 1.726, 95% CI: 1.289–2.311, and RFS, HR 1.431, 95% CI: 1.117–1.837 in multivariable model) (Table S1 and S2, http://links.lww.com/MD/C492). However, the impact of anemia on survival in patients with ESRD was unavailable in our cohort due to a small population (n = 6).

Six studies with a total of 1776 participants and our present cohort were included in the systematic review and meta-

analysis.[2,10–14,18] The characteristics of studies included are summarized in Table 4. The pooled results showed that anemia was associated with worse CSS (HR 2.05, 95% CI: 1.73–2.44), RFS (HR 1.57, 95% CI: 1.30–1.90), and OS (HR 1.53, 95% CI: 1.10–2.13), but not related to IVR (HR 1.10, 95% CI: 0.83–1.46) in UTUC patients (Fig. 2). No publication bias was observed among studies analyzing the impact of anemia on CSS
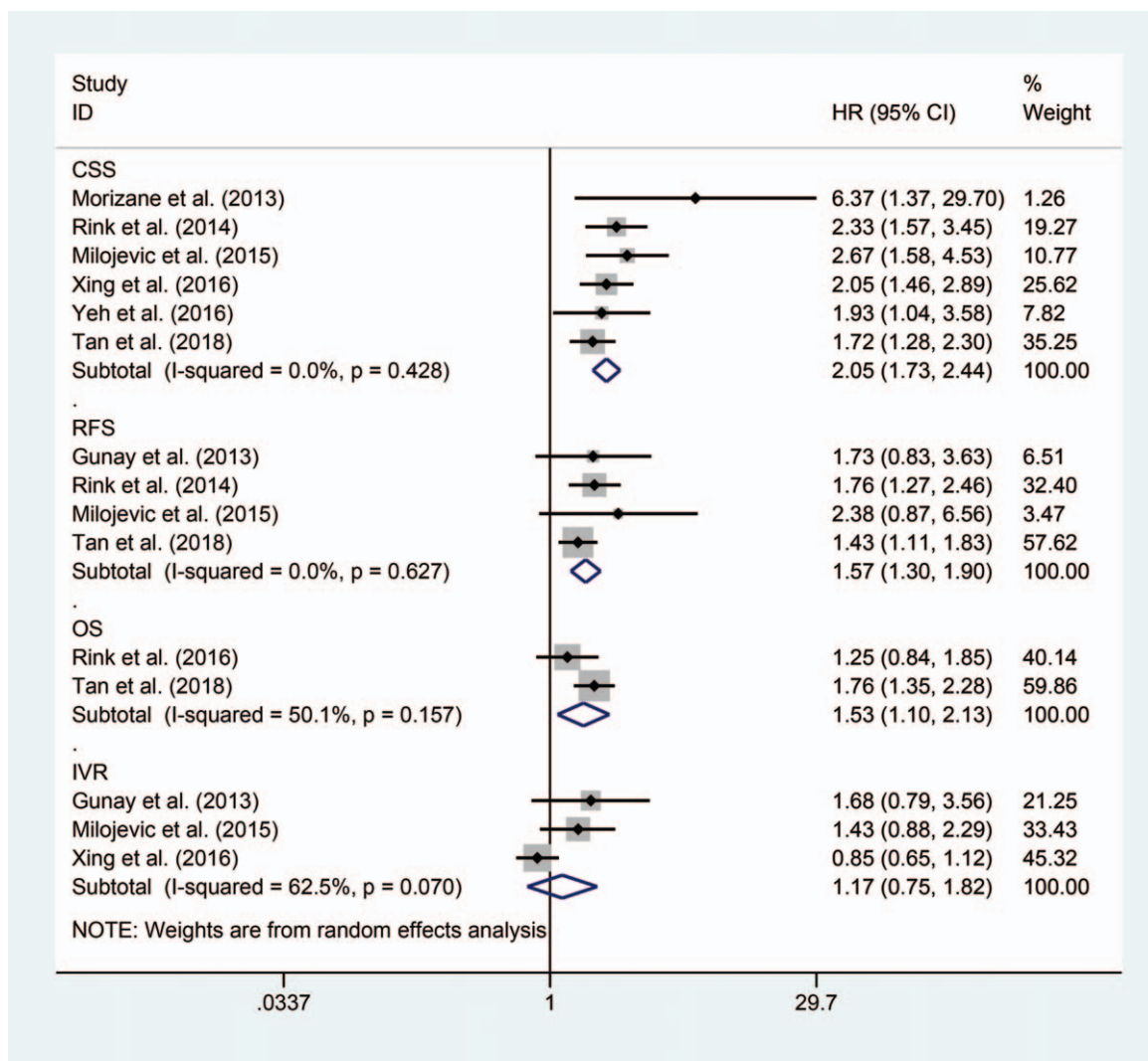

Figure 2. Forrest plots of meta-analyses of the effect of preoperative anemia on oncologic outcomes in patients with UTUC after RNU.

(Begg $P = .133$) (Figure S1, http://links.lww.com/MD/C492). The pooled results also found anemia could lead to inferior CSS (HR 1.82, 95% CI: 1.44–2.31) and MFS (HR 2.21, 95% CI: 1.54–3.18) in those without ESRD (Fig. 3).

4. Discussion

Anemia can result from many causes, such as blood loss, renal insufficiency, bone marrow disorders, and hypothyroidism.[19] Anemia is also common in cancer patients and significantly influenced by the type of malignancy, tumor stage and grade, lymph node metastasis, and the choice of treatment.[11] Caro et al[20] conducted a comprehensive analysis to estimate the effect of anemia on survival in patients with malignant disease. Their result suggested that the relative risk of death increased by 65% in anemic cancer patients; however, the impact of preoperative anemia on patients with UTUC has seldom been assessed. In our cohort, the results found that anemia was an independent predictor of survival outcomes in UTUC patients. Anemia was also associated with high grade, sessile architecture, advanced T stage, LVI, and high stage CKD. But anemia had no association with tumor size and CVH. The pooled results from meta-analysis also suggested that preoperative anemia was associated with worse CSS, RFS, and OS in patients with UTUC after RNU regardless their renal function, but it did not affect IVR.

As we known, renal insufficiency could not only contribute to the poor outcomes of urothelial carcinoma but also related to

causing anemia due to erythropoietin deficiency, uremic-induced inhibitors of erythropoiesis, shortened erythrocyte survival, and iron deficiency.[6,21] Therefore, it is noteworthy to understand the association of anemia with UTUC oncologic outcome at different stages of renal function. Our study revealed that anemia contributed to worse CSS, RFS, and OS in patients without ESRD, while its impact on patients with ESRD was unavailable in this study due to a small population of ESRD patients. The pooled results from meta-analysis also suggested that anemia was related to worse CSS and MFS in patients without ESRD. Moreover, Yeh et al[13] found that there was no difference in CSS or MFS in patients with renal insufficiency ranging from stage 1 to 4 CKD. And they also found in patients with ESRD, preoperative anemia was not related to CSS or MFS ($P = .590$ and $P = .379$, respectively).[13] Anemia occurred more commonly in patients with ESRD, over 90%.[13,15] Consequently, anemia in uremic patients was generally attributed to the process of renal function deterioration rather than the carcinogenesis. Thus, the ESRD may play the main role in causing the worse outcomes in urothelial cancer and anemia is a mere result of ESRD in patients with ESRD, which means anemia was not a predictor of adverse prognosis in this population. Also, Yeh et al[13] thought that the cancer-related anemia was the actual prognostic factor for patients with UTUC.

The relationship between anemia and cancer pathophysiology is complex and multifactorial. In UTUC patients, the impact of adjuvant chemotherapy on anemia by bone marrow suppression
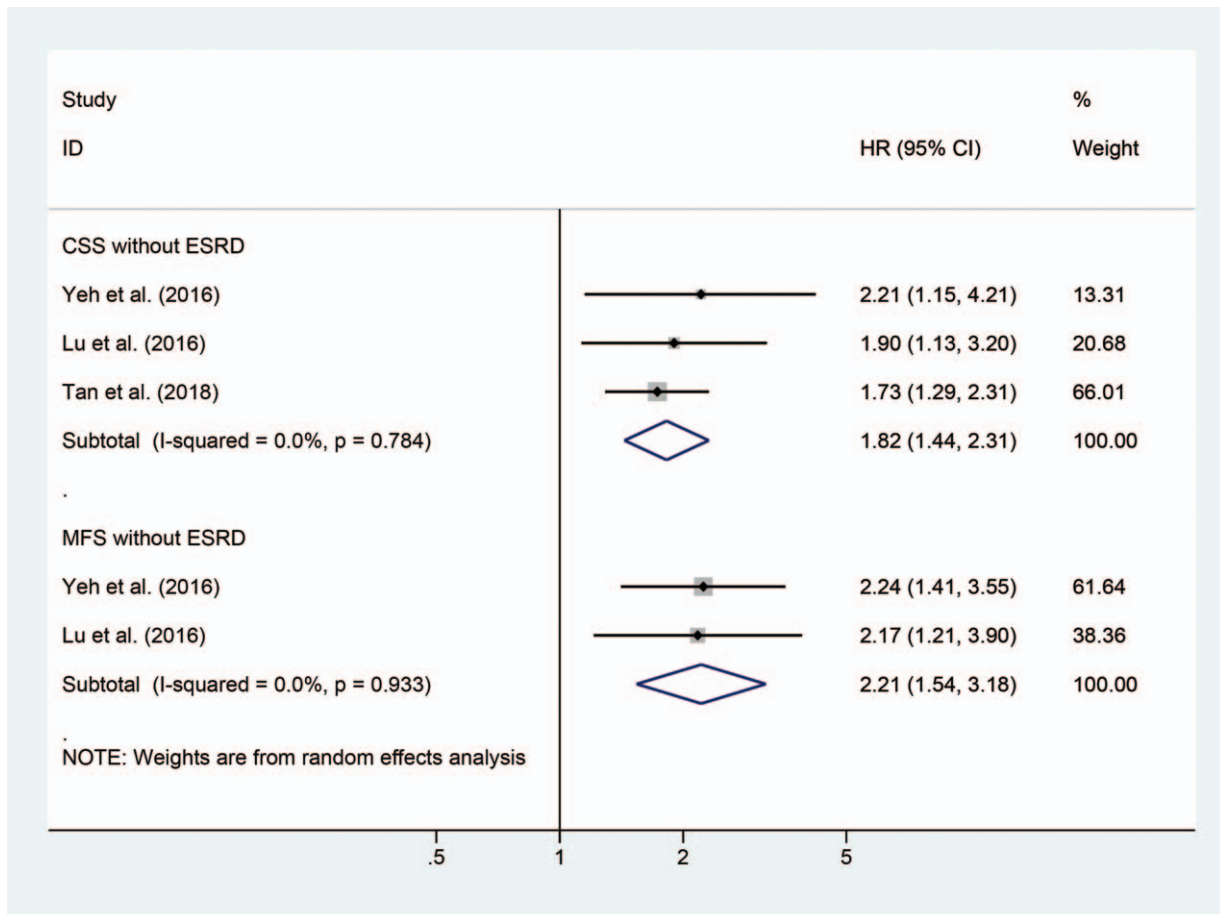

Figure 3. Forrest plots of meta-analyses of the effect of preoperative anemia on oncologic outcomes in UTUC patients without end-stage renal disease.

was controversial, even in opposite directions.[11–13] Gross hematuria is an important but common symptom for the diagnosis of UTUC, which also contribute to the anemia due to blood loss. However, no data on gross hematuria were available currently. Blood loss might also be attributed to the preoperative manipulation, but the only evidence reported that there was no association between interventions and hemoglobin level.[12]

In patients with malignancy, cancer-related anemia is a cytokine-mediated disorder resulting from complex interactions between tumor cells and the immune system. It usually occurs long before the diagnosis of the underlying disease and often a sign of potentially decreased function of organs and systems. Overexpressed certain inflammatory cytokines could shorten survival of red blood cells, suppress erythroid progenitor cells, impair iron utilization, and result in inadequate erythropoietin production.[22] Moreover, low hemoglobin levels correlated with poor performance status and clinical outcome.[22] Therefore, preoperative anemia could be considered as a strong prognostic predictor of worse outcome in patients with UTUC.

Regardless, it is now clear that preoperative anemia is a significant prognostic factor in UTUC following RNU, but whether correcting the preoperative anemia could improve the survival after RNU remains unknown. Currently, managements such as transfusions, erythropoiesis-stimulating agents (ESAs), and iron supplements were normally used to correct the anemia.[23] Because transfusions could quickly correct anemia, doctors often suggested the blood transfusion for anemic patients with cancer who need confine operation, radiotherapy, or chemotherapy. Around 15% anemic patients with cancer were treated with blood transfusions, but its safety and impact on prognosis remain as an issue of debate.[24] Several reports have shown that transfusion contributes to poor prognosis in some kinds of cancers.[24] However, limited evidence suggested that perioperative blood transfusion was associated with inferior OS (HR 1.6, $P=.027$), but not with disease recurrence or cancer-specific mortality in anemic patients with UTUC after RNU.[18] Treatment of ESAs might increase the risk of thrombosis and mortality, although it could improve patients' quality of life.[25] Thus, transfusions and ESAs should be carefully used to treat anemic patients with UTUC.[24,25]

Some limitations of this study should be mentioned; first, its retrospective nature, which may have led to a selection bias. In addition, the surgery methods and adjuvant therapy treatments were a little different between the 2 groups, although we found that these 2 factors did not affect the survival outcomes. Meanwhile, lymphadenectomy was not routinely performed; only 148 patients received lymphadenectomy in our cohort, which may decrease the accuracy of our results even though there was no difference between the 2 groups. Compared with previous studies, we analyzed the impact of different anemia level on survival outcomes and found both the slight and moderate anemia cause worse survival status, while severe anemia had no impact on UTUC patients. Moreover, renal function was fully considered in the present study and was included in multivariable model. Due to the small population of ESRD (n=6), the impact of anemia on patients with ESRD was unavailable in the present study. Future studies are needed to investigate this topic in population with ESRD.

5. Conclusion

Preoperative anemia was significantly associated with worse oncologic outcomes in patients with UTUC following RNU. At

the moment, no evidence investigated whether correcting the preoperative anemia could improve the survival after RNU. Thus, more prospectively designed studies are needed to validate our results.

Author contributions

Q.W. carried out project design, participated in data explanation and manuscript revision. P.T. and N.X. participated in project design, performed data collection and statistical analysis. HT. L. and LQ.Z. helped data collection and provided statistical advice. H.X. reviewed all specimens and made pathology classification. L.Y. and LR.L. checked for statistical inconsistency and interpreted data. L.Y. contributed to data interpretation. P.T. and N.X. drafted the manuscript and all other authors critically reviewed the article.
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