

# Prognostic and clinicopathological significance of Gamma-Glutamyltransferase in patients with hepatocellular carcinoma

## A PRISMA-compliant meta-analysis

Ping Sun, MD, Yanlong Li, MD\*, Lijun Chang, MD, Xudong Tian, BS

### Abstract

**Background:** Many studies explored the prognostic and clinicopathological significance of pretreatment serum Gamma-Glutamyltransferase (GGT) level in hepatocellular carcinoma (HCC). However, there are inconsistent results in the prognostic and clinicopathological significance of pretreatment serum GGT level in HCC. Thus, we conducted this meta-analysis to comprehensively assess the prognostic and clinicopathological significance of pretreatment serum GGT level in HCC patients.

**Methods:** We systematically searched PubMed, EMBASE and Web of Science for relevant studies (up to June 14, 2018). The estimated hazard ratios (HRs) were used to assess the association between pretreatment serum GGT level and survival in HCC patients. The estimated odds ratios (ORs) were applied to evaluate the correlation between pretreatment serum GGT and clinicopathological features in HCC.

**Results:** Our results showed that high pretreatment serum GGT level was significantly correlated with poor overall survival (OS) (HR = 1.70, 95% CI: 1.54–1.87;  $P < .01$ ) and disease-free survival/relapse-free survival (DFS/RFS) (HR = 1.56, 95% CI: 1.42–1.71;  $P < .01$ ). Additionally, our results also revealed that there was a close correlation between GGT level and several clinicopathological features in HCC patients, including vascular invasion, tumor size, tumor number and Alpha-fetoprotein (AFP) level.

**Conclusions:** This meta-analysis shows that high pretreatment serum GGT level is significantly correlated with poor survival and unfavorable clinicopathological features in HCC patients, suggesting that pretreatment serum GGT may be an economical and effective prognostic biomarker for HCC patients. However, more high-quality studies are still warranted to further validate our findings, considering there are several limitations in this meta-analysis.

**Abbreviations:** AFP = alpha-fetoprotein, CI = confidence interval, DFS = disease-free survival, GGT = Gamma-Glutamyltransferase, HCC = hepatocellular carcinoma, HR = hazard ratio, NOS = Newcastle-Ottawa Scale, OR = odds ratio, OS = overall survival, RFS = recurrence-free survival, TNM = tumor node metastasis.

**Keywords:** Gamma-Glutamyltransferase, hepatocellular carcinoma, meta-analysis, survival

## 1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and sixth cause of cancer-related death worldwide.<sup>[1,2]</sup> Despite substantial advances in the diagnostic procedures, therapy, and perioperative management over the past

decade, most of HCC patients still have poor prognosis due to recurrence and metastasis.<sup>[3,4]</sup> To date, several prognostic scoring models for HCC patients have been reported, such as TNM (Tumor Node Metastasis) staging, Cancer of the Liver Italian Program staging, Barcelona-clinic Liver Cancer staging, and Japanese Integrated Staging scoring system.<sup>[5]</sup> Nevertheless, these scoring models are rather intricate. Furthermore, currently there is no international consensus on the optimal model of prognostic prediction in HCC patients. Alpha-fetoprotein (AFP) has been routinely used for diagnosing and predicting HCC recurrence due to additional prognostic information,<sup>[6]</sup> but some AFP-negative HCC patients with identical TNM stage have completely different prognosis. Thus, it remains imperative and urgent to identify novel biomarkers to guide prognostic assessment and individualized treatment in HCC patients.<sup>[7–12]</sup>

Gamma-Glutamyltransferase (GGT), also termed as Gamma-glutamylpeptidase, is a cell membrane-bound enzyme, which plays a crucial role in glutathione (GSH) metabolic processes.<sup>[13]</sup> GGT is an easily obtainable serum biomarker in HCC patients. Several studies suggested that serum GGT was an effective diagnostic biomarker of hepatobiliary diseases and various tumors.<sup>[14,15]</sup> Moreover, many studies explored the prognostic and clinicopathological significance of pretreatment serum GGT

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level in HCC. However, the results were conflicting in the prognostic and clinicopathological significance of pretreatment serum GGT level in HCC.<sup>[16–20]</sup> Therefore, we performed this meta-analysis to comprehensively assess the prognostic and clinicopathological significance of pretreatment serum GGT level in HCC patients.

## 2. Materials and methods

This meta-analysis was conducted according to the PRISMA statement issued in 2011.<sup>[21]</sup> Moreover, this study was approved by Ethics Committee of Gansu Provincial Hospital of Traditional Chinese Medicine.

### 2.1. Search strategy

We searched PubMed, EMBASE and Web of Science from inception to June 14, 2018 to identify relevant studies. The following terms were used to formulate the search strategy: (Gamma-Glutamyltransferase or GGT or  $\gamma$ -Glutamyltransferase or  $\gamma$ -GT or Gamma-glutamylpeptidase or GGTP or  $\gamma$ -glutamylpeptidase) and HCC or liver cancer or liver primary cancer or hepatomas) and (prognosis or prognostic or survival). We only searched studies published in English. Additionally, reference lists of retrieved studies and pertinent reviews were also scanned to identify eligible studies.

### 2.2. Study selection

The inclusion criteria included:

1. The diagnosis of HCCs were primarily made based on imaging characteristics and then were further confirmed by pathological examination on the excised lesions;
2. The association between serum GGT level and survival, including overall survival (OS), disease-free survival (DFS) or recurrence-free survival (RFS) in patients with HCC.

Exclusion criteria included:

1. Publications were conference abstracts, case reports, reviews, meta-analysis, or letters;
2. Studies enrolled overlapping patients;
3. Studies did not provided HRs for OS, DFS, or RFS directly;
4. The association between serum GGT level and survival was only assessed by univariate analysis, which did not balance many other survival-associated factors;
5. Studies were performed in non-human or non-clinical context.

### 2.3. Data extraction and quality assessment of studies

Two investigators (Ping Sun and Yanlong Li) independently used the identical and pre-designed table to extract the following data: first author's last name, publication year, country, recruitment time, median age and age range of the patients, the number of patients, tumor type, initial treatment, cut-off value for high GGT level, follow-up time, survival outcomes and several clinicopathological characteristics. The outcomes of interest included OS, DFS or RFS. OS was defined as the interval from the date of surgery to the date of death or the last follow-up.<sup>[22]</sup> RFS was defined as the interval from the date of surgery to the date of confirmed HCC recurrence or the last follow-up.<sup>[22]</sup> DFS was defined as the time from the date of surgery to locoregional recurrence, distant metastasis, second primary same or other

cancer, death due to same or other cancer, treatment-associated death or non-cancer-associated death.<sup>[23]</sup> Any discrepancy was resolved by discussion among all the authors.

The methodological quality of studies was evaluated based on the Newcastle-Ottawa Quality Assessment Scale (NOS).<sup>[24]</sup> NOS is a 9-point system, in which 3 aspects including patient selection, comparability and ascertainment of outcome, are assessed. In our meta-analysis, a study with 6 or more scores was considered as high quality.

### 2.4. Statistical analysis

The statistical work in this meta-analysis was performed using Stata version 12.0 (StataCorp, College Station, TX). A 2-sided  $P < .05$  was defined as statistical significance. Synthesized hazard ratio (HRs) and their 95% confidence intervals (95% CIs) were used to assess the association of serum GGT level with OS, and disease-free survival/recurrence-free survival (DFS/RFS). In addition, synthesized odds ratios (ORs) and their 95% CIs were used to assess the relationship between pretreatment serum GGT and clinicaopathological characteristics of HCC patients, including age, Alpha-fetoprotein (AFP) level, tumor number, tumor size and vascular invasion. Heterogeneity among the included studies was evaluated using Chi-square-based  $Q$  and  $I^2$  tests. If  $I^2 > 50\%$  and  $P < .05$ , the heterogeneity was considered statistically significant, and a random-effects model was used. Inversely, if no significant heterogeneity existed ( $I^2 \leq 50\%$ ), fixed-effect model was applied. Subgroup analyses and sensitivity analyses were conducted to test the robustness of the pooled results. Subgroup analyses were performed according to five stratified factors, including ethnicity (Asian and Non-Asian), sample size ( $\leq 400$  and  $> 400$ ), cut-off value ( $\leq 50$ ,  $50-100$ ,  $> 100$  U/L), initial treatment (liver resection, transcatheter arterial chemoembolization, ablation, and liver transplantation), and recruitment starting time (before 2006 and at or after 2006). Sensitivity analyses were undertaken by omitting 1 study in each step. The Egger and Begg Tests were used to evaluate the potential publication bias.<sup>[25]</sup> When publication bias was significant, the Trim-and-Fill method was used to estimate a corrected effect size after adjustment, which helped to determine whether the publication bias substantially affected the robustness of the pooled effect size.<sup>[26]</sup>

## 3. Results

### 3.1. Characteristics of included studies

The initial search yielded a total of 473 relevant studies, but only 20 studies with 7773 patients were finally included into this meta-analysis according to inclusion and exclusion criteria.<sup>[16–20,27–36,22,37–40]</sup> The flow chart describing literature search and selection was shown in Figure 1. Of the 20 included studies, 18 included Chinese population and 2 enrolled populations from Italy and US. The sample size of the included studies ranged from 130 to 750. The cut-off value for high GGT level varied from 50 to 150 (U/L). A total of 16 studies investigated the link between GGT and OS. Five studies explored the association between GGT and DFS. Six studies referred to the relationship between GGT and RFS. The more detailed information about baseline characteristics was summarized in Table 1. Additionally, some of the included studies also investigated the correlation of GGT with several clinicopathological features, including Alpha-fetoprotein (AFP), tumor number, tumor size, and vascular

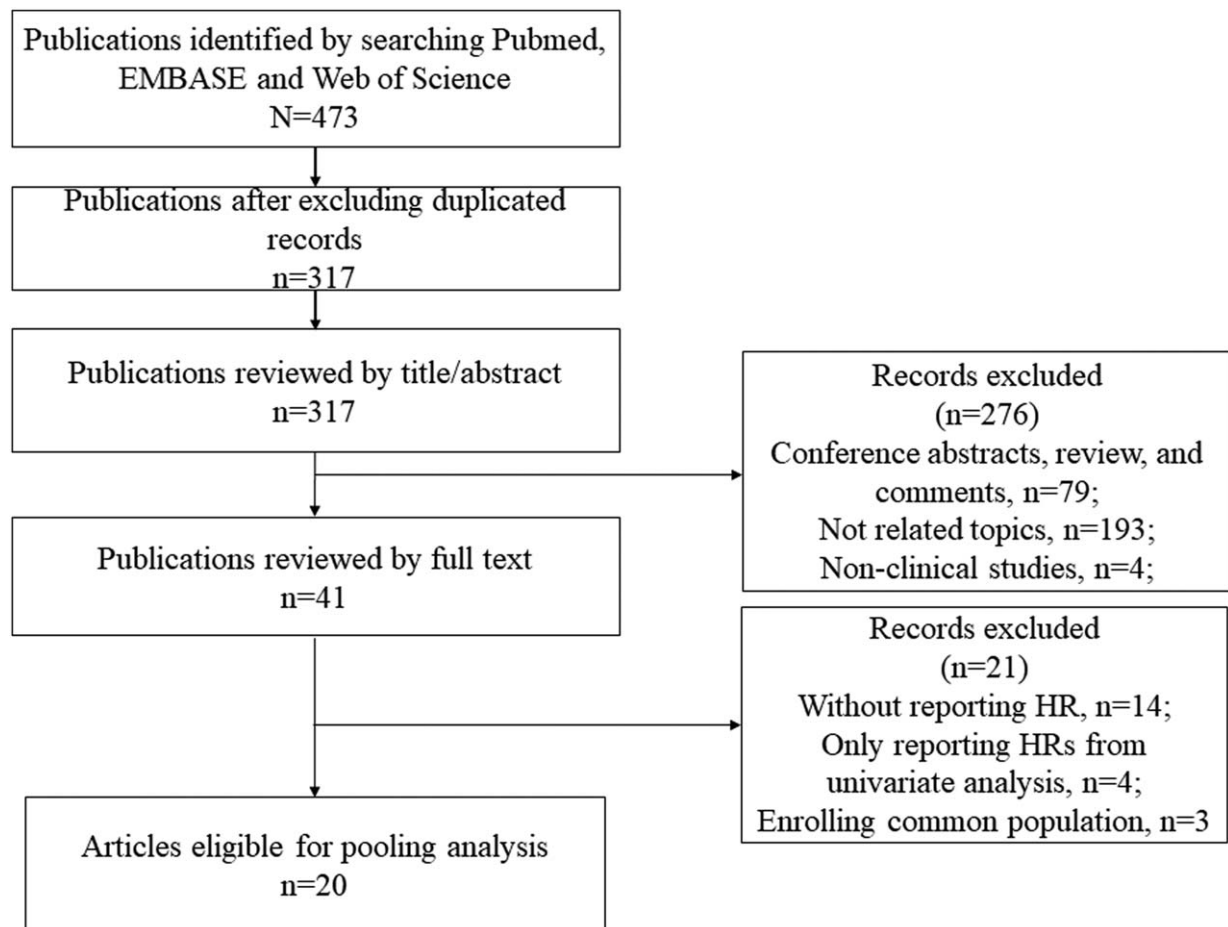


Figure 1. The flow chart describing literature search and selection.

Table 1

## The main characteristics of eligible studies.

Author/publication year	Country	Study design	Recruitment time	Median Age (range)	No. of patients	Tumor type	Initial treatment	Cut-off value (UL)	Follow up (month)	Survival outcomes	Newcastle-Ottawa Scale
Carr, 2013	Italy	Retrospective	NR	NR	344	HCC	TACE	150	NR	OS	7
Chen, 2014	China	Retrospective	2004.01–2010.12	55 (23–71)	154	HCC	TACE	85	NR	OS	6
Dong, 2017	China	Retrospective	2005.01–2010.12	NR	654	HCC	Curative resection	50	NR	OS, DFS	8
Dvorchik, 2007	USA	Retrospective	1989–1999	NR	750	HCC	TACE	100	NR	OS	8
Fu, 2016	China	Retrospective	2006–2009	51 (21–79)	308	HCC	Liver resection	88	29	OS, DFS	7
Fu, 2016	China	Retrospective	2008.01–2013.05	49.5 (13–72)	130	HCC	Liver transplantation	128	40.3	OS, DFS	6
Ju, 2009	China	Retrospective	NR	NR	219	HCC	Curative resection	60	26.76	OS	6
Ma, 2014	China	Retrospective	2007.01–2011.12	NR	254	HCC	RFA	75	27	OS, RFS	6
Shi, 2017	China	Retrospective	2008–2011	60 (27–81)	271	HCC	Liver resection	50	26	OS	7
Song, 2015	China	Retrospective	1997–2007	65 (19–85)	384	HCC	Liver resection	100	57.5	OS, RFS	8
Su, 2013	China	Retrospective	1990–2007	56	333	HCC	Liver resection	60	45.9	RFS	8
Tian, 2017	China	Retrospective	2012.01–2013.09	NR	189	HCC	Liver resection	54	30.9	RFS	6
Wang, 2012	China	Retrospective	1995.08–2008.07	53 (12–86)	441	HCC	TACE	75	12	OS	7
Wang, 2016	China	Retrospective	2010.10–2013.12	NR	221	HCC	WMA	50	41	OS, RFS	7
Wu, 2016	China	Retrospective	2007.06–2013.03	NR	469	HCC	Liver resection	81.5	42	OS, RFS	7
Xu, 2014	China	Retrospective	2002.12–2012.07	53.5 (24–80)	172	HCC	Liver resection	117	34.92	OS	6
Zhang, 2014	China	Retrospective	2002.03–2012.08	56.8	138	HCC	TACE	50	12	OS	6
Zhang, 2016	China	Retrospective	2004.01–2010.12	53 (16–83)	601	HCC	Liver resection	50	NR	DFS	8
Zhang, 2011	China	Retrospective	2003.12–2005.11	54 (12–85)	277	HCC	TACE	50	18.7	OS	7
Zhong, 2018	China	Retrospective	2002.02–2012.07	NR	175	HCC	Liver resection	60	NR	DFS	7

DFS=disease-free survival, HCC=hepatocellular carcinoma, NR=not reported, OS=overall survival, PEI=percutaneous ethanol injection, RFA=radiofrequency-ablation, RFS=recurrence-free survival, TACE=transcatheter arterial chemoembolization, WMA=microwave ablation.

**Table 2**  
**Association between pretreatment serum GGT level and clinico-pathological characteristics.**

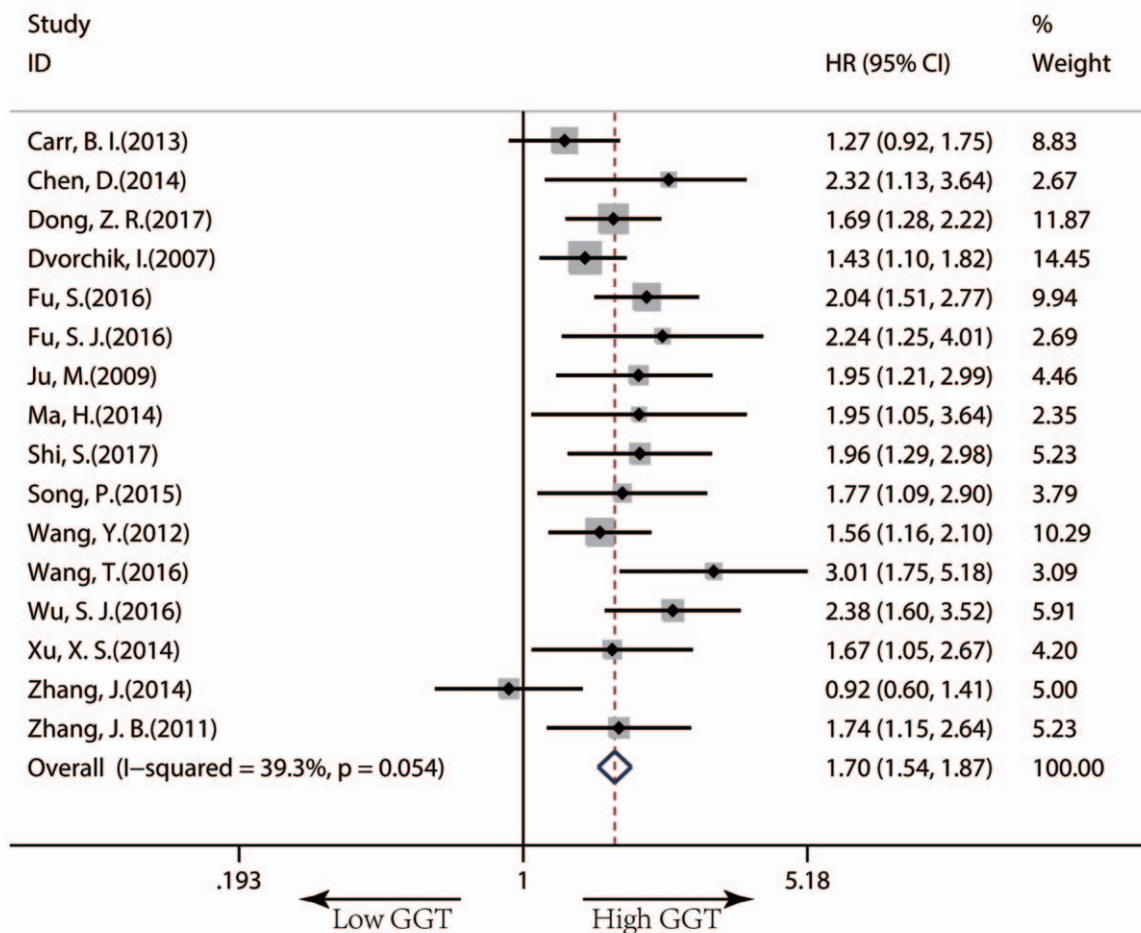
AFP	High GGT		Low GGT	
	Positive (n)	Total (n)	Positive (n)	Total (n)
Fu, 2016	96	162	76	146
Fu, 2016	28	53	20	77
Ju, 2009	45	110	43	109
Shi, 2017	97	142	73	129
Wu, 2016	107	218	72	251
Tumor number (n≥3)	Multiple (n)	Total (n)	Multiple (n)	Total (n)
Fu, 2016	59	162	32	146
Fu, 2016	18	53	19	77
Ju, 2009	30	110	23	109
Ma, 2014	9	108	17	146
Shi, 2017	39	142	25	129
Wu, 2016	46	218	29	251
Zhang, 2011	94	239	15	38
Tumor size (>5 cm)	Larger size (n)	Total (n)	Larger size (n)	Total (n)
Fu, 2016	128	162	74	146
Fu, 2016	34	53	22	77
Ju, 2009	68	110	44	109
Shi, 2017	97	142	53	129
Wu, 2016	80	218	51	251
Vascular Invasion	Present (n)	Total (n)	Present (n)	Total (n)
Fu, 2016	48	162	11	146
Fu, 2016	15	53	5	77
Ju, 2009	62	110	37	109
Shi, 2017	53	142	37	129
Wu, 2016	52	218	32	251

invasion (Table 2). Based on the Newcastle-Ottawa Quality Assessment Scale (NOS), quality score of the included studies ranged from 6 to 7 (Table 1), indicating that the included studies had moderate to high quality, and were eligible for meta-analysis.

**3.2. Pooled analysis**

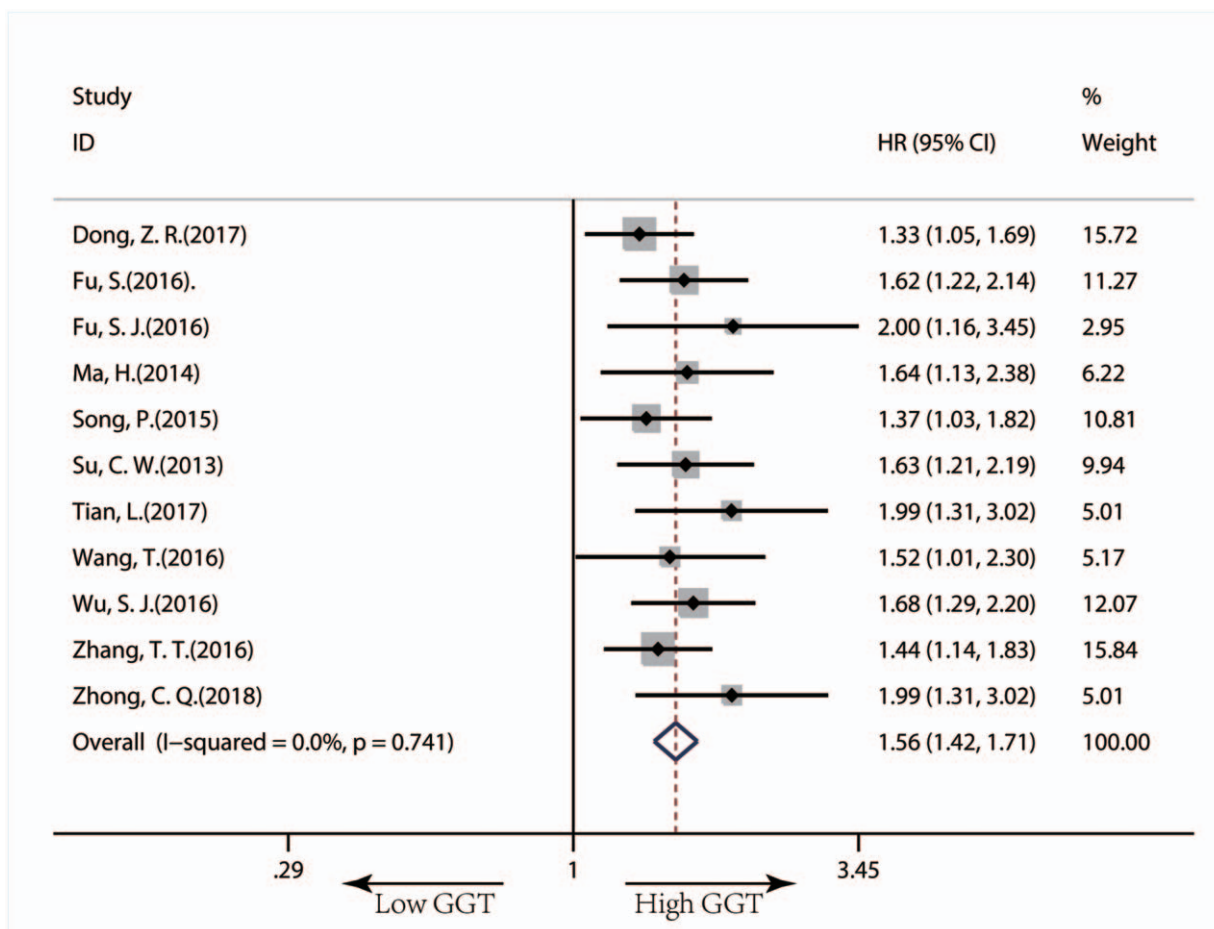
**3.2.1. The prognostic value of pretreatment serum GGT level.**

A total of 16 eligible studies provided available data for synthetically analyzing the association between GGT and OS in HCC patients. Because no significant heterogeneity ( $I^2 = 39.9\%$ ;  $P = .054$ ) existed, the fixed-effect model was used to pool the hazard ratio (HRs) for the association between GGT and OS. The pooled result showed that HCC patients with higher serum GGT level had a significant shorter OS (HR = 1.70, 95% CI: 1.54–1.87;  $P < .01$ ; Fig. 2). Five studies explored the association between GGT and DFS and 6 studies referred to the relationship between GGT and RFS. In view of the similarity between DFS and RFS, we mixed them together for meta-analysis. As Figure 3 shown, the pooled result indicated that higher serum GGT level was significantly correlated with worse DFS/RFS (HR = 1.56, 95% CI: 1.42–1.71;  $P < .01$ ; heterogeneity:  $I^2 = 0.0\%$ ;  $P = .741$ ).



**Figure 2.** Meta-analysis of correlation between pretreatment serum GGT level and OS in HCC patients. GGT = Gamma-Glutamyltransferase, HCC = hepatocellular carcinoma.





**Figure 3.** Meta-analysis of correlation between serum GGT level and DFS/RFS in HCC patients. DFS = disease-free survival, GGT = Gamma-Glutamyltransferase, HCC = hepatocellular carcinoma, RFS = recurrence-free survival.

**3.2.2. The clinicopathological value of pretreatment serum GGT level.** From the pooled results, we found that higher serum GGT level was related to higher incidence of vascular invasion [odds ratio (OR)=2.68, 95% CI: 1.70–4.22;  $P < .01$ , Fig. 4A], a larger tumor size (OR=2.88, 95% CI: 2.30–3.62;  $P < .01$ , Fig. 4B), multiple tumor (OR=1.54, 95% CI: 1.23–1.94;  $P < .01$ , Fig. 4C) and positive of Alpha-fetoprotein (AFP) (OR=1.74, 95% CI: 1.22–2.47;  $P < .01$ , Fig. 4D).

### 3.3. Subgroup and sensitivity analyses

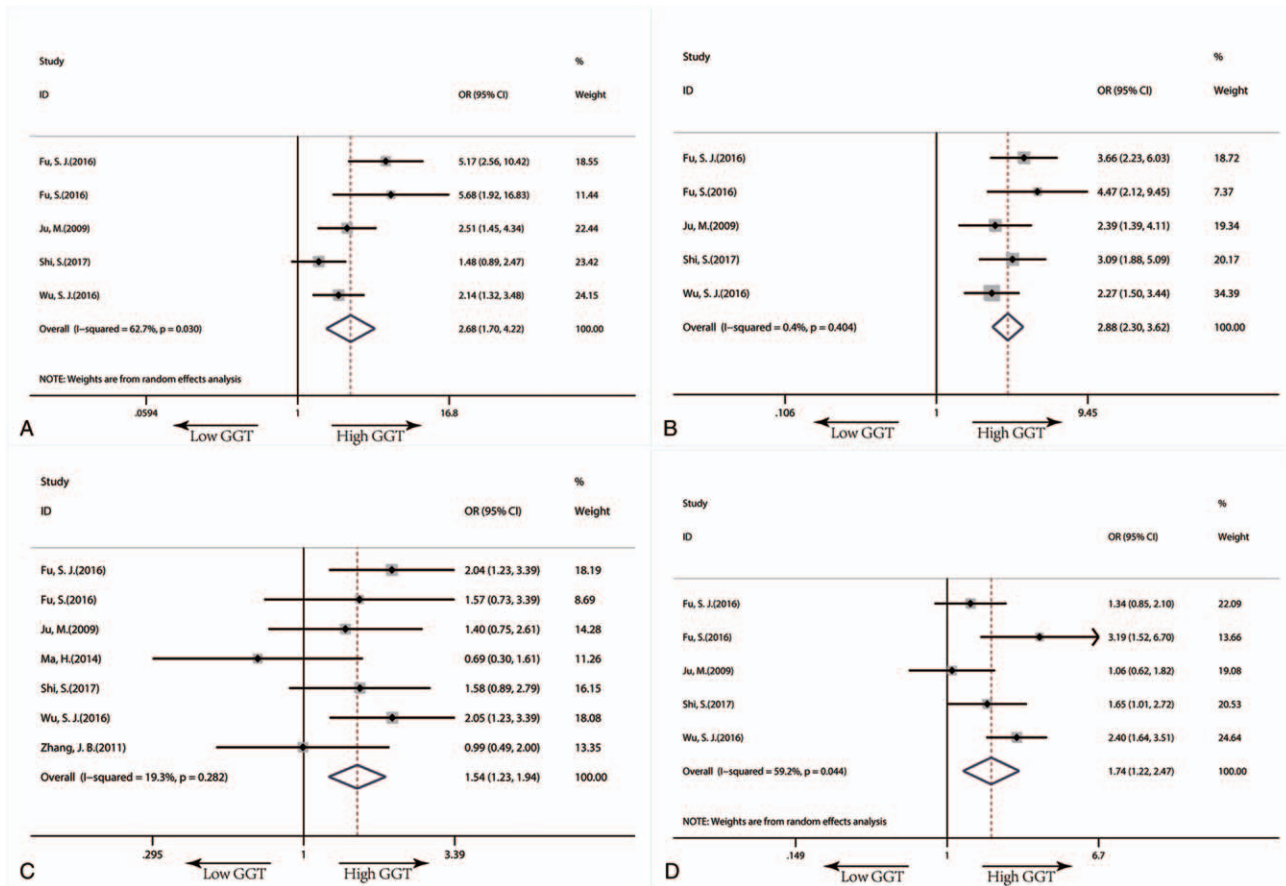
Subgroup and sensitivity analyses were performed to test the robustness of our pooled results. Subgroup analyses were performed by 5 stratified factors, including ethnicity (Asian and Non-Asian), sample size ( $\leq 400$  and  $> 400$ ), cut-off value ( $\leq 50$  U/L, 50–100,  $> 100$ ), initial treatment (liver resection, transcatheter arterial chemoembolization, ablation, and liver transplantation), and recruitment starting time (before 2006 and at or after 2006). The results of subgroup analyses showed that the positive association of higher GGT level with shorter OS (Fig. 5) and DFS/RFS continuously existed in any subgroup (Fig. 6). However, subgroup analyses were not applicable for the pooled results regarding the association between GGT and clinicopathological features owing to the limited number of eligible studies.

Sensitivity analyses were performed by omitting 1 study in each step. From the results of sensitivity analyses, we observed

that the pooled hazard ratios (HRs) for OS (Fig. 7A) and DFS/RFS (Fig. 7B) did not fluctuate significantly, suggesting that our pooled results were stable and dependable. Additionally, it was observed that the pooled odds ratios (ORs) assessing the correlation of GGT level with vascular invasion (Fig. 8A), tumor size (Fig. 8B), tumor number (Fig. 8C) and Alpha-fetoprotein (AFP) level (Fig. 8D) did not alter significantly either, which suggested these pooled results had substantial robustness.

### 3.4. Publication bias assessment

The Egger and Begg tests were used to evaluate the potential publication bias. The  $P$  values of Egger and Begg test for OS were .100 and .163, respectively, and the funnel plot was symmetrical, suggesting that there is no significant publication bias for OS (Fig. 9A). However, the  $P$  values of Egger and Begg test for DFS/RFS were  $< .05$ , suggesting that statistically significant publication bias existed, which was further demonstrated by the asymmetrical shape of funnel plot (Fig. 9B). Thus, we further performed the trim-and-fill analysis to explore whether the publication bias for DFS/RFS significantly influence the stability of the pooled result. The result of trim-and-fill analysis showed that the updated pooled hazard ratio (HR) was still more than 1 and its 95% confidence intervals (95% CIs) did not include 1



**Figure 4.** Meta-analysis of correlation between serum GGT level and clinicopathological features in HCC patients, including vascular invasion (A), tumor size (B), tumor number (C) and AFP level (D). GGT = Gamma-Glutamyltransferase, HCC = hepatocellular carcinoma.

Subgroup	No. of studies	HR (95% CI)				Z-value	p-value	Heterogeneity	
		0.35	0.7	1.4	2.8			I <sup>2</sup> (%)	p-value
(1) Ethnicity									
Asian	14					1.7	<0.01	29.2	0.15
Non-Asian	2					3.1	<0.01	0	0.57
(2) Sample size									
>400	4					6.62	<0.01	36.4	0.05
≤400	12					8.64	<0.01	36.4	0.19
(3) Cut-off value									
≤50	5					3.26	<0.01	68.3	0.01
50-100	8					2.51	0.01	39.7	0.19
>100	3					2.8	<0.01	34.7	0.22
(4) Initial treatment									
Liver resection	7					8.91	<0.01	0	0.86
TACE	6					3.73	<0.01	40.6	0.135
Ablation	2					4.27	<0.01	4.7	0.31
Liver transplantation	1					2.71	<0.01	-	-
(5) Recruitment started year									
Before 2006	8					5.82	<0.01	22.2	0.25
At and after 2006	6					8.69	<0.01	0	0.84

**Abbreviation:** HR: hazard ratios; TACE: transcatheter arterial chemoembolization;

**Figure 5.** Subgroup analysis of pooled HR for OS in HCC patients. HCC = hepatocellular carcinoma.

Subgroup	No. of studies					HR (95% CI)	Z-value	p-value	Heterogeneity	
		0.35	0.7	1.4	2.8				I <sup>2</sup> (%)	p-value
<b>(1) Sample size</b>										
>400	3			■	■	1.46(1.27-1.69)	5.27	<0.01	0	0.44
≤400	8			■	■	1.64(1.45-1.86)	7.77	<0.01	0	0.8
<b>(2) Cut-off value</b>										
≤50	3			■	■	1.41(1.20-1.64)	4.32	<0.01	0	0.82
50-100	8			■	■	1.66(1.47-1.86)	8.42	<0.01	0	0.82
<b>(3) Initial treatment</b>										
Liver resection	8			■	■	1.54(1.40-1.71)	8.41	<0.01	0	0.55
Ablation	2			■	■	1.58(1.20-2.09)	3.25	<0.01	0	0.79
Liver transplantation	1			■	■	2.00(1.16-3.45)	2.49	0.01	-	-
<b>(4) Recruitment starting year</b>										
Before 2006	5			■	■	1.47(1.30-1.66)	6.01	<0.01	0	0.5
At and after 2006	6			■	■	1.69(1.47-1.95)	7.19	<0.01	0	0.93

**Abbreviation:** HR: hazard ratios

**Figure 6.** Subgroup analysis of pooled HR for DFS/RFS in HCC patients. DFS=disease-free survival, HCC=hepatocellular carcinoma, RFS=recurrence-free survival.

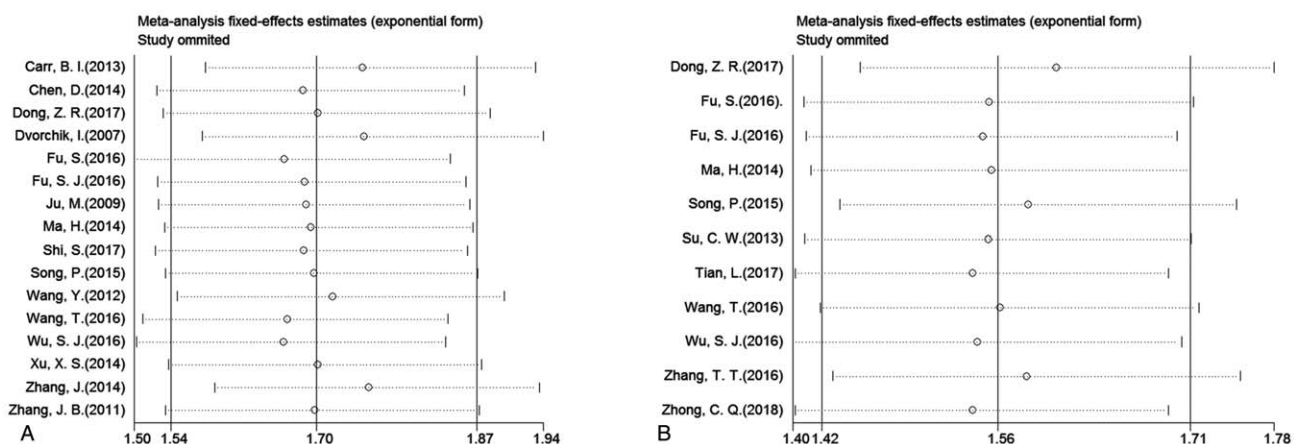
(HR = 1.548, 95%CI: 1.504–1.377; *P* < .001), suggesting that the pooled result of DFS/RFS was reliable.

**4. Discussion**

This study is the first meta-analysis to systematically assess the prognostic and clinicopathological significance of pretreatment serum GGT in HCC patients. Overall, our results revealed that patients with higher GGT level had worse prognosis and unfavorable clinicopathological features. In particular, our present meta-analysis only included studies that calculated hazard ratios (HRs) for OS and DFS/RFS based on multivariate analysis. Therefore, our meta-analysis suggested that pretreatment serum GGT level may be an independent prognostic factor for HCC patients.

There are some possible mechanisms for the prognostic value of serum GGT in HCC patients. Some serum inflammatory cytokines that are closely associated with HCC prognosis, such

as tumor necrosis factor alpha and interferon-alpha, could upregulate GGT expression.<sup>[41,42]</sup> Moreover, serum GGT level has a close association with the active status, fibrosis and cirrhosis stage of chronic hepatitis,<sup>[43,44]</sup> and even is considered as a biomarker of the inflamed liver microenvironment in hepatitis patients.<sup>[45]</sup> These evidence support that GGT may reflect the status of chronic inflammation in HCC patients, which could partly account for the prognostic value of GGT in HCC. Additionally, other evidence suggested that GGT overexpression could break the oxidant/antioxidant balance by its pro-oxidant effects, subsequently resulting in persistent oxidative response in cancer and then promoting cancer progression.<sup>[46,47]</sup> Moreover, it has been reported that GGT could induce DNA damage and genome instability by disturbing CpG island methylation, which plays a critical role in promoting tumor development and progression.<sup>[48,49]</sup> Taken together, the mechanisms mentioned above supported the findings in our meta-analysis.



**Figure 7.** Sensitivity analysis of pooled HRs for OS (A) and DFS (B).

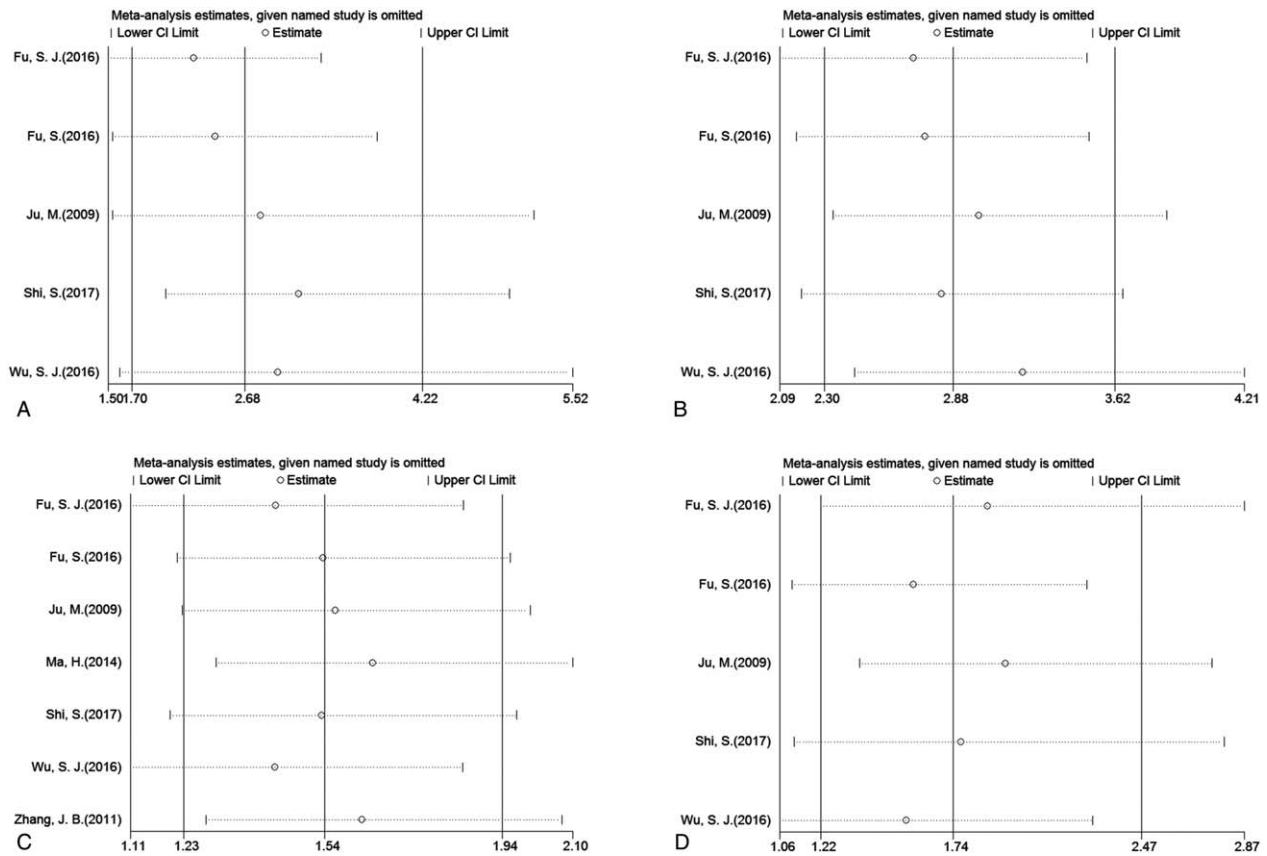


Figure 8. Sensitivity analysis plot of pooled ORs for vascular invasion (A), tumor size (B), tumor number (C) and AFP level (D).

Several limitations in our meta-analysis should be considered when interpreting our finding. First, the cut-off values of high serum GGT levels were inconsistent in the included studies. Although the cut-off value of 50 U/L was used in most of included studies, it cannot be definitely determined whether 50 U/L is the optimal cut-off value for evaluating the prognostic value of serum GGT level. Therefore, further high-quality clinical studies with large sample size are needed to determine an optimal cut-off value for high serum GGT level in HCC patients. Second, among all the included studies, 18 were from China, and only 2 studies were

conducted in western world. Thus, it may not be reasonable to generate our conclusion to western population. Third, considering that we and some authors cannot understand other languages, we only included studies published in English in our meta-analysis. This may lead to a degree of bias. Fourth, all included studies were retrospectively designed, which may inevitably cause a degree of bias as well.

In conclusion, this meta-analysis shows that high pretreatment serum GGT level is significantly correlated with poor survival and unfavorable clinicopathological features in HCC patients,

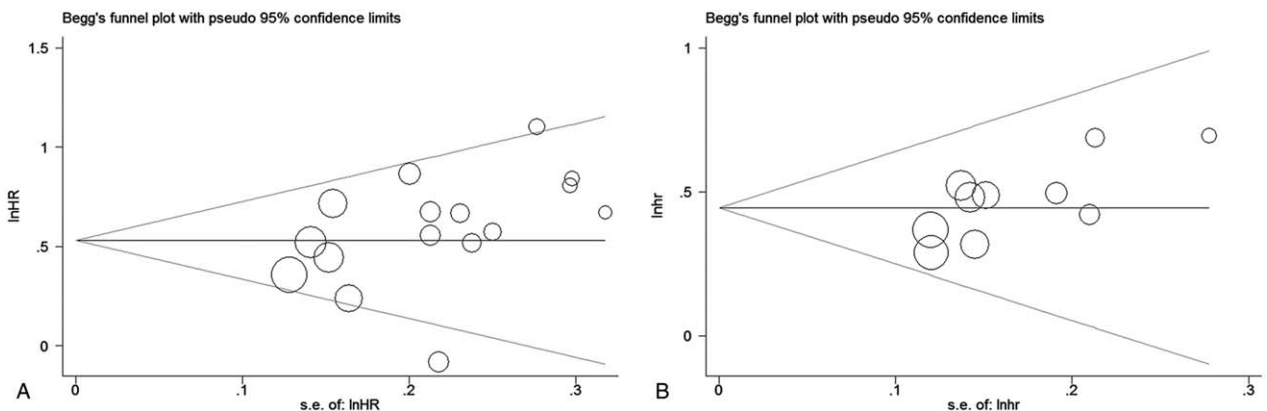


Figure 9. Funnel plots for publication bias assessment of the pooled HRs for OS (A) and DFS/RFS (B). DFS = disease-free survival, RFS = recurrence-free survival.



suggesting that pretreatment serum GGT may be an economical and effective prognostic biomarker for HCC patients. However, more high-quality studies are still warranted to further validate our findings, considering there are several limitations in this meta-analysis.

### Author contributions

**Investigation:** Xudong Tian, Lijun Chang.

**Methodology:** Ping Sun, Yanlong Li.

**Software:** Xudong Tian, Lijun Chang.

**Supervision:** Yanlong Li.

**Writing – original draft:** Ping Sun.

**Writing – review & editing:** Yanlong Li.

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