

Prognostic value of aspartate transaminase to alanine transaminase (De Ritis) ratio in solid tumors: a pooled analysis of 9,400 patients

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Jiayuan Wu^{1,*}

Lin Chen^{2,*}

Yufeng Wang^{3,*}

Wenkai Tan⁴

Zhe Huang⁵

¹Clinical Research Center, The Affiliated Hospital of Guangdong Medical University, Zhanjiang 524001, Guangdong Province, People's Republic of China;

²Department of Cardiac Surgery, The Affiliated Hospital of Guangdong Medical University, Zhanjiang 524001, Guangdong Province, People's Republic of China;

³School of Public Health, Guangdong Medical University, Zhanjiang 524023, Guangdong Province, People's Republic of China;

⁴Department of Gastroenterology, The Affiliated Hospital of Guangdong Medical University, Zhanjiang 524001, Guangdong Province, People's Republic of China; ⁵Department of Gastrointestinal Surgery, The Affiliated Hospital of Guangdong Medical University, Zhanjiang 524001, Guangdong Province, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jiayuan Wu
Department of Clinical Research, The Affiliated Hospital of Guangdong Medical University, No 57, South of People's Avenue, Zhanjiang 524001, Guangdong, People's Republic of China
Tel +86 0 759 238 7506
Fax +86 0 759 238 7612
Email 87537665@qq.com

Zhe Huang
Department of Gastrointestinal Surgery, The Affiliated Hospital of Guangdong Medical University, No 57, South of People's Avenue, Zhanjiang 524001, Guangdong, People's Republic of China
Email 396018618@qq.com

Background: Numerous studies have reported the association between pretreatment serum aspartate transaminase to alanine transaminase (AST/ALT) ratio and prognosis in multiple cancers. However, the results remain controversial and no consensus has been reached. Thus, we conducted this meta-analysis to quantitatively assess the prognostic value of pretreatment AST/ALT ratio in solid tumors.

Methods: A systematic literature search was conducted by using PubMed, EMBASE, Web of Science, Cochrane Library, and Wanfang databases, as well as several trial registry platforms, including ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, and Chinese Clinical Trial Registry, up to April 5, 2019. HR and 95% CI for overall survival (OS), cancer-specific survival (CSS), and recurrence-free survival (RFS) were calculated to estimate the effect size.

Results: A total of 18 studies with 9,400 patients were included. Overall, a high level of pretreatment AST/ALT ratio was significantly associated with worse OS (pooled HR=1.70, 95% CI=1.38–2.09). The statistical significance was observed in all cancer types, including renal cell carcinoma (pooled HR=1.64, 95% CI=1.30–2.05), liver cancer (pooled HR=1.16, 95% CI=1.04–1.29), urinary tract urothelial carcinoma (pooled HR=1.96, 95% CI=1.53–2.51), bladder cancer (pooled HR =2.66, 95% CI=1.69–4.20), and other cancers (pooled HR=1.44, 95% CI=1.18–1.76). Moreover, an increased level of serum AST/ALT ratio predicted unfavorable CSS (pooled HR=2.07, 95% CI=1.74–2.46) and RFS (pooled HR=1.51, 95% CI=1.15–1.99).

Conclusion: Elevated level of serum AST/ALT ratio before treatment is significantly associated with poor clinical outcomes of OS, CSS, and RFS in patients with solid tumors. Pretreatment AST/ALT ratio can serve as a useful prognostic predictor for malignant patients.

Keywords: aspartate transaminase to alanine transaminase ratio, prognosis, solid tumor, meta-analysis

Introduction

Cancer accounts for the majority of global deaths due to its rapidly growing incidence and mortality. Moreover, cancer is one of the most important barriers to prolonging life expectancy in most countries in the twenty-first century.¹ Different types of malignancies comprise distinct morphologies and behaviors, including tumorigenic properties, metastatic potential, and therapeutic response. This heterogeneity of cancer can be resolved by developing cancer biomarkers with clinical utility.² Biomarkers are helpful for cancer diagnosis, and provide actionable information for risk stratification, optimal therapy, and prognostic

prediction.³ However, only a handful of biomarkers, including CA125 for ovarian cancer, prostate-specific antigen for prostate cancer (PC), and CA19-9 for pancreatic cancer, are routinely used in clinical settings for specific cancer types because biomarker development is complex, time-consuming, and costly.⁴ Until now, a considerable proportion of cancer patients show advanced disease stages upon diagnosis, and this phenomenon gives way to complicated therapy and poor prognosis. Therefore, identifying clinically applicable and effective pan-cancer biomarkers for the detection and prognosis of cancer is necessary.

Considering that aspartate transaminase (AST) and alanine transaminase (ALT) are the main circulating enzymes *in vivo*, their serum levels not only represent hepatocellular damage or death, but also have significant prognostic roles in several malignancies, such as pancreatic and breast cancers.^{5,6} The ratio of serum activities of AST and ALT (AST/ALT ratio), also termed as De Ritis ratio, was first reported in 1957 as a useful indicator for hepatitis etiology,⁷ and is the only enzyme ratio for predicting viral hepatitis that has stood the test of time.⁸ Nowadays, the AST/ALT ratio is accepted as a good predictor of liver function damage, and is widely used for evaluating various causes of liver disease. Moreover, the AST/ALT ratio is closely correlated with several non-hepatic diseases, such as type 2 diabetes mellitus, peripheral arterial occlusive disease, acute ischemic stroke, and esophageal cancer.^{9–12} Furthermore, the De Ritis ratio is closely associated with markers for impaired renal function (eGFR), cardiac strain (NT-proBNP), and inflammation (CRP), suggesting that it could serve as a surrogate marker for end-organ damage in impaired systemic perfusion.¹³

AST and ALT production might be influenced by cancer-related changes in metabolism, and pretreatment AST/ALT ratio is closely associated with the survival outcomes of patients with various carcinomas.¹⁴ However, these results are conflicting due to variance in study designs and sample sizes, resulting in the unknown prognostic role of AST/ALT ratio in patients with solid tumors. Therefore, we searched for available studies and conducted this first meta-analysis to reveal the prognostic value of AST/ALT ratio in solid tumors.

Materials and methods

Literature search

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA).¹⁵ This study was prospective registered in PROSPERO (<http://www.crd.york.ac.uk/PROSPERO/>; CRD42019122772).

A comprehensive electronic search was performed based on PubMed, EMBASE, Web of Science, Cochrane Library, and Wanfang databases without any language restrictions. The databases of trial registries, including ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, and Chinese Clinical Trial Registry (ChiCTR.org.cn), were also checked for eligible studies. The following search terms were used: (((“Aspartate Aminotransaminase”[All Fields] OR “AST” [All Fields]), OR (“Alanine Transaminase” [All Fields] OR “ALT” [All Fields]) OR (“De Ritis ratio” [All Fields])), AND (“Neoplasms” [All Fields] OR “Tumor” [All Fields] OR “Cancer” [All Fields] OR “Malignancy” [All Fields] OR “Carcinoma” [All Fields]), AND (“Prognosis” [All Fields] OR “Survival” [All Fields] OR “Outcome” [All Fields] OR “Mortality” [All Fields])). The last search was updated on April 5, 2019. In order to widen the literature search, the reference lists of the retrieved studies were also screened manually to identify potentially relevant studies.

Study selection

The literature search, study selection, and validation were systematically carried out by two independent reviewers (LC and WKT) who were blinded to the authors and publication years. Reviewers addressed disagreements by discussion, and the arbitrator (JYW) adjudicated any unsolved disagreement. Studies were considered eligible in this meta-analysis according to the following criteria: 1) cohort studies reported the association between AST/ALT ratio and prognosis of non-hematologic solid tumors; 2) serum AST/ALT ratio was measured before any treatment; 3) publications provided sufficient information to extract or calculate HR estimations; and 4) full-text articles. The following studies were excluded: 1) abstracts, letters, reviews, editorials, case reports, basic studies, or non-human studies; 2) studies with insufficient data for the estimation of HRs and 95% CIs; and 3) overlapping or duplicate studies.

Data extraction and quality assessment

The data extraction and quality assessment were independently performed by two reviewers (ZH and WKT) using a standardized extraction form. Discrepancies were settled by discussion and consensus were reached in all cases.

The following information was recorded from each eligible study: name of first author, year of publication, study region, duration time, cancer type, clinical stage, primary treatment, follow-up time, sample size, cutoff value, case number with elevated AST/ALT ratio, analysis method, survival outcomes, HR estimation, and quality scores. Overall survival (OS), cancer-specific survival (CSS), and recurrence-free survival (RFS) were analyzed. HR estimation was extracted from multivariate analyses when available. Otherwise, it was obtained from univariate analysis or calculated from the Kaplan–Meier curves.

The quality of each included study was systematically evaluated using the Newcastle-Ottawa Scale (NOS) for cohort studies. The total score of NOS ranged from 0 to 9, and studies with scores ≥ 7 were defined as high-quality.

Statistical analysis

STATA 14.0 (STATA Corporation, College Station, TX, USA) was used for all statistical analyses. Pooled HRs and 95% CIs were used to assess the strength of pretreatment AST/ALT ratio with survival endpoints. HR >1 denoted a worse prognosis in patients with elevated serum AST/ALT ratio, and the result was statistically significant if the 95% CI did not overlap 1. The significance of the pooled HR was determined by using Z-test, of which the results were statistically significant if $P<0.05$. The inter-study heterogeneity was examined by using Cochran's Q test and Higgins I^2 metric. If $P<0.05$ or $I^2>50\%$, a random-effects model (DerSimonian and Laird method) was applied to calculate the pooled HRs because of the possibility of substantial heterogeneity. Otherwise, a fixed-effect model was utilized (Mantel–Haenszel method) in the data synthesis. Subgroup and meta-regression analyses were performed to explore the potential factors for heterogeneity. Sensitivity analysis was conducted using a “one-study removed” model to assess the stability of the overall results. Potential publication bias was assessed by using funnel plots visually, whose results were confirmed by using Begg's and Egger's tests. The trim-and-fill method was performed to estimate an adjusted effect size if significant publication bias was identified.¹⁶ All the statistical tests were two-tailed, and $P<0.05$ was considered statistically significant.

Results

Study characteristics

A total of 328 individual studies were identified through an initial literature search. Afterward, 219 studies were excluded due to obvious irrelevance. After the titles and

abstracts were screened, 66 studies that did not meet the inclusion criteria were removed. A total of 25 publications were excluded from the remaining 43 potential studies after full-text evaluation, including 5 without survival analysis, 6 without sufficient information for HR estimation, 2 with other survival outcome reports, and 12 without AST/ALT ratio data. Ultimately, 18 studies were included in the meta-analysis^{17–34} (Figure 1).

The basic characteristics of the included studies are summarized in Table 1. The 18 included studies published between 2011 and 2019 provided an overall sample size of 9,400, with a range of 74–2,965. The six studies were carried out in People's Republic of China (including Taiwan),^{21,22,24,26,33,34} followed by Japan (n=4),^{20,23,28,31} Korea (n=5),^{17,18,27,29,30} Turkey (n=2),^{19,25} and the USA (n=1).³² Regarding cancer type, 6 studies reported renal cell cancer (RCC),^{18,19,22,23,30,32} 4 reported liver cancer with hepatocellular carcinoma (HCC),^{21,26,33,34} 3 reported urinary tract urothelial carcinoma (UTUC),^{27–29} 2 reported PC,^{20,24} 2 reported bladder cancer,^{17,25} and 1 reported head and neck cancer.³¹ Considering survival endpoint, 16 studies focused on OS,^{17–23,25–27,29–34} 8 focused on CSS,^{17–19,23,25,27,29,30} and 5 focused on RFS.^{24,27,28,30,34} All the 18 studies were written in English. The HR estimations in the 14 studies were directly extracted from multivariate analyses, and those of the other 4 studies were obtained from univariate analyses.^{19,20,26,34} All included studies had a score of 7 or more and were of high quality based on the NOS criteria.

Primary outcome: OS

A total of 16 studies with 8,853 enrolled patients provided sufficient data for OS (Table 2). The overall outcome demonstrated that increased pretreatment AST/ALT ratio was significantly associated with worse OS (pooled HR=1.70, 95% CI=1.37–2.09, $P<0.001$, random effects, Figure 2) with significant heterogeneity across studies ($I^2=85.4\%$, $P_h<0.001$). A high AST/ALT ratio was related to the decreased OS in patients with RCC (pooled HR=1.64, 95% CI=1.30–2.05, $P<0.001$, random effects), liver cancer (pooled HR=1.16, 95% CI=1.04–1.29, $P=0.006$, random effects), UTUC (pooled HR=1.96, 95% CI=1.53–2.51, $P<0.001$, fixed effects), bladder cancer (pooled HR=2.66, 95% CI=1.69–4.20, $P<0.001$, fixed effects), and other cancers (pooled HR=1.44, 95% CI=1.18–1.76, $P=0.001$, fixed effects) when the subgroup analyses were conducted according to various cancer types. A significant relationship of elevated AST/ALT ratio and poor OS was found in patients that underwent surgery (pooled HR=1.74, 95%

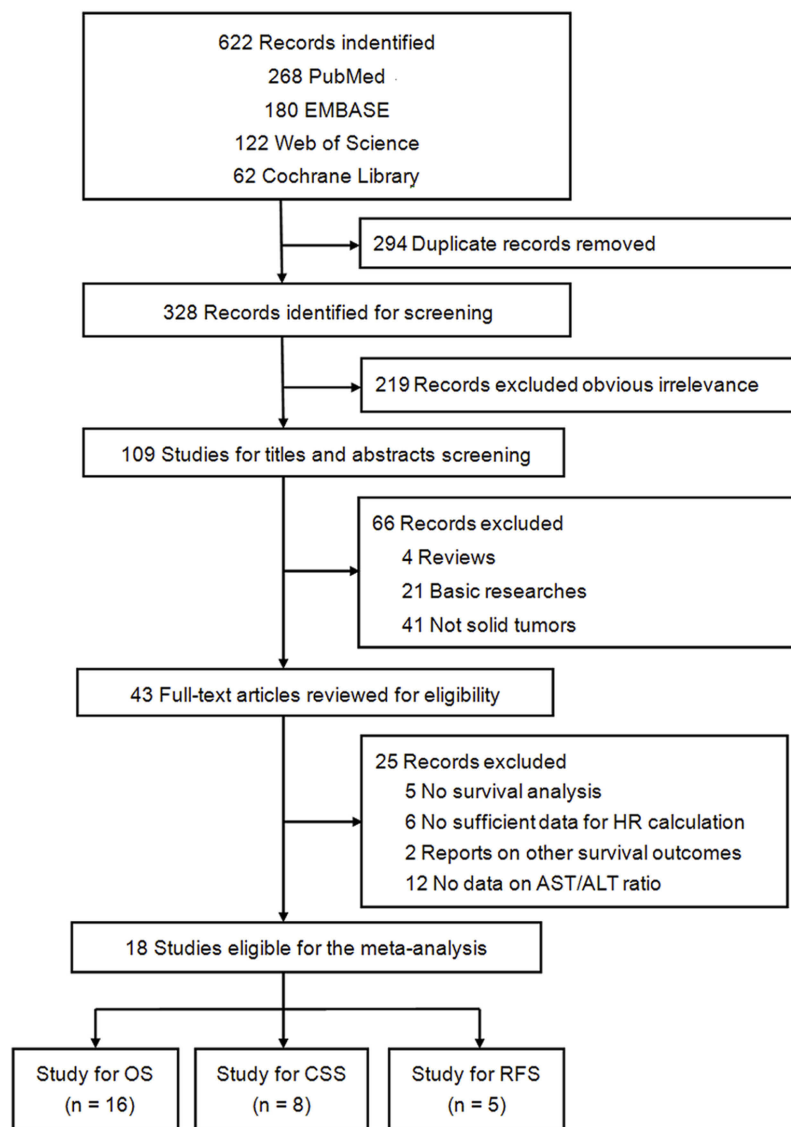


Figure 1 Flow diagram of the study selection process.

Abbreviations: AST/ALT ratio, aspartate transaminase to alanine transaminase ratio; OS, overall survival; CSS, cancer-specific survival; RFS, recurrence-free survival.

CI=1.34–2.25, $P<0.001$, random effects) and did not undergo surgery (pooled HR=1.50, 95% CI=1.26–1.78, $P<0.001$, fixed effects) upon stratification by the primary treatment. Additionally, the overall results did not show obvious alterations when the included studies were grouped on the basis of study population, clinical stage, cutoff value, analysis method, and sample size.

Secondary outcome: CSS and RFS

Eight cohorts with 5,640 patients reported the CSS outcome (Table 3), and the pooled outcome suggested that a high level of pretreatment AST/ALT ratio was significantly associated with short CSS (pooled HR=2.07, 95% CI=1.74–2.46, $P<0.001$, fixed effects, Figure 3A) with insignificant

heterogeneity ($I^2=38.1\%$, $P_h=0.126$). An elevated AST/ALT ratio predicted poor CSS for patients with RCC (pooled HR=1.78, 95% CI=1.42–2.22, $P<0.001$, fixed effects), bladder cancer (pooled HR=3.78, 95% CI=2.02–7.04, $P<0.001$, fixed effects), and UTUC (pooled HR=2.38, 95% CI=1.76–3.22, $P<0.001$, fixed effects) when subgroup analysis was conducted based on cancer type. These positive results did not change when the subgroup analyses of clinical stage, cutoff value, and sample size were conducted. However, the positive correlation of the increased AST/ALT ratio and poor CSS existed in the Asian (pooled HR=2.12, 95% CI=1.76–2.56, $P<0.001$, fixed effects) but not in the Caucasian studies (pooled HR=2.60, 95% CI=0.61–11.09, $P=0.198$, random effects) upon study population stratification.

Table 1 Characteristics of the included studies

Author (year)	Region	Duration	Cancer type	Clinical stage	Primary treatment	Follow up (month)	Sample size	Cutoff (high/low)	Analysis method	Outcome	Language	NOS
Ha YS (2019) ¹⁷	Korea	2008–2013	Bladder cancer	T1-T4	Surgery	Median 34.1	118	1.3 (69/49)	Multivariate	OS, CSS	English	8
Kang MY (2018) ¹⁸	Korea	2001–2016	RCC	IV	TKI	Median 29 (24.1–33.9)	360	1.2 (136/224)	Multivariate	OS, CSS	English	8
Canat L (2018) ¹⁹	Turkey	2006–2013	RCC	I-IV	Surgery	Mean 37.9 ±22.3	298	1.5 (80/218)	Univariate	OS, CSS	English	7
Miyake H (2018) ²⁰	Japan	2014–2017	PC	IV	ADT	Median 14 (2–29)	74	1.35 (37/37)	Univariate	OS	English	7
Chen JW (2018) ²¹	People's Republic of China	2003–2010	HCC	I-IV	Surgery	Median 58.5 (1–185)	226	1.40 (111/115)	Multivariate	OS	English	8
Gu LY (2017) ²²	People's Republic of China	2006–2016	RCC	I-IV	Surgery	Median 30.2 (12.1–48.4)	185	1 (93/92)	Multivariate	OS	English	8
Ishihara H (2017) ²³	Japan	2003–2015	RCC	IV	Surgery	Mean 23.0 ±28.8	118	1.24 (52/66)	Multivariate	OS, CSS	English	8
Wang HT (2017) ²⁴	People's Republic of China	2004–2015	PC	T2-T3	Surgery	Median 52.0	438	1.325 (220/218)	Multivariate	RFS	English	8
Gorgel SN (2017) ²⁵	Turkey	2006–2016	Bladder cancer	T1-T4	Surgery	NR	149	1.3 (66/83)	Multivariate	OS, CSS	English	8
Liu C (2017) ²⁶	People's Republic of China	2007–2013	HCC	NR	TACE	Up to Dec 2013	760	1.2 (406/354)	Univariate	OS	English	7
Cho YH (2016) ²⁷	Korea	2004–2015	UTUC	I-IV	Surgery	Median 40.0	1049	1.6 (264/785)	Multivariate	OS, CSS, RFS	English	9
Nishikawa M (2016) ²⁸	Japan	2005–2014	UTUC	T1-T4	Surgery	NR	109	1.3 (57/52)	Multivariate	RFS	English	8
Lee H (2016) ²⁹	Korea	1994–2013	UTUC	T1-T4	Surgery	Median 35.0	583	1.5 (141/442)	Multivariate	OS, CSS	English	8
Lee HM (2016) ³⁰	Korea	2006–2013	RCC	T1-T4	Surgery	Median 37.0	2965	1.5 (437/2528)	Multivariate	OS, CSS, RFS	English	9
Takenaka Y (2016) ³¹	Japan	2004–2012	HNC	III-IV	CRT	Median 57.2	356	2.3 (38/318)	Multivariate	OS	English	8
Bezan A (2015) ³²	USA	2005–2013	RCC	T1-T4	Surgery	Median 60	698	1.26 (251/447)	Multivariate	OS	English	8
Xie XM (2015) ³³	People's Republic of China	2009–2013	Liver cancer	NR	Surgery	Up to Dec 2014	724	1.47 (482/242)	Multivariate	OS	English	8
Kao WY (2011) ³⁴	Taiwan	2002–2007	HCC	BCLC 0-B	Surgery	Median 30.7	190	1 (90/100)	Univariate	OS, RFS	English	7

Abbreviations: NR, none reported; RCC, renal cell carcinoma; PC, prostate cancer; HCC, hepatocellular carcinoma; UTUC, urinary tract urothelial carcinoma; HNC, head and neck cancer; BCLC, the Barcelona Clinic Liver Cancer; TKI, tyrosine kinase inhibitor; ADT, androgen-deprivation therapy; CRT, chemoradiation therapy; OS, overall survival; CSS, cancer-specific survival; RFS, recurrence-free survival; NOS, Newcastle-Ottawa Scale.

Table 2 Pooled and subgroup analyses of data synthesis of overall survival for this meta-analysis

Categories	Study (case)	Model	HR (95% CI)	Z	P _Z	Heterogeneity		P _m
						I ²	P _h	
Overall survival (OS)	16 (8853)	Random	1.70 (1.37–2.09)	4.96	<0.001	85.4%	<0.001	
Study population								0.105
Asian	13 (7708)	Random	1.73 (1.35–2.22)	4.32	<0.001	87.1%	<0.001	
Caucasian	3 (1145)	Random	1.59 (1.05–2.42)	2.17	0.030	79.4%	0.008	
Cancer type								0.090
RCC	6 (4624)	Random	1.64 (1.30–2.05)	4.26	<0.001	55.6%	0.046	
Liver cancer	4 (1900)	Random	1.16 (1.04–1.29)	2.75	0.006	95.1%	<0.001	
UTUC	2 (1632)	Fixed	1.96 (1.53–2.51)	5.31	<0.001	0.0%	0.538	
Bladder cancer	2 (267)	Fixed	2.66 (1.69–4.20)	4.21	<0.001	0.0%	0.910	
Others	2 (430)	Fixed	1.44 (1.18–1.76)	3.62	<0.001	26.8%	0.242	
Primary treatment								0.783
Surgery	13 (8063)	Random	1.74 (1.34–2.25)	4.21	<0.001	88.0%	<0.001	
None surgery	3 (790)	Fixed	1.50 (1.26–1.78)	4.61	<0.001	0.0%	0.374	
Clinical stage								0.111
I-IV	4 (1758)	Random	1.65 (1.15–2.35)	2.74	0.006	70.5%	0.017	
T1-T4	5 (4513)	Fixed	1.89 (1.59–2.25)	7.26	<0.001	0.0%	0.450	
IV	3 (552)	Fixed	1.83 (1.43–2.34)	4.79	<0.001	0.0%	0.695	
Others	4 (2030)	Random	1.17 (1.06–1.29)	3.11	0.003	94.9%	<0.001	
Cutoff value								0.114
>1.3	8 (6275)	Random	1.48 (1.08–2.02)	2.44	0.015	89.4%	<0.001	
≤1.3	8 (2578)	Fixed	1.78 (1.59–2.00)	9.79	<0.001	0.0%	0.550	
Analysis method								0.890
Univariate	4 (1322)	Random	1.56 (1.20–2.04)	3.32	0.001	68.8%	0.022	
Multivariate	12 (7531)	Random	1.76 (1.33–2.33)	3.95	<0.001	87.6%	<0.001	
Sample size								0.586
≥200	10 (8019)	Random	1.50 (1.17–1.92)	3.20	0.001	89.1%	<0.001	
<200	6 (834)	Fixed	2.18 (1.75–2.72)	6.96	<0.001	0.0%	0.899	

Notes: P_Z denotes P-value for statistical significance based on Z test; P_h denotes P-value for heterogeneity based on Q test; P_m denotes P-value for statistical outcome based on multivariate meta-regression analysis.

Abbreviations: RCC, renal cell carcinoma; UTUC, urinary tract urothelial carcinoma.

Five studies comprising 4,751 cases provided the data for the RFS endpoint (Table 3). A random-effects model was applied to calculate the pooled result due to the significant heterogeneity ($I^2=64.2\%$, $P_h=0.025$), which indicated that elevated AST/ALT ratio was obviously correlated with poor RFS (pooled HR=1.51, 95% CI=1.15–1.99, $P=0.003$, random effects, Figure 3B).

Sensitivity analysis and meta-regression analysis

The results of sensitivity analysis suggested that the conclusions for OS, CSS, and RFS were stable because the

observed effect size (the pooled HRs) was not significantly affected by the exclusion of any individual study (Figure 4).

We performed meta-regression analyses to investigate the suspected causes of heterogeneity among studies for each survival outcome. The results demonstrated that study population ($P=0.105$), cancer type ($P=0.090$), primary treatment ($P=0.783$), clinical stage ($P=0.111$), cutoff value ($P=0.114$), analysis method ($P=0.890$), and sample size ($P=0.586$) have no effects on the heterogeneity for OS (Table 2). Moreover, study population ($P=0.893$), cancer type ($P=0.574$), clinical stage ($P=0.536$), cutoff value ($P=0.316$), and sample size ($P=0.199$) did not contribute to the source of heterogeneity for CSS (Table 3).

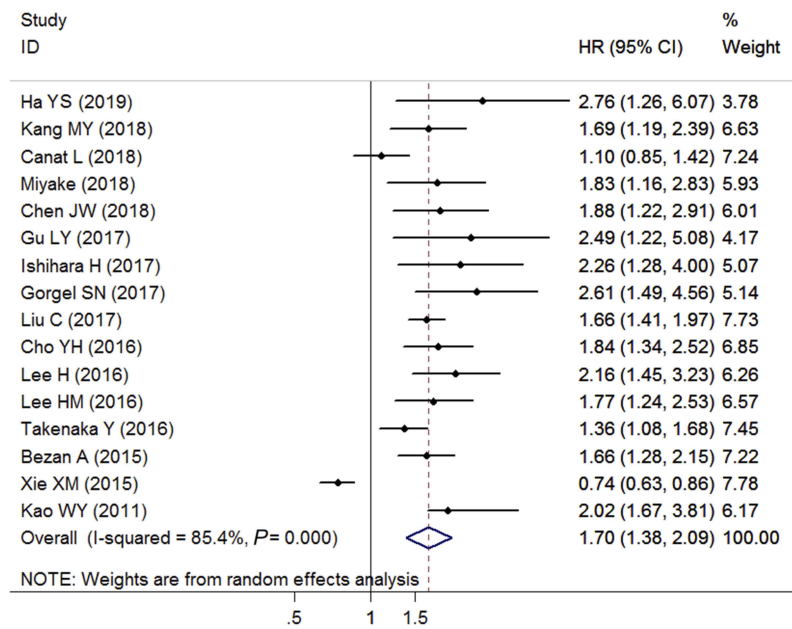


Figure 2 Forest plots of the association between AST/ALT ratio and overall survival.
Abbreviation: AST/ALT ratio, aspartate transaminase to alanine transaminase ratio.

Table 3 Pooled and subgroup analyses of data synthesis of cancer-specific survival and recurrence-free survival for this meta-analysis

Categories	Study (case)	Model	HR (95% CI)	Z	P _Z	Heterogeneity		P _m
						I ²	P _h	
Cancer-specific survival (CSS)	8 (5640)	Fixed	2.07 (1.74–2.46)	8.25	<0.001	38.1%	0.126	
Study population								0.893
Asian	6 (5193)	Fixed	2.12 (1.76–2.56)	7.86	<0.001	0.0%	0.605	
Caucasian	2 (447)	Random	2.60 (0.61–11.09)	1.29	0.198	86.2%	0.007	
Cancer type								0.574
RCC	4 (3741)	Fixed	1.78 (1.42–2.22)	5.01	<0.001	18.0%	0.301	
Bladder cancer	2 (267)	Fixed	3.78 (2.02–7.04)	4.17	<0.001	24.4%	0.250	
UTUC	2 (1632)	Fixed	2.38 (1.76–3.22)	5.63	<0.001	0.0%	0.697	
Clinical stage								0.536
I-IV	2 (1347)	Random	1.85 (1.05–3.48)	2.10	0.046	75.0%	0.045	
T1-T4	4 (3815)	Fixed	2.55 (1.90–3.45)	6.30	<0.001	9.5%	0.345	
IV	2 (478)	Fixed	1.74 (1.28–2.34)	3.53	<0.001	0.0%	0.416	
Cutoff value								0.316
>1.3	5 (5044)	Random	2.26 (1.63–3.15)	4.83	<0.001	53.0%	0.074	
≤1.3	3 (596)	Fixed	1.84 (1.38–2.45)	4.16	<0.001	0.0%	0.419	
Sample size								0.199
≥200	5 (5255)	Fixed	1.95 (1.62–2.36)	6.95	<0.001	33.8%	0.196	
<200	3 (385)	Fixed	2.82 (1.83–4.34)	4.69	<0.001	32.1%	0.229	
Recurrence-free survival (RFS)	5 (4751)	Random	1.51 (1.15–1.99)	2.95	0.003	64.2%	0.025	

Note: P_Z denotes P-value for statistical significance based on Z test; P_h denotes P-value for heterogeneity based on Q test; P_m denotes P-value for statistical outcome based on multivariate meta-regression analysis.

Abbreviations: RCC, renal cell carcinoma; UTUC, urinary tract urothelial carcinoma.

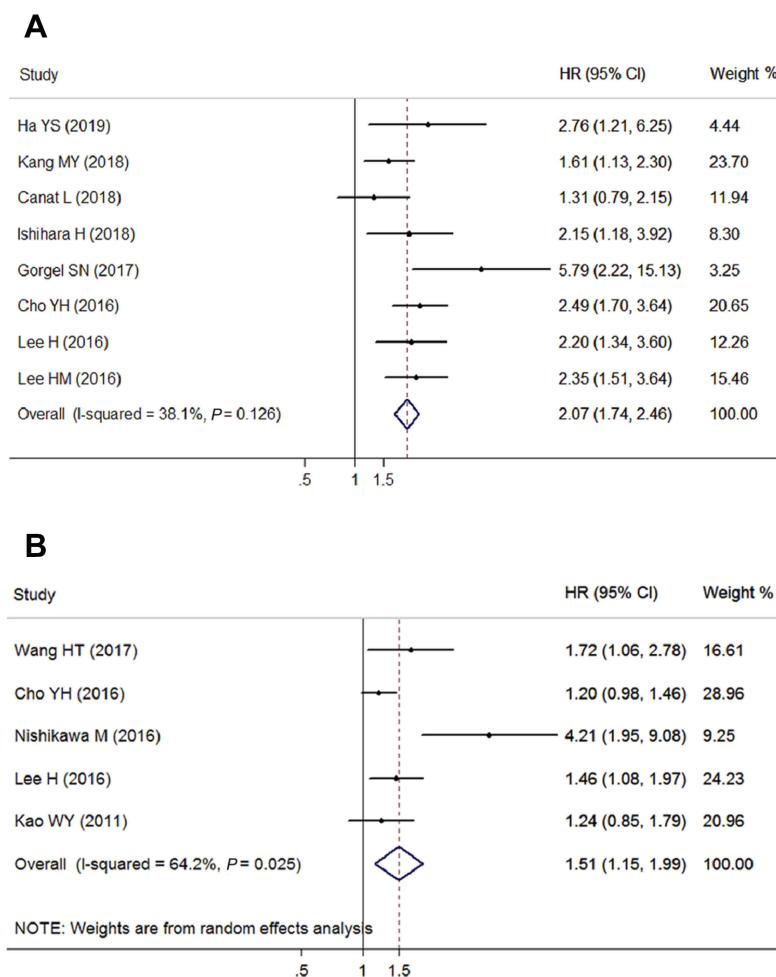


Figure 3 Forest plots of the association between AST/ALT ratio and (A) cancer-specific survival; (B) recurrence-free survival. **Abbreviation:** AST/ALT ratio, aspartate transaminase to alanine transaminase ratio.

Publication bias

Upon visual inspection of the funnel plot (Figure 5A) confirmed by Egger's test ($P=0.004$), significant publication bias was found with regard to the pooled outcome of OS. The trim-and-fill analysis suggested that five non-published studies were needed to balance the funnel plot (Figure 5B). The adjusted HR and 95% CI were attenuated but remained significant (pooled HR=1.51; 95% CI=1.26–1.82; random effects), thereby suggesting that the potential publication bias had minimal impact on the overall outcome. Moreover, the funnel plots did not show unsymmetrical evidence, and neither Begg's nor Egger's test demonstrated evidence of publication bias concerning CSS (Begg's test, $P=0.536$; Egger's test, $P=0.166$; Figure 5C) and RFS (Begg's test, $P=0.186$; Egger's test, $P=0.148$; Figure 5D).

Discussion

To date, numerous studies have reported the application of aminotransaminase as a prognostic indicator in various cancers, regardless of the presence of liver-specific disease.^{35–37} AST is predominantly expressed in the mitochondria and is widely found in several organs, including the liver, heart, kidney, brain, and skeletal muscle, whereas ALT is only present in the hepatocyte cytoplasm. AST and ALT are the major critical enzymes in biological processes, of which their functions reflect the important link between carbohydrate and protein metabolism. The serum AST level should be higher than that of ALT due to the 2.5:1 hepatic proportion of AST/ALT. However, the resulting serum levels of AST and ALT are fairly similar due to the quicker removal rate of AST ($t_{1/2}=18$ hrs) by the liver sinusoids compared with that of ALT ($t_{1/2}=36$ hrs). The

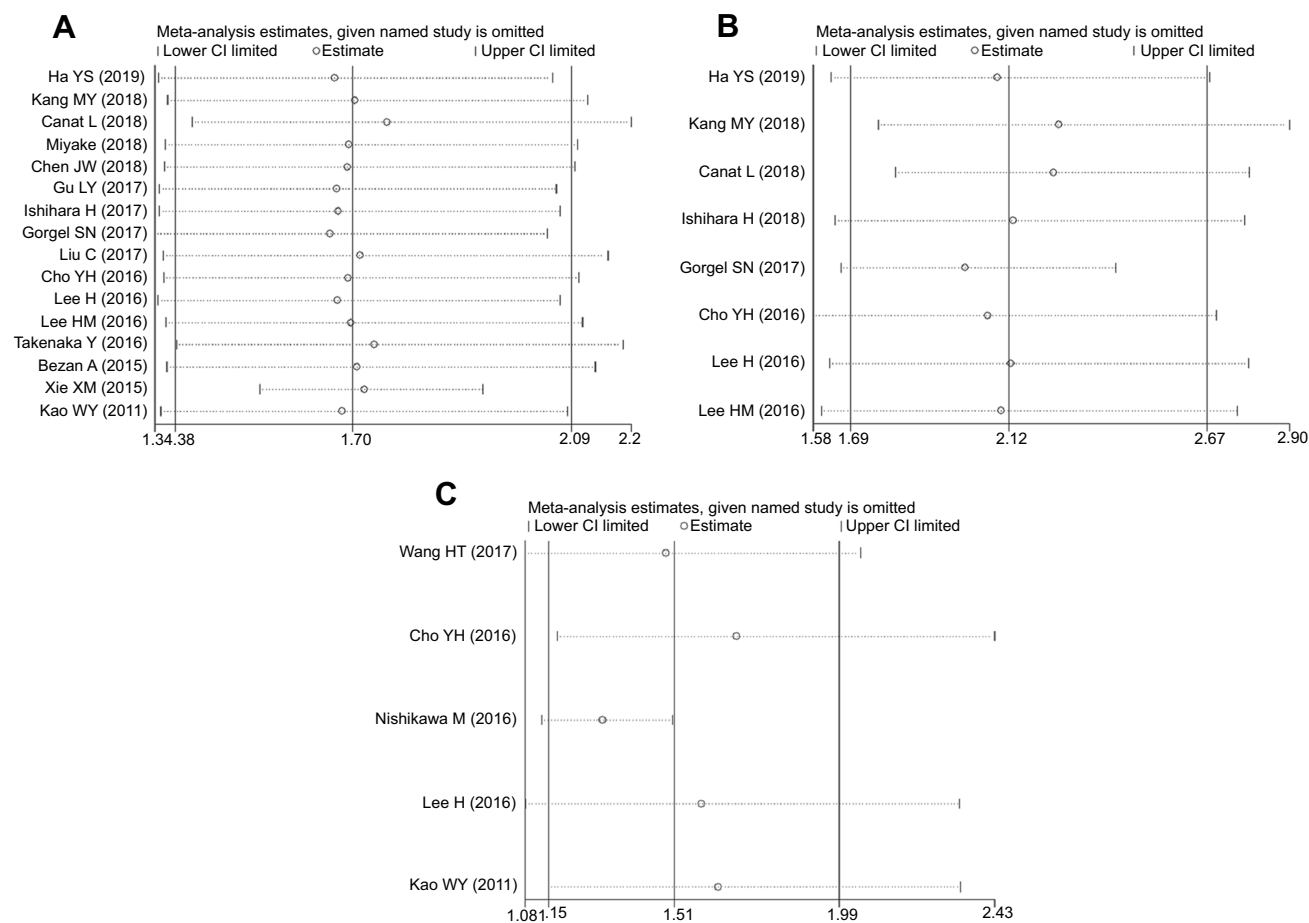


Figure 4 Sensitivity analysis for (A) overall survival; (B) cancer-specific survival; (C) recurrence-free survival.

ratio of AST and ALT is normally constant among healthy individuals. Serum AST and ALT levels, as part of “liver function tests” panel, are routinely assessed before clinical treatment. Compared with tissue biomarkers, hematological biomarkers are easier to obtain, do not involve invasive operations, and involve inexpensive operations, thus making them convenient and reproducible preoperative parameters for risk prediction.³⁸ All laboratories that report abnormal ALT are recommended to report the patients’ AST levels to allow the calculation of the De Ritis ratio, which provides valuable diagnostic and prognostic information.³⁹ Moreover, the serum level of AST and ALT can be influenced by many other non-tumor-related factors, including chronic hepatitis, coronary heart disease, impaired renal function, and drugs. Hence, their numerical values are unstable when they act as single predictors. Instead, the combination of AST and ALT is more appropriate as a composite parameter and can counteract the effects of other factors.

AST/ALT ratio has been frequently used as a predictive index for various diseases, including critical limb ischemia,¹⁰ arterial stiffness,⁴⁰ and renal and respiratory dysfunction.⁴¹ The effect of AST/ALT ratio on cancer prognosis has been declared in several studies. However, these studies presented extremely different results. Thus, the exact value of AST/ALT ratio on malignancy prognosis remains uncertain. We conducted this first meta-analysis to comprehensively examine the association between pretreatment AST/ALT ratio and the prognosis of solid tumors. The pooled risk of increased AST/ALT ratio for worse OS in patients with malignancies was considerably with a combined HR of 1.70 (95% CI: 1.38–2.09). Generally, in the subgroup analyses, elevated AST/ALT ratio is an important prognostic predictor in patients with cancer for OS, regardless of study population, cancer type, primary treatment, clinical stage, cutoff value, analysis method, and sample size. Furthermore, a significantly negative association was found between pretreatment AST/ALT ratio and both CSS (pooled HR=2.07,

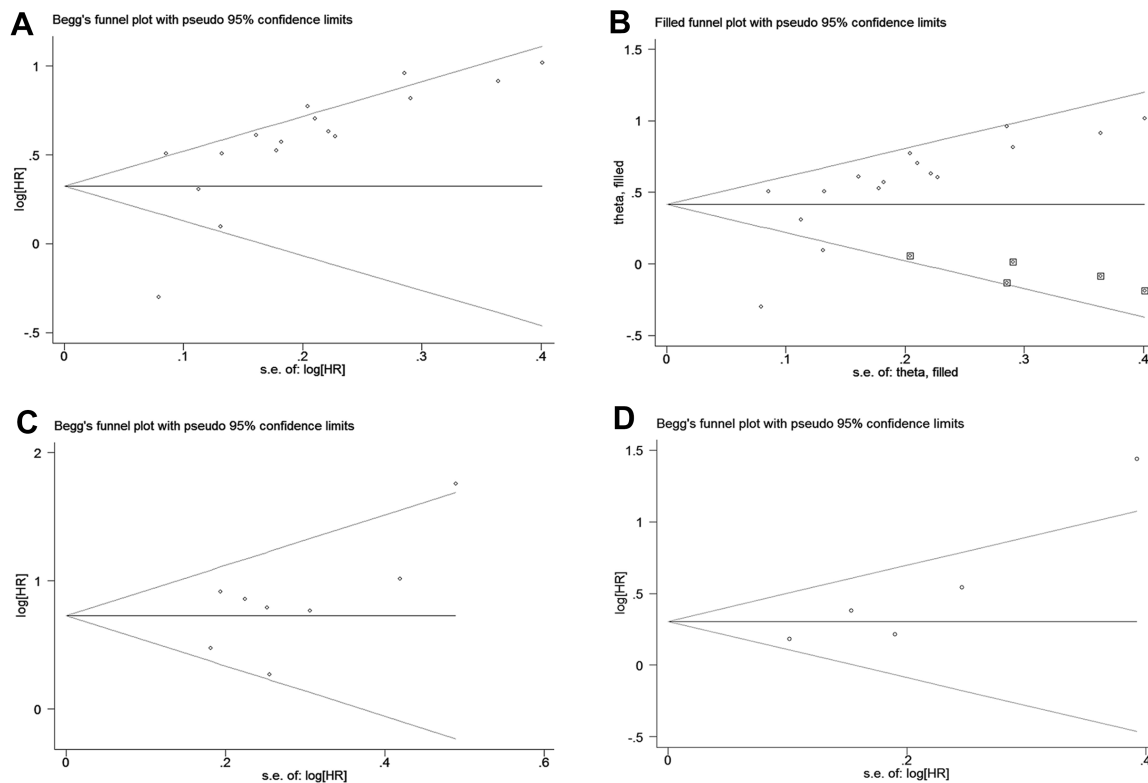


Figure 5 Funnel plots assessing the potential publication bias of the included studies. **(A)** Funnel plot of publication bias for overall survival. **(B)** Funnel plot adjusted by trim-and-fill analysis for overall survival. **(C)** Funnel plot of publication bias for cancer-specific survival. **(D)** Funnel plot adjusted by trim and fill analysis for recurrence-free survival.

95% CI=1.74–2.46, $P<0.001$) and RFS (pooled HR=1.51, 95% CI=1.15–1.99, $P=0.003$). Hence, the serum AST/ALT ratio before treatment may be a negative prognostic factor for malignant patients. However, the insignificant correlations of AST/ALT ratio and CSS were unveiled in the subgroup of Caucasian patients. Notably, these insignificant results were achieved based on limited studies and insufficient sample sizes. Hence, they should be interpreted with caution, and additional studies are needed to support or validate the conclusion.

Sensitivity analyses have confirmed the robustness of the pooled outcomes, but moderate to extreme inter-study heterogeneity were found for each survival endpoint, and this finding might be attributed to the different baseline characteristics of the individual studies. Thus, we employed meta-regression analysis by using study population, cancer type, clinical stage, primary treatment, cutoff value, analysis method, and sample size to investigate the potential source of heterogeneity. However, none of these factors could explain the heterogeneity for OS. Similar results were achieved concerning CSS. Subgroup analyses were conducted to assess the source of heterogeneity, which was slightly reduced in most subgroups, but remained statistically

significant ($P<0.05$) in several subgroups. Instead, we calculated the effect size by using a random-effects model to minimize the effects of heterogeneity on the pooled outcome. Due to the limited number of included studies, we did not perform subgroup analysis and meta-regression analysis on RFS. Moreover, although we have performed a broad literature search, a potential publication bias was still found among the studies reporting OS, which may have inflated the pooled outcomes. After trim-and-fill analysis recalculation, the adjusted HR estimation reinforced the prognostic value of AST/ALT ratio concerning OS but remained statistically, indicating that the publication bias may have little systematic impact on the overall finding. Therefore, the results of this meta-analysis are robust and reliable.

The internal mechanisms of elevated AST/ALT ratio associated with poor outcomes of patients with cancer remain unclear. Previous studies hypothesized the involvement of glucose metabolism. Cancer cells favor a high rate of aerobic glycolysis for a high proliferative status compared with normal cells.⁴² AST is known to play a vital role in aerobic glycolysis by relocating nicotinamide adenine dinucleotide hydrogen into the mitochondria through malate-shuffling, as well as α -ketoglutarate, aspartate and glutamate.⁴³ This

pathological condition leads to the activation of more AST than ALT in rapidly growing cancer tissues.⁴⁴ Moreover, pyruvate production and glutaminolysis are enhanced in malignant cells, of which the conversion of pyruvate and glutamate to alanine and α -ketoglutarate, respectively, is catalyzed by ALT.⁴⁵ ALT level is lower in highly invasive cells than in less invasive cells to meet the demand for tumor cell metabolism.⁴⁶ The major cancer types involved in our meta-analysis, including RCC, UTUC, PC, bladder cancer, and HCC, are known as glucose-dependent malignancies. Thus, the AST/ALT ratio may reflect the metabolic alterations in these glucose-utilizing cancers, which are possibly related to tumor growth and progression. Furthermore, oxidative stress and inflammation are closely related to cancer development.^{47,48} Simultaneously, oxidative stress and inflammation can cause liver injury.⁴⁹ The changes in serum ALT and AST levels have become common diagnostic markers for assessing hepatic function.⁵⁰ Thus, the elevated AST/ALT ratio represents high oxidative stress and inflammatory environment in vivo that are linked to the poor survival of patients with different cancer types.

Some potential limitations should be acknowledged in the present meta-analysis. First, heterogeneity may result from the inconsistencies in the cutoff values and follow-up periods among the individual studies. Second, several individual HR estimations were obtained from univariate analyses or survival curves, which have not adjusted the confounding factors, leading to less reliability than those HRs that were directly calculated from multivariate analyses. Third, the included studies were mainly conducted in East Asian countries, of which the racial representation was limited; thus, conclusions should be cautiously applied for other racial populations. Fourth, this meta-analysis was limited to published literature, which represents positive results over negative findings, resulting in an overestimation of the overall outcomes to some extent. The enrolled studies provided low-quality data with short follow-up period. Fifth, the number of included studies for several cancer types was extremely small, and this low number might weaken the reliability of the overall results. Finally, only the evidence for the correlation study was provided by this meta-analysis, which cannot be simply interpreted as a causal relationship.

Conclusion

Our meta-analysis revealed that a high level of AST/ALT ratio before treatment is significantly associated with worse OS, CSS, and RFS in patients with solid tumors. We conclude that serum AST/ALT ratio can serve as a reliable index for

risk stratification of cancer patients in clinical settings because it has low cost and involves convenient operations. However, further high-quality clinical research must be performed to validate the prognostic role of pretreatment AST/ALT ratio in patients with malignancies due to the aforementioned limitations.

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Disclosure

The authors report no conflicts of interest in this work.

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