Pre-treatment De Ritis ratio serves as a potential prognostic biomarker in renal cell carcinoma: a systematic review and meta-analysis

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Abstract

Background Previous studies have evaluated the associations of aspartate transaminase to alanine transaminase (De Ritis) ratio with clinical outcome of renal cell carcinoma (RCC), but the findings are inconsistent. We therefore performed this meta-analysis to explore the prognostic value of the pre-treatment De Ritis ratio in patients with RCC.

Methods PubMed, EMBASE, Science and Cochrane Library were searched systematically to identify all eligible studies as of February 2020. The hazard ratio (HR) with 95% confidence interval (CI) were extracted to evaluate their correlation.

Results A total of 5,025 patients from 8 studies were included in the meta-analysis. Patients with an increased pre-treatment De Ritis ratio had worse overall survival (HR = 1.52, 95% CI 1.27 to 1.82, P < 0.001), cancer-specific survival (HR = 1.81, 95% CI 1.47 to 2.23, P < 0.001), progression-free survival (HR = 1.24, 95% CI 1.05 to 1.47, P = 0.011), and metastasis-free survival (HR = 1.61, 95% CI 1.25 to 2.07, P < 0.001). Subgroup analysis according to disease stage and cut-of value revealed that De Ritis ratio had a significant prognostic value for OS and PFS in all subgroups.

Conclusion The available evidence suggests that an increased De Ritis ratio was significantly correlated with worse survival in patients with RCC. Pre-treatment De Ritis ratio may serve as a potential prognostic biomarker in patients with RCC, but further studies are warranted to support these results.

Background

Renal cell carcinoma (RCC) is a common malignant tumor in adults and has an increasing incidence in the past two decades[1]. In 2020, approximately 73,750 new RCC cases and 14,830 deaths predicted in the United States[2]. Despite an increase in early detection of RCC, nearly 20% of patients already have local progression or metastasis disease at the time of initial diagnosis[3]. Moreover, postoperative cancer recurrence occurs in 20%-40% of patients with localized RCC[4]. Thus, it is of great value to define the prognostic indicators of survival, metastasis or recurrence in patients with RCC.

Tumor, node and metastasis (TNM) staging is an important traditional prognostic factor for RCC, with limited accuracy when used alone[5]. Numerous clinical prognostic or predictive factors have been identified based on clinical trials and retrospective univariate or multivariate analysis, including performance status, appearing symptoms, and paraneoplastic syndromes[6]. Besides, laboratory values are also used for prognosis, such as serum protein, corrected calcium, erythrocyte sedimentation rate, and neutrophil to lymphocyte ratio[7, 8].

Aspartate transaminase (AST) and alanine transaminase (ALT) are the most important transaminase in the body, reflecting hepatocellular damage[9]. The ratio of serum AST to ALT, i.e. De Ritis ratio, is usually used to identify the etiology of various hepatitis[10]. Recent studies confirmed De Ritis ratio as a biomarker can predict the prognosis of several tumors, such as breast cancer, gastric adenocarcinoma

and nasopharyngeal cancer[11–13]. However, the prognostic value of this ratio in patients with RCC remains unclear. Bezan et al. [14] found that patients with a high De Ritis ratio had inferior overall survival (OS) and metastasis-free survival (MFS), whilst another study reported no correlation between high DR Ritis rate and OS[15]. Therefore, this study aims to explore the prognostic value of the pretreatment De Ritis ratio in patients with RCC and provide higher-level medical evidence for clinical practice.

Materials And Methods

Search strategy

This present study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria[16]. PubMed, EMBASE, Science and Cochrane Library were comprehensively searched to identify eligible studies up to February 2020 without the restriction of language. The search was produced using the following terms: (“aspartate transaminase” OR “AST” OR “alanine transaminase” OR “ALT” OR "aspartate transaminase/alanine transaminase ratio" OR "AST/ALT ratio” OR " AST to ALT ratio OR "De Ritis ratio”) AND (“renal cell carcinoma" OR "renal cell cancer” OR “renal tumor” OR “kidney cancer” OR “kidney tumor”) AND ("prognostic" OR “prognosis” OR “survival” OR “outcome” OR “recurrence” OR “mortality”). A manual search of reference lists of related studies was also performed. Two authors reviewed the literature independently, any differences settled through discussion with a third author.

Inclusion and exclusion criteria

Qualified studies should meet the following inclusion criteria: (1) randomized controlled studies, cohort studies, or observational studies; (2) patients with RCC were histopathologically confirmed; (3) pre-treatment De Ritis ratio was obtained, (4) estimating the relationship between De Ritis ratio and RCC prognosis; (5) reported available data for analysis, including OS, cancer-specific survival (CSS), progression-free survival (PFS), and MFS. Exclude studies based on the following criteria: (1) studies involving animal; (2) reviews, comments, letters, case reports, and unpublished articles; (3) studies with unavailable data or insufficient data for analyses; (4) duplicated studies based on the same cohort.

Data extraction and quality assessment

Two reviewers independently extracted the required data from eligible studies, which were as follows: the first author's name, year of publication, study region, study design, tumor type, treatment, sample size, patient age, the cut-off value of De Ritis ratio, analysis method, follow-up period. Furthermore, all outcome parameters were directly extracted with hazard ratio (HR) and 95% confidence interval (CI). The main outcome was OS, while the secondary outcomes were CSS, PFS, and MFS. When both univariate and multivariate analysis were used in the study, data from the multivariate analysis was extracted. The quality of all included studies was estimated utilizing the Newcastle-Ottawa scale (maximum score 9) described by Wells et al[17], and studies with a score of ≥ 7 were deemed high-quality. All discrepancies were discussed through negotiation or finally decided by a third reviewer.

Statistical analyses

The statistical analysis of this study was performed using Stata v.15.0 (Stata Corp, College Station, TX, USA). The merged HRs with 95% CIs were adopted to evaluate the correlation between pre-treatment AST / ALT ratio and prognosis. Heterogeneity between studies was estimated using Cochran's Q and I^2 tests. P < 0.10 or I^2 > 50% represented a significant heterogeneity, and a random-effects model was chosen. Otherwise, a fixed-effects model was applied. Moreover, we performed a subgroup analysis to investigate the cause of heterogeneity. Sensitivity analysis was also performed by dropping each study individually to assess the stability of the findings. Publication bias was evaluated by using Egger's and Begg's tests, as the number of included studies is less than 10. Statistical significance was defined as a P value of less than 0.05.

Results

Study characteristics

Initially identified 267 articles through the search strategy, 19 studies remained after removing duplicates and excluding articles by viewing titles and abstracts. Based on corresponding inclusion and exclusion criteria, 8 articles comprising 5,025 patients were finally included in the present study[14, 15, 18-23] (**Figure 1**). All studies had a retrospective design, two of which were propensity score-matched analyses. 3 studies focused on metastatic RCC[19, 21, 22], 5 studies focused on non-metastatic RCC[14, 15, 18, 20, 23]. These studies were conducted in five countries, including China, Korea, Turkey, Japan, and the United States. The median age of patients included in the study ranged from 55 to 65 years. Cut-off values for the De Ritis ratio ranged from 1.0 to 1.5. The median follow-up period for the included studies ranged from 21 to 60 months, and only one study not reported the follow-up period[22]. 7 studies recorded the connections of De Ritis ratio with OS, 5 studies recorded CSS, 2 studies recorded PFS, and only study recorded MFS[14]. All studies were regarded as high-quality based on the NOS score. **Table 1** records the basic characteristics and quality assessments of all included studies.

Overall survival

Seven studies including 4,782 patients recorded about OS[14, 15, 18-22]. Since moderate heterogeneity was found, the random-effects model was adopted (I^2 = 47.5%, P = 0.076). The merged results demonstrated that patients with an increased pre-treatment De Ritis ratio had inferior OS (HR = 1.52, 95% CI 1.27 to 1.82, P < 0.001, **Figure 2**).

Cancer-specific survival

Five studies recorded the prognostic role of pre-treatment the De Ritis ratio in patients with RCC on CSS, including 3,884 patients[15, 19-21, 23]. The pooled results revealed that high pre-treatment De Ritis ratio was related to worse CSS (fixed-effects model: HR = 1.81, 95% CI 1.47 to 2.23, P < 0.001), and with no heterogeneity (I^2 = 16.1%, P = 0.312, **Figure 3A**).

Progression-free survival and metastasis-free survival

Two studies with 3,123 patients provided the PFS data[20, 22]. The combined results presented that RCC patients with an increased De Ritis ratio had a higher risk of progression (fixed-effects model: HR = 1.24, 95% CI 1.05 to 1.47, P = 0.011, **Figure 3B**), and without heterogeneity (I^2 = 0.0%, P = 0.416). Besides, only one study reported about MFS[14], and patients with elevated pre-treatment De Ritis ratio was related to the increased MFS (HR = 1.61, 95% CI 1.25 to 2.07, P < 0.001).

Subgroup analyses

Limited to the number of studies included in the meta-analysis, we only conducted subgroup analysis for OS and CSS oncologic outcomes, and stratified by disease stage, treatment method, cut-off value, analysis method, or sample size (**Table 2**). Subgroup analysis by disease stage demonstrated that high pre-treatment De Ritis ratio was related to inferior OS (HR = 1.46, 95% CI 1.29 to 1.63, P < 0.001) and CSS (HR = 1.79, 95% CI 1.35 to 2.38, P < 0.001) in patients with metastatic RCC, and the similar results were observed in patients with non-metastatic RCC (OS: HR = 1.54, 95% CI 1.13 to 2.08, P = 0.006; CSS: HR = 1.84, 95% CI 1.36 to 2.49, P < 0.001). In terms of subgroup analysis of treatment method, the high pre-treatment De Ritis ratio in patients with RCC was an independent predictor of OS (surgery: HR = 1.60, 95% CI 1.20 to 2.13, P < 0.001; non-surgery: HR = 1.42, 95% CI 1.19 to 1.70, P < 0.001). For subgroup with cut-off value of > 1.3, the patients with higher pre-treatment De Ritis ratio had poor OS (HR = 1.82, 95% CI 1.49 to 2.20, P = 0.001) and CSS (HR = 1.84, 95% CI 1.36 to 2.49, P < 0.001). Likewise, in the cut-off value of $\leq$ 1.3 group, increased De Ritis ratio was correlated with worse OS (HR = 1.29, 95% CI 1.11 to 1.49, P < 0.001) and CSS outcomes (HR = 1.79, 95% CI 1.35 to 2.38, P < 0.001). High pre-treatment De Ritis ratio was found to be independent prognostic factor for OS in the analysis method subgroup analyses (multivariate: HR = 1.71, 95% CI 1.43 to 2.06, P < 0.001; univariate: HR = 1.34, 95% CI 1.27 to 1.82, P = 0.002). Additionally, stratified by sample size, the higher pre-treatment De Ritis ratio had steep inferior OS (HR = 1.69, 95% CI 1.40 to 2.04, P < 0.001) and CSS (HR = 1.74, 95% CI 1.31 to 2.30, P < 0.001) in the sample size > 300 subgroup, which was consistent with the results of the sample size $\leq$ 300 subgroup (OS: HR = 1.43, 95% CI 1.27 to 1.82, P = 0.015; CSS: HR = 1.91, 95% CI 1.40 to 2.60, P < 0.001).

Sensitivity analysis and publication bias

Restricted to the number of articles included in the study, we performed sensitivity analysis for OS and CSS outcomes only. After removing each study one by one, no significant change in the pooled HR was observed, which undoubtedly proved the reliability of our results (**Figure 4**). Also, Egger's and Begg's tests were applied to estimate the publication bias. Based on the Egger's test (OS: P = 0.084, CSS: P = 0.279) and Begg's test (OS: P = 0.368, CSS: P = 0.462) results, there was no significant evidence of publication bias.

Discussion

RCC is one of the most common solid lesions in the kidney, accounting for about 80%-90% of all renal malignancies[1]. The prognosis of RCC is affected by a variety of factors, including patient age, clinical manifestations, laboratory values, and tumor pathologic variables such as pathological stage, nuclear grade, and histological subtype[6, 24]. Tumor stage and grade are considered as common prognostic markers for RCC, but the application of these factors in clinical practice remains problematic[25]. How to more accurately identify those patients with poor prognosis before treatment, and carry out the risk stratification of tumors are of great significance for the choice of treatment options and the guidance of postoperative follow-up. Therefore, finding potential prognostic markers for RCC prognosis has become a hot spot in clinical research.

Serum De Ritis ratio was originally adopted to evaluate the prognosis of various liver diseases, including viral hepatitis, alcoholic hepatitis, and fatty liver[10]. Due to laboratory tests are routinely performed before treating cancer patients, De Ritis ratio can be a simple, convenient, and inexpensive measurement method. Previous studies have reported De Ritis ratio was significantly associated with the prognosis of several tumors, including RCC[11–14]. However, the true prognostic value of this ratio in patients with RCC remains controversial.

For all we know, this is the first meta-analysis to appraise the prognostic value of pre-treatment De Ritis ratio in patients with RCC. The study revealed that patients with higher pre-treatment De Ritis ratio had worse survival outcomes regarding OS, CSS, PFS, and MFS. Subgroup analyses of OS and CSS by disease stage, treatment method, cut-off value, analysis method, or sample size obtained similar results. We also performed sensitivity analyses to explore potential sources of heterogeneity, and no significant change was observed. There was no significant evidence of publication bias. Thus, the meta-analysis indicates that pre-treatment De Ritis ratio is an important prognostic predictor for the survival of RCC patients.

ALT and AST are common blood tests for liver disease and can reflect hepatocellular damage or death. ALT is mainly present in the liver, while AST is widely distributed in various tissues such as the heart, liver, brain, muscle, and kidney tissues[10]. Hence, ALT suggests liver disease specifically, whilst AST may be associated with several diseases that affect other organs. Pathological processes that have been proved to cause tissue damage, high proliferative states and faster tumor cell turnover tend to enhance serum AST level rather than ALT level, making the De Ritis (AST/ALT) ratio an attractive potential clinical biomarker[26].

Although the De Ritis ratio is a promising marker, the specific mechanism of higher this ratio and inferior prognosis of cancer patients remains unclear. Indeed, cancer cells have a higher rate of glycolysis compared with normal cells, even in the presence of oxygen, and abnormal glycolytic metabolism produces sufficient ATP to promote cancer cell proliferation, this phenomenon is known as the “Warburg effect”[27, 28]. Increased glycolysis in tumor cells is thought to be related to changes in nicotinamide adenine dinucleotide (NAD)-related enzymes and glucose transporters within mitochondria, according to Dorward et al[29]. Higher lactate dehydrogenase and cytosolic (NADH)/NAD + ratio play an important role

in maintaining enhanced glycolysis[30]. It must be highlighted that AST is a pivotal component of the malate-aspartate shuttle in the glycolysis pathway that relocates NADH into mitochondria[10]. Moreover, the previous study had confirmed von Hippel-Lindau (VHL) significantly associated with renal clear-cell type RCC was presented in the cytoplasm of mitochondria[31]. The loss of VHL and an increase in hypoxia-inducible factor expression influence several metabolic pathways, including glycolysis and oxidative phosphorylation[32]. Accordingly, AST is most probably involved in the glycolysis mechanism of clear-cell type RCC with VHL loss[20]. However, further investigation is needed to explore the exact mechanism.

As a promising biomarker, De Ritis ratio has significant implications for clinical practice. Our meta-analysis affirms that patients with an increased pre-treatment De Ritis ratio had worse survival outcomes. It could be a potential selection criterion for the hierarchical management of risk factors for RCC and adjuvant therapies[14]. Given that a prognostic factor must be verified in well-designed, large-scale with an independent cohort before it can be applied universally, the findings should be interpreted cautiously.

Despite the study provides stronger evidence for the prognostic value of the pre-treatment De Ritis ratio in patients with RCC, there are certain limitations. Firstly, only 8 studies involving 5,025 patients were included in the meta-analysis, which is a relatively small sample size and may lead to a biased conclusion. Secondly, all included studies were retrospective, which may have an inherent structural bias, and the duration of follow-up was relatively short. Thirdly, although the included studies attempted to exclude all patients with liver disease, there were still undetected liver pathological conditions that could affect the serum AST or ALT levels and distort the De Ritis ratio.

Conclusion

The available evidence suggests that patients with an increased pre-treatment De Ritis ratio had worse OS, CSS, PFS, and MFS, indicating that this ratio may serve as a potential prognostic biomarker in patients with RCC. However, prospective, well-designed, and large-scale studies are warranted to validate our findings.

Abbreviations

RCC: Renal cell carcinoma; AST: Aspartate transaminase; ALT: Alanine transaminase; OS: Overall survival; CSS: Cancer-specific survival; PFS: Progression-free survival; MFS: Metastasis-free survival; NOS: Newcastle–Ottawa scale; HR: Hazard ratio; CI: Confidence interval; VHL: Von Hippel-Lindau.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All the data (pooled HR with 95% CI of OS, CSS, PFS, RFS, and MFS) used to support the findings of this study are included within the article.

Competing interests

The authors declare that they have no competing interests.

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article.

Authors' contributions

Protocol/project development: YXL and JZL; Data collection or management: JZL, LP and JML; Data analysis: JZL, BC and HCG; Manuscript writing/editing: JZL, LP. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics of include studies and methodological assessment.

Authors (year)	Country	Study design	Tumor type	Treatment	Number of patients	Age (years)	Cutoff value (AST/ALT)	Analysis method	Outcomes	Follow-up (months)	Quality score
Bezan 2015 [14]	America	Retrospective	Non-metastatic	Surgery	698	Median 65.4 (55.8-73.4)	1.26	Multivariate	OS, MFS	Median 60	8
Canat 2017 [15]	Turkey	Retrospective	Non-metastatic	Surgery	298	Median 61 (22-86)	1.5	Univariate	OS, CSS	Mean 37.8 ± 22.3	7
Gu 2017 [18]	China	Retrospective	Non-metastatic	Surgery	185	Mean 56.1 ± 11.8	1.0	Univariate	OS	Median 30.2 (12.1-48.4)	8
Ishihara 2017 [19]	Japan	Propensity scorematching	Metastatic	Surgery	118	Median 65	1.24	Multivariate	OS, CSS	Mean 21.0 ± 24.3	8
Lee 2017 [20]	Korea	Propensity score matching	Non-metastatic	Surgery	2965	Median 55 (47-65)	1.5	Multivariate	OS, CSS, PFS	Median 37 (24-73)	9
Kang 2018 [21]	Korea	Retrospective	Metastatic	TKI	360	Median 58 (51-67)	1.2	Multivariate	OS, CSS	Median 29 (24.1-33.9)	8
Kim 2018 [22]	Korea	Retrospective	Metastatic	TT	158	Mean 58.6 ± 10.6	1.38	Univariate	OS, PFS	NR	7
Ikeda 2019 [23]	Japan	Retrospective	Non-metastatic	Surgery	243	Median 61 (55-67)	1.42	Multivariate	CSS	Median 60 (25-103)	7

TKI tyrosine kinase inhibitor, *TT* targeted therapy, *AST* aspartate transaminase, *ALT* alanine transaminase, *OS* overall survival, *CSS* cancer-specific survival, *PFS* progression-free survival, *MFS* metastasis-free survival, *NR* not report.

Table 2. Subgroup analyses of OS and CSS.

Outcome	Variable	No. of studies	Model	HR (95% CI)	P	Heterogeneity	
						I^2 (%)	P
OS	All	7	Random	1.52 (1.20, 1.82)	< 0.001	47.5	0.076
Disease stage	Metastatic	3	Fixed	1.46 (1.29, 1.63)	< 0.001	26.2	0.258
	Non-metastatic	4	Random	1.54 (1.13, 2.08)	0.006	65.6	0.033
Primary treatment	Surgery	5	Random	1.60 (1.20, 2.13)	0.001	60.3	0.039
	Non-surgery	2	Fixed	1.42 (1.19, 1.70)	< 0.001	21.1	0.260
Cut-off value	> 1.3	4	Fixed	1.82 (1.49, 2.22)	0.001	22.9	0.722
	≤ 1.3	3	Fixed	1.29 (1.11, 1.49)	< 0.001	0.0	0.273
Analysis method	Multivariate	4	Fixed	1.72 (1.43, 2.06)	< 0.001	0.0	0.838
	Univariate	3	Random	1.34 (1.27, 1.82)	0.002	59.0	0.087
Sample size	> 300	3	Fixed	1.69 (1.40, 2.04)	< 0.001	0.0	0.879
	≤ 300	4	Random	1.43 (1.27, 1.82)	0.015	57.3	0.071
CSS	All	5	Fixed	1.81 (1.47, 2.23)	< 0.001	16.1	0.312
Disease stage	Metastatic	2	Fixed	1.79 (1.35, 2.38)	< 0.001	0.0	0.327
	Non-metastatic	3	Fixed	1.84 (1.36, 2.49)	< 0.001	47.3	0.150
Cut-off value	> 1.3	3	Fixed	1.84 (1.36, 2.49)	< 0.001	47.3	0.150
	≤ 1.3	2	Fixed	1.79 (1.35, 2.38)	< 0.001	0.0	0.327
Sample size	> 300	2	Fixed	1.74 (1.31, 2.30)	< 0.001	0.0	0.495
	≤ 300	3	Random	1.91 (1.40, 2.60)	< 0.001	51.4	0.128

OS overall survival, *CSS* cancer-specific survival, *HR* hazard ratio, *CI* confidence interval.

Figures

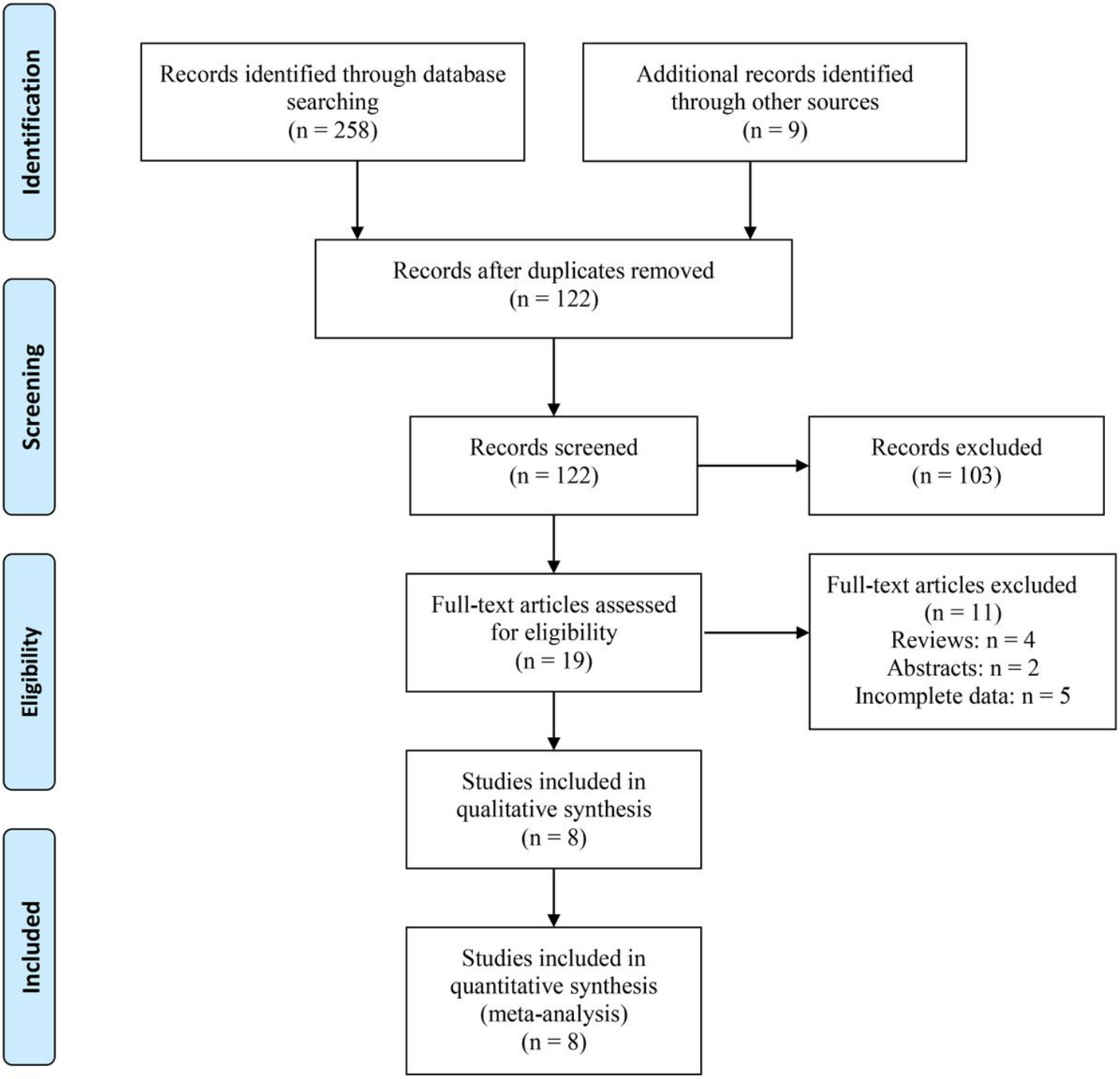

Figure 1

Flow diagram of studies identified, included and excluded.

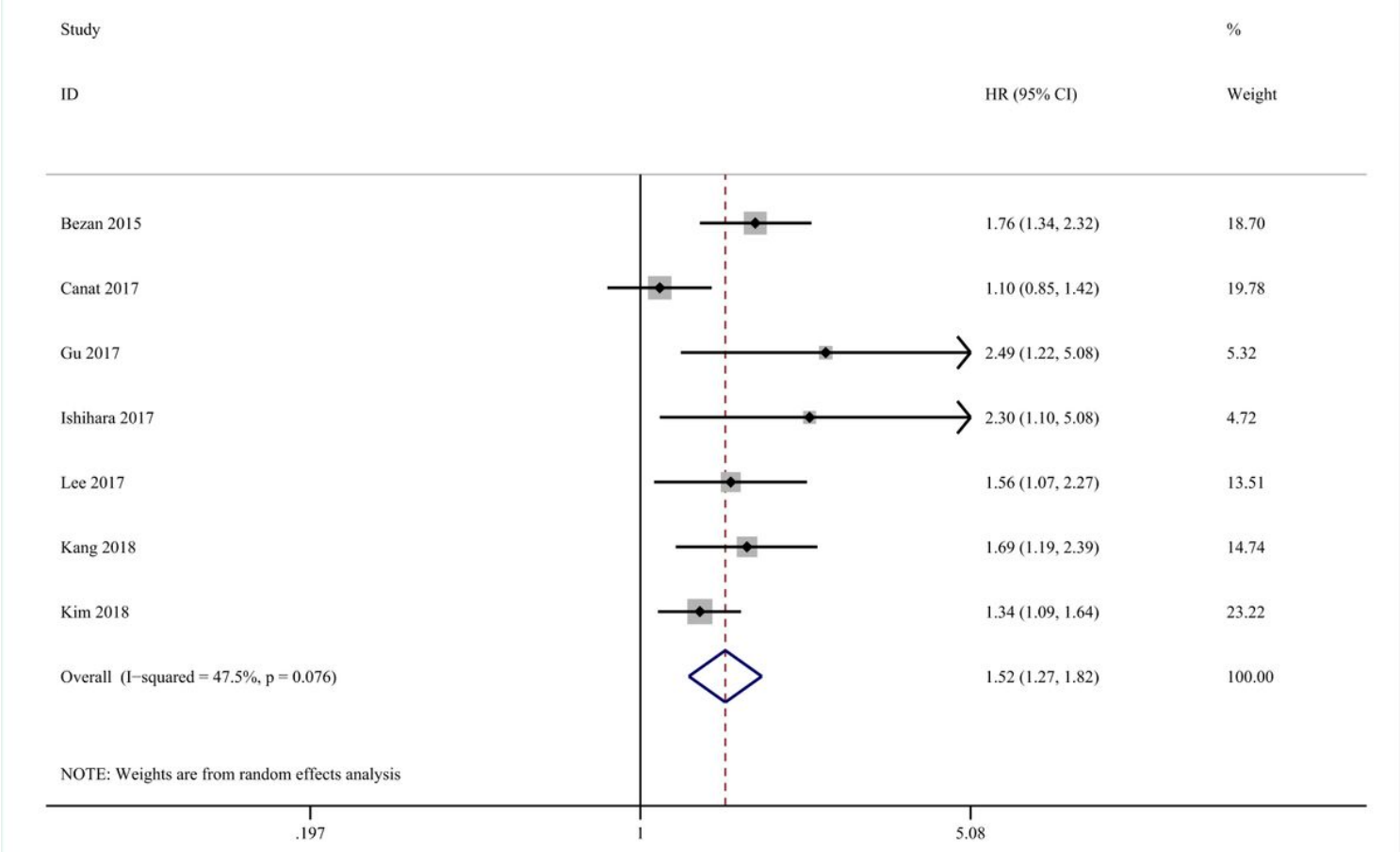

Figure 2

Forest plots of the association between De Ritis ratio and overall survival.

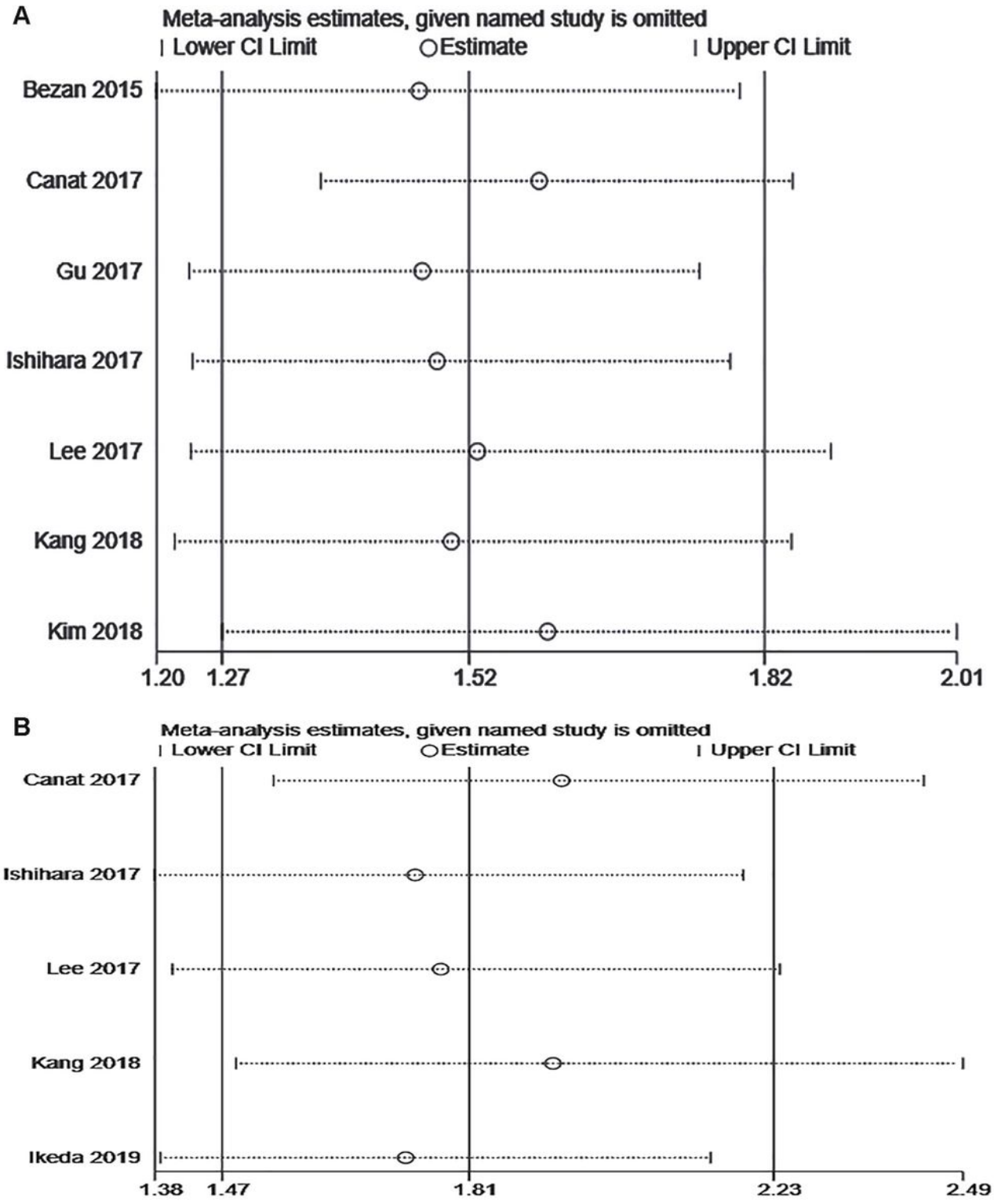

Figure 4

Sensitivity analysis for (A) overall survival; (B) cancer-specific survival.

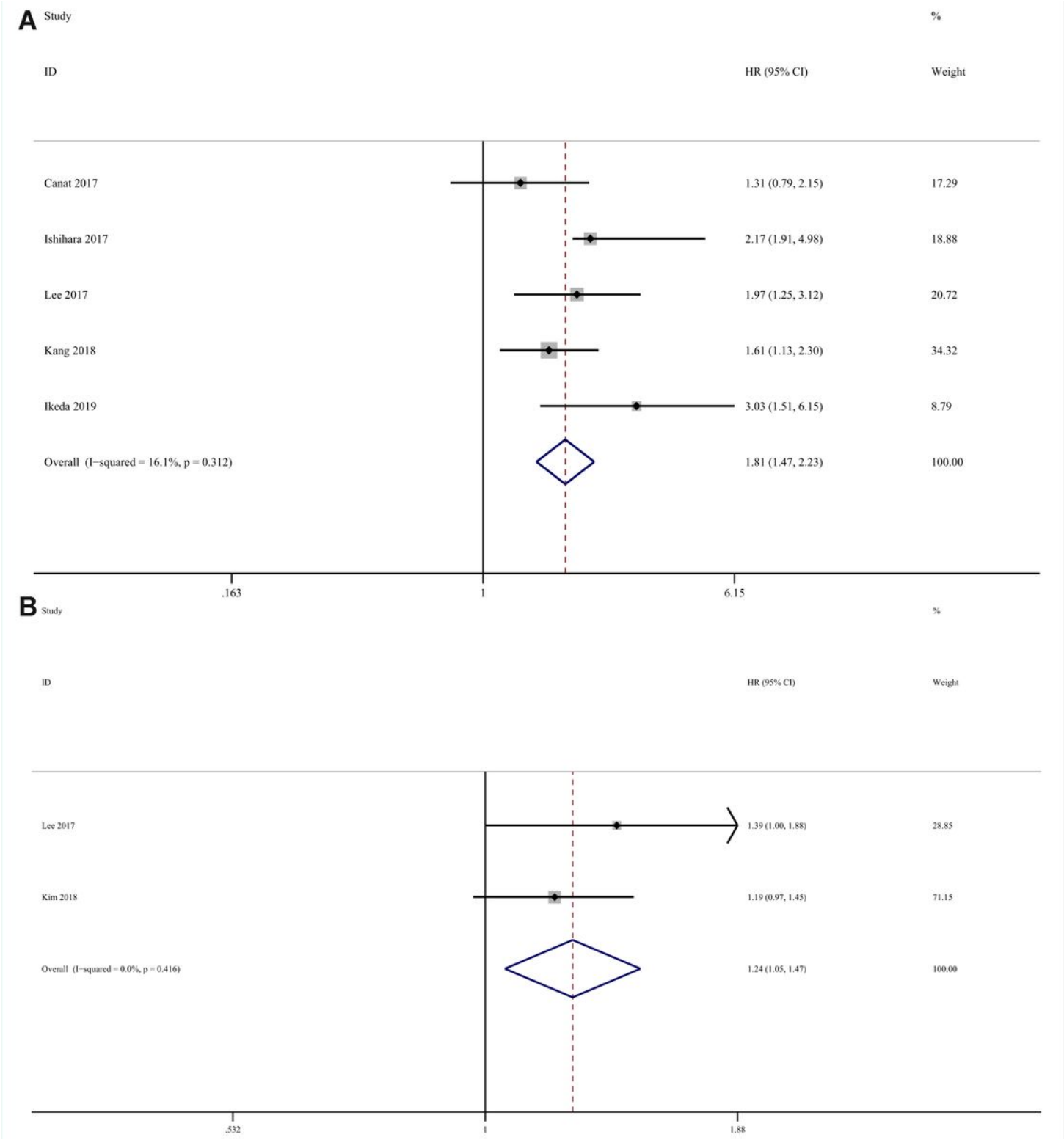

Figure 5

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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