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Original Article

Prognostic role of corrected calcium levels in renal cell carcinoma: a systematic review and meta-analysis

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Abstract: Several recent studies have demonstrated that corrected calcium levels may be closely associated with prognosis in patients with renal cell carcinoma (RCC). In the present study, we conducted a meta-analysis of all available studies in the English literature to assess the prognostic value of corrected calcium levels in patients with RCC. We searched online databases that included PubMed, Embase, and Web of Science, for information on corrected calcium and its association with the outcomes of RCC. A total of 13 studies that included 6,705 patients were analyzed. Elevated corrected calcium levels were associated with a lower overall survival (OS) (hazard ratio = 1.84; 95% confidence interval [CI] = 1.67-2.02; P < 0.001). Furthermore, the association of elevated corrected calcium levels with poor survival was significant even on sub-group analyses for different tumor types, analysis types, cut-off values, and ethnicity. In conclusion, elevated corrected calcium concentration is associated with poor prognosis in patients with RCC, and may be considered as a potential biomarker for assessing the prognosis of this disease.

Keywords: Corrected calcium levels, prognosis, renal cell carcinoma, meta-analysis

Introduction

Renal cell carcinoma (RCC) is the second leading cause of death from urological cancers, and accounts for 2-3% of all cancers in adults [1]. More than 50% of all cases of RCC are diagnosed incidentally. The five-year survival rates of patients diagnosed with early-stage RCC and treated with nephrectomy are high [2]. In contrast, survival is poor among patients with local recurrences or distant metastasis [3]. Several of the prognostic parameters tested for predicting outcomes of renal cell carcinoma have limited reliability [4]. Thus, there is a need for more precise prognostic biomarkers for RCC.

Hyperparathyroidism and malignancy are the cause of increased calcium levels in 90% of cases [5]. The different mechanisms responsible for elevated calcium levels in the setting of RCC include osteolytic bone metastases, tumor secretion of parathyroid hormone-related peptide (PTHrP), and production or activation of calcitriol [6]. Recent studies have demonstrated an association between the corrected calcium levels and the prognosis of RCC [7-18]. However, the results of different studies do not demonstrate a consistent association. Therefore, we conducted this meta-analysis to systematically evaluate the prognostic value of corrected calcium levels in patients with RCC.

Materials and methods

Search strategy

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. A systematic search of PubMed, Embase, and Web of Science, for articles published in the English language, was performed by using the following search terms: "corrected calcium or calcium" (all fields), "prognosis or prognostic or survival or outcome" (all fields), and "kidney cancer or renal cancer or renal carcinoma or renal cell carcinoma" (all fields). In addition, we also checked the references of all identified studies in order to retrieve unpublished but relevant studies.

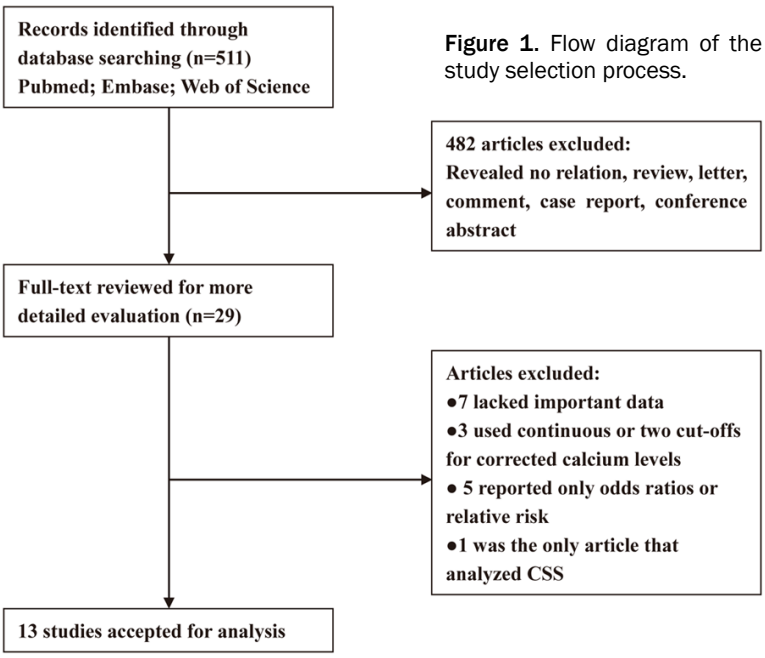

Figure 1. Flow diagram of the study selection process.

Selection criteria

The inclusion criteria to select relevant published studies were as follows: (1) Diagnosis of RCC was histopathologically confirmed, and no other malignancies were studied; (2) Treatment of RCC was limited to surgery, targeted therapy, or immunotherapy; (3) Studies included measurement of corrected calcium levels and analyzed its potential association with RCC; (4) Retrospective or prospective study design; and (5) studies that directly offered the hazard ratio (HR) and 95% confidence interval (CI) or allowed for their calculation. Our exclusion criteria were: (1) Publications related to meeting records, letters, review papers, comments, case reports, or clinical guidelines; (2) Articles concerning cell lines or animal studies; (3) Studies with sample sizes smaller than 40; (4) In cases where duplicate studies were retrieved, all but the study with the largest sample size were excluded.

Quality assessment

The eligible studies included in our meta-analysis were independently assessed by two researchers according to the Newcastle-Ottawa Scale (NOS) guidelines on a rating scale from 0 (lowest) to 9 (highest) [20]. Studies with scores of 6 or more were rated as being of high quality.

Data extraction and conversion

Relevant characteristics and outcome data were extracted from the literature by two independent reviewers. The main data of articles were tabulated as follows: (1) Basic characteristics: first author's last name, publication year, country, and ethnicity; (2) Clinical data: case number, age, gender, tumor type, TNM stage, Fuhrman grade, pathological grade, and follow-up duration; (3) Cut-off value of corrected calcium; and (4) HR for overall survival (OS), cause-specific survival (CSS), and 95% CI. In cases wherein the study provided the results of univariate and multivariate analyses, we chose the latter. Any disagreement was resolved by discussion among the investigators.

Most of the eligible studies included data pertaining to HRs and 95% CIs. If the HR and 95% CI were not available, we calculated the values by using the original data according to the methods described by Tierney *et al*. [21]. We also communicated with the corresponding authors of the published studies by email to request any additional data that were required for the meta-analysis.

Statistical analyses

Pooled HRs and 95% CIs were used to analyze the association between the corrected calcium levels and survival of RCC patients. An observed HR > 1 implied a poorer prognosis in patients with high corrected calcium level, while HR < 1 indicated a better prognosis. We used Cochran's Q test and Higgins I-squared statistic (I^2) for measuring the heterogeneity of the combined HRs. If the *P* value was less than 0.05 and/or I^2 was larger than 50%, the heterogeneity of the combined HRs was considered statistically significant. A random-effects model (DerSimonian-Laird method) was used. In the absence of heterogeneity among the studies, a fixed-effects model (the Mante-Haenszel method) was applied. The factors that may have led to heterogeneity were further analyzed by subgroup analysis. Publication bias was assessed

Table 1. Main characteristics of all studies included in the meta-analysis

Study	Country	Ethnicity	Tumor type	Case number	Age (years)	Gender (M/F)	TNM stage (I/II/III/IV)	Fuhrman grade (I/II/III/IV)	Treatment	Follow-up (months)	Survival analysis	Cut-off value (mg/dl)	Multivariate analysis	HR
Fukushima 2015	Japan	Asian	mRCC	92	65	77/15	NR	NR	MT	Median 19	OS	10	YES	Report
Bodnar 2015	Poland	Caucasian	mRCC	58	60	19/39	NR	NR	Everolimus	NR	OS	10	YES	Report
Koie 2014	Japan	Asian	CCRCC	400	65	286/114	261/41/88/10 (T stage)	NR	Surgery	36	OS	10	YES	Calculate
Heng 2014	Canada	Mixed ethnicity	mRCC	2210	60/61	NR	NR	NR	Targeted therapy	NR	OS	12	NO	Report
Yoon 2013	Korea	Asian	RCC	44	19/25 (< 60/≥60)	32/12	NR	NR	Targeted therapy	Mean 21.9	OS	9	NO	Report
Motzer 2013	USA	Mixed ethnicity	mRCC	1059	60	70%/30%	NR	NR	Sunitinib	NR	OS	10	YES	Report
Du 2013	China	Asian	RCC	286	55.72	185/101	165/55/52/4 (T stage)	17/134/112/23	Surgery	NR	OS	11	YES	Report
Azuma 2012	Japan	Asian	mRCC	84	66.7	58/26	NR	NR	IFN-α	18.3	OS	10	YES	Report
Shinohara 2013	Japan	Asian	mRCC	473	64	329/144	NR	NR	MT	18	OS	10	YES	Report
Richey 2011	USA	Mixed ethnicity	mRCC	188	60.8	123/65	45/28/89/26 (T stage)	NR	Targeted therapy	NR	OS	10	YES	Report
Patil 2011	USA	Caucasian	mRCC	750	NR	NR	NR	NR	MT	NR	OS	NR	YES	Report
Motzer 2010	USA	Caucasian	mRCC	416	61/60	322/94	NR	NR	Everolimus	NR	OS	10	YES	Report
Heng 2009	Canada	Caucasian	mRCC	645	60	473/172	NR	NR	Targeted therapy	24.5	OS	10	YES	Report

Abbreviation: RCC, renal cell carcinoma; mRCC, metastatic renal cell carcinoma; CCRCC, clear cell renal cell carcinoma; mCCRCC, metastatic clear cell renal cell carcinoma; OS, overall survival; CSS, cancer-specific survival; PFS, progression-free survival; HR, hazard ratio; NR, not reported; MT, multiple therapy.

Table 2. Pooled hazard ratios for OS according to subgroup analyses

Variables	Studies	Patients	HR (95% CI)	*P* value	Model	Heterogeneity	
						I^2 (%)	*P*
All	13	6705	1.95 (1.67, 2. 27)	< 0.001	Random	46.9%	0.031
Tumor type							
RCC (all-stage)	2	686	1.37 (1.07, 1.74)	0.011	Fixed	0.0%	0.727
RCC (metastatic)	11	6019	1.94 (1.75, 2.16)	< 0.001	Fixed	36.0%	0.111
Analysis type							
Univariate	2	2254	2.75 (1.96, 3.85)	< 0.001	Fixed	0.0%	0.649
Multivariate	11	4451	1.77 (1.60, 1.96)	< 0.001	Fixed	39.2%	0.087
Cut-off value							
= 10 mg/dl	9	3415	2.07 (1.80, 2.37)	< 0.001	Fixed	0.0%	0.640
Others	4	3290	1.81 (1.31, 2.49)	< 0.001	Random	73.3%	0.010
Ethnicity							
Asian	6	1379	1.62 (1.34, 1.97)	< 0.001	Fixed	31.2%	0.201
Caucasian	4	1869	1.72 (1.50, 1.98)	< 0.001	Fixed	48.0%	0.123
Mixed ethnicity	3	3457	2.31 (1.92, 2.78)	< 0.001	Fixed	0.0%	0.570

Abbreviation: RCC, renal cell carcinoma; OS, overall survival; HR, hazard ratio; CI, confidence intervals.

by using Begg's and Egger's tests. All data analyses were performed with STATA 12.0 (Stata Corporation, College Station, TX, USA). A *P* value lower than 0.05 was considered statistically significant on two-sided tests.

Results

Search results

The process of searching and filtering the literature is shown in **Figure 1**. A total of 511 records were retrieved in accordance with our search method. Following screening of the titles, abstracts, publication categories, and the full text of each article, only 29 articles qualified for the present analysis. Among these, 16 articles were excluded (7 lacked important data, 3 used continuous or two cut-offs for corrected calcium levels, 5 reported only odds ratios or relative risk, and 1 was the only article that analyzed CSS). Finally, 13 articles comprising 6705 patients were included for the meta-analysis [7-17, 22, 23].

Study characteristics

The characteristics of the studies are presented in **Table 1.** The 13 included studies were published between the years 2009 and 2015, and included patients from Japan, Poland, Canada, Korea, China, and the USA, respectively. The ethnicity of the patients was either Asian (20.6%, 1379), Caucasian (27.9%, 1869), or mixed (51.5%, 3457; of Asian and Caucasian descent). Among these studies, the effect of corrected calcium level was explored in cases of metastatic RCC in 11 (that included 6019 patients), and in patients with all-stage RCC in 2 (686 patients). Statistical tests included multivariate analysis in 11 studies (4451 patients) and univariate analysis in 2 studies (2254). Treatment methods included targeted therapies in 7 studies (4620 patients), multiple therapies in 3 studies (1315), surgery in 2 studies (686), and immunotherapy in 1 study (84). HRs were retrieved directly from 12 studies, and calculated by using the original data indirectly for the remaining 1 study. The cut-off value of corrected calcium level in most studies was set at 10 mg/dL (the lower limit of normal).

Quality assessment

According to the Newcastle-Ottawa scale, we assessed the quality of the 13 eligible studies included in our meta-analysis. The quality scores of the studies varied from 4 to 9, with a mean score of 6. A higher score was indicative of better methodology. All 13 studies were included in the subsequent analysis.

Meta-analysis results

The main results of this meta-analysis are shown in **Table 2**. We used a random model to pool the HRs because of the existence of statis-

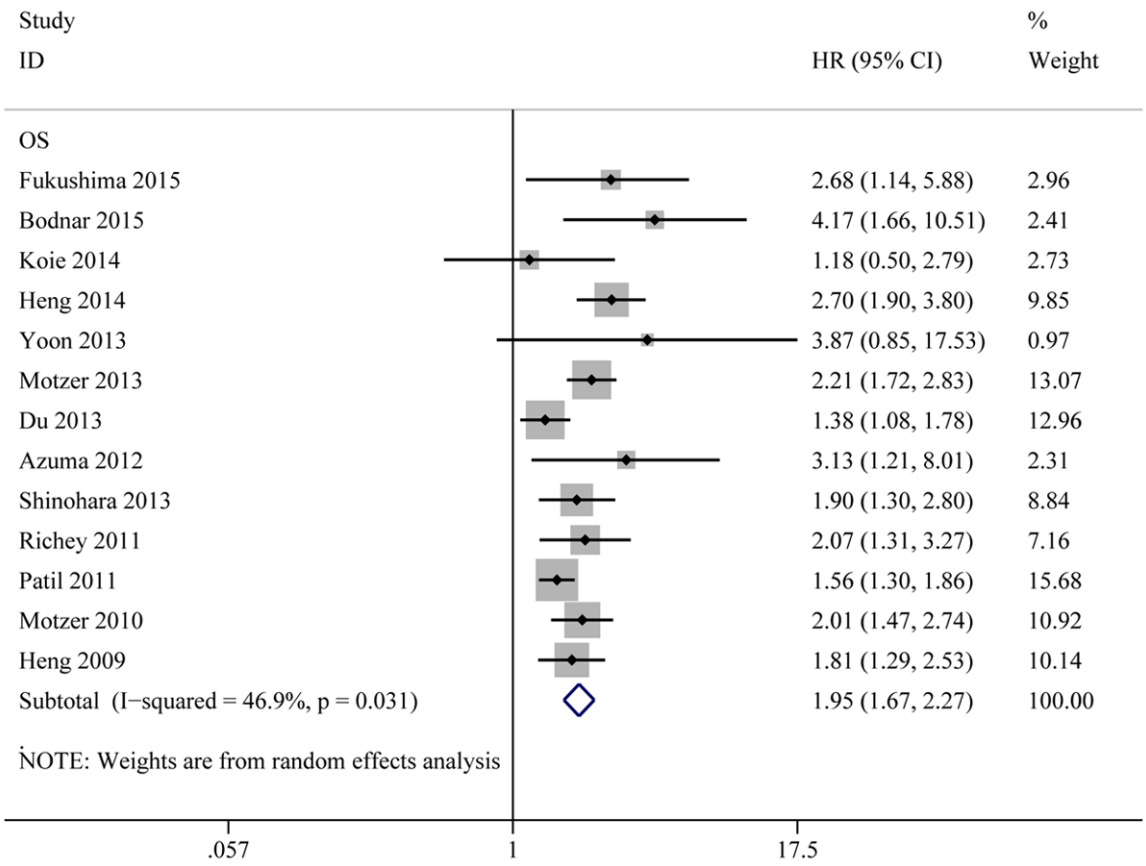

Figure 2. Forest plots of studies evaluating hazard ratios of elevated corrected calcium levels for overall survival in all stages of renal cell carcinoma (RCC).

tical heterogeneity (I^2 = 46.9%; P = 0.031). The pooled data demonstrated that elevated corrected calcium levels predicted poorer overall survival (OS) (HR = 1.95; 95% CI = 1.67-2.27; P < 0.001; **Figure 2**). In order to further test the heterogeneity between these studies, the significance of corrected calcium levels was evaluated by subgroup analysis that included tumor type, analysis type, cut-off value, and ethnicity. Elevated corrected calcium levels were associated with poorer OS for all stages of RCC (HR = 1.37; 95% CI = 1.07-1.74; P = 0.011) as well as for patients with metastatic RCC (HR = 1.94; 95% CI = 1.75-2.16; P < 0.001; **Table 2**). Corrected calcium levels remained significantly associated with poor OS on subgroup analysis as well: univariate analysis (HR = 2.75; 95% CI = 1.96-3.85; P < 0.001) and multivariate analysis (HR = 1.77; 95% CI = 1.60-1.96; P < 0.001); Asian ethnicity (HR = 1.62; 95% CI = 1.34-1.97; P < 0.001), Caucasian ethnicity (HR = 1.72; 95% CI = 1.50-1.98; P < 0.001), and mixed ethnicity (HR = 2.31; 95% CI = 1.92-2.78; P < 0.001); and cut-off value of 10 mg/dl (HR = 2.07; 95% CI = 1.80-2.37; P < 0.001) and other cutoff values (HR = 1.81; 95% CI = 1.31-2.49; P < 0.001).

Sensitivity analysis

Sensitivity analysis, conducted to assess the consistency of the above results, was performed by sequential omission of each individual study by using the "metaninf" STATA command (**Figure 3**). There was no significant change in the pooled HR suggesting that our results were robust.

Publication bias

The Begg's funnel plot, which provides a visual assessment of the included studies and identifies any overt publication bias, was found to be symmetrical (**Figure 4**). An Egger's test, which was applied for the formal evaluation of the studies, confirmed the absence of significant publication bias (P > 0.1).

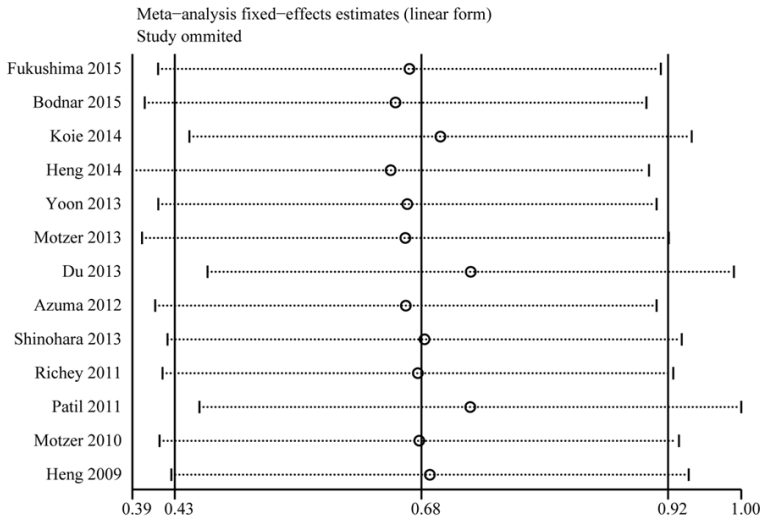

Figure 3. Sensitivity analysis of the included studies.

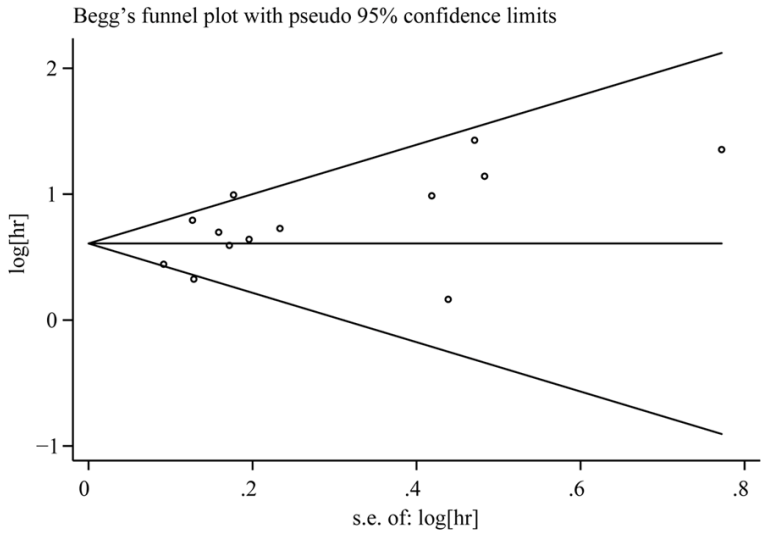

Figure 4. Funnel plots for the evaluation of potential publication bias.

Discussion

Our study provides a systematic analysis of the role of corrected calcium level as a prognostic factor for RCC. We found that an elevated corrected calcium level was associated with shorter OS, regardless of the tumor type, analysis type, cut-off value, or ethnicity, thus confirming its role as a predictor of poor survival in patients with RCC.

Hypercalcemia is defined as elevated serum calcium greater than 2 standard deviations above the normal mean. The serum concentration of total calcium in adults usually ranges between 2.15 and 2.60 mmol/L (8.6-10.4 mg/dL; 4.3-5.2 mEq/L). About 45% of calcium in the peripheral blood is bound to plasma proteins, particularly albumin; approximately 10% is bound to anions such as phosphate and citrate; and the remaining 45% is the free or ionized calcium. Although the ionized fraction of calcium is the component that is readily available for activating cellular processes, most laboratory tests measure the total serum calcium, the levels of which vary according to the fluctuation in serum protein concentration [24]. Therefore, a more accurate diagnosis of hypercalcemia requires interpretation of the calcium values in relation to serum albumin levels, in addition to ensuring that the hypercalcemia is not secondary to lipemia or hemolysis. The correction to account for the serum level of albumin is given as follows: corrected calcium = (total calcium in mg/dL + [0.8 × {4-serum albumin in g/dL}]); if serum albumin is ≥4.0 g/dL, the corrected calcium level is equal to the total calcium level in mg/dL [25].

The concentration of calcium in the extracellular fluid (ECF) is tightly maintained within a narrow range owing to the important role of ionic calcium in numerous cellular functions including cell division, cell adhesion and plasma membrane integrity, protein secretion, muscle contraction, neuronal excitability, glycogen metabolism, and coagulation [26]. Any elevation in the ECF calcium above the normal range results in the stimulation of the calcium sensing receptor (CaSR) and the inhibition of parathyroid hormone (PTH) release, both of which facilitate a reduction in renal calcium reabsorption. Further, PTH results in reduced bone resorption, and therefore, diminished release of calcium from bone. Decreased PTH and hypercalcemia will also result in the reduction of renal production of the active

form of vitamin D, 1,25-dihydroxyvitamin D (1,25[OH]2D), and a subsequent reduction in the gut absorption of calcium. The net effect of this entire process is to normalize the ECF calcium concentration [27].

Hypercalcemia is a common paraneoplastic syndrome (PNS) of RCC, accounting for 13-20% of all PNS in general (with the exception of bone metastasis-related hypercalcemia) [28]. Hypercalcemia of malignancy is classified into 4 types based on its mechanism: malignant humoral hypercalcemia (80%), local osteolytic hypercalcemia (20%), secondary to secretion of 1.25-dihydroxyvitamin D (< 0.1%), and ectopic hyperparathyroidism (< 0.1%) [29]. Non-metastatic hypercalcemia is probably caused by the release of PTH and parathyroid hormone-related peptide (PTHrP) by the tumor cells [30]. Circulating tumor-derived factors and other humoral local factors secreted from metastatic cells drive the receptor activator of nuclear factor kappa-B ligand (RANKL)-mediated osteoclast activation and bone resorption. The resulting osteolysis leads to the release of bone-derived growth factors, which in turn promote cancer cell proliferation and further PTHrP production via transforming growth factor-beta and mitogen-activated protein kinase pathways [31]. Recent studies have demonstrated that vascular endothelial growth factor (VEGF) expression is also related to hypercalcemia, implying that the release of PTH and PTHrP may be regulated by VEGF or by its upstream protein that is related to the von Hippel-Lindau (VHL) gene [32].

Corrected calcium levels are easy to monitor and require a simple biochemical examination, thus making it a convenient and cost-effective prognostic indicator in patients with RCC. However, the presence of hypercalcemia in association with other medical conditions may limit its role as a prognostic indicator for RCC.

This meta-analysis has several limitations. First, our sample size is relatively small as only 13 studies and 6705 patients were included. Second, we only considered studies that calculated, or allowed for the calculation of HR and 95% CI. Other studies that provided odds ratios and relative risk for survival were excluded. Third, although meta-analysis is now a widely used technique for summarizing evidence from multiple studies, it has its own limitations. All meta-analyses are affected by the quality of the included studies, and by the possibility of publication bias. Finally, owing to the lack of sufficient data, we could not explore the association between corrected calcium and other clinical parameters.

This meta-analysis demonstrated that elevated levels of corrected calcium were associated with poor prognosis among patients with RCC. Corrected calcium is a convenient and cost-effective prognostic indicator that may aid in risk stratification and formulating personalized treatment plans for patients with RCC. However, there is a need for further studies with larger sample sizes and standardized investigations to confirm our findings.

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Disclosure of conflict of interest

None.

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