

Prognostic value of IGFBP7 in solid tumors: a meta analysis of 1,305 patients

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Abstract

Background : Insulin-like growth factor-binding protein 7 (IGFBP7) has been detected to act as a cancer suppressor gene in different types of human carcinoma. Previous studies have presented controversial evidences between the expression of IGFBP7 and prognosis in solid tumors. A comprehensive meta-analysis was performed to investigate the prognostic role of IGFBP7 expression.

Methods: The studies were identified through extensive electronic search of Web of Science, PubMed and Embase up to Jun 2019. The pooled hazard ratios (HR) with corresponding 95% confidence intervals (CI) for overall survival (OS) were calculated through univariate analysis and multivariate analysis to investigate the prognostic value of IGFBP7 expression . Heterogeneity, publication bias and subgroup analyses were also performed.

Results: Seven eligible studies including 1,305 patients were extracted in this analysis. The pooled hazard ratio of univariable analysis for OS (HR = 0.60; 95% CI, 0.54–0.66, P < 0.001). The pooled hazard ratio of multivariate analysis for OS (HR = 0.57; 95% CI, 0.50–0.64, P < 0.001). In addition, subgroup analysis showed that low IGFBP7 expression was significantly associated with poor prognosis in patients with digestive system cancer.

Conclusions: Low-expression of IGFBP7 was correlated strongly with worse OS, which indicated that IGFBP7 might be a new biomarker for prognosis prediction and a promising therapeutic target in solid tumors. **Keywords:** IGFBP7, prognosis, meta-analysis

Background

Insulin-like growth factor-binding protein 7 (IGFBP7) also called as IGFB-related protein 1 or mac25, which is a secreted protein belongs to the IGFBPs family.[1, 2] IGFBP7 has been detected in various normal human tissues including brain, heart and kidney.[3] Functionally, IGFBP7 play central roles in the process of cellular senescence and apoptosis. Wajapeyee *et al.*[4] demonstrated that IGFBP7 through inhibit BRAF-MEK-ERK signaling pathways to induce cellular senescence and apoptosis. Subsequently, Severino *et al.*[5] reported that IGFBP7 could induce senescence in mesenchymal stromal cells. In vitro studies shown that IGFBP7 might inhibit cancer cells proliferation via a senescence-like mechanism.[6] Indeed, IGFBP7 was well known for its function as a growth-suppressing factor.[7] Precious study suggested that IGFBP7 could markedly suppressed growth of BRAFV600E -positive tumors in xenografted mice.[4] Suzuki *et al.*[8] indicated that IGFBP7 is a direct region of p53-dependent growth inhibition in colorectal cancer. Further researches reported that IGFBP7 could through suppress the phosphorylation of the mitogen-activated protein kinases ERK–1/2 to mediate the growth of breast cancer cells.[9] In addition, IGFBP7 via delaying the cells in the G1 phase of the cell cycle to suppress prostate cancer cells growth.[2] Consistently, the tumor suppressor role of IGFBP7 has been identified in lung cancer,[10] thyroid tumour,[11] hepatocellular carcinoma.[12]

There is increasing evidence showing that IGFBP7 downregulation was significantly associated with unfavorable clinical outcome in several types of human malignant tumors, including two gastric cancer, [13, 14] cholangiocarcinoma,[15] human glioma,[16] pancreatic ductal adenocarcinoma,[17] hepatocellular carcinoma,[18]and colorectal cancer.[19] However, previous studies have presented controversial evidences between the expression of IGFBP7 and prognosis in solid tumors. Therefore, we conducted this comprehensive meta-analysis to summarize the clinical role of IGFBP7 expression with overall survival (OS) for cancer patients.

Methods

Literature search and selection criteria

In order to obtaining latent eligible studies, an electronic literature retrieval was undertaken for articles about IGFBP7 expression and clinical prognosis in Web of Science, PubMed and Embase until Jun 2019. The keywords for searching terms including: “Insulin-like growth factor-binding protein 7” or “IGFBP7” “IGFBP-rP1” or “mac25”and “cancer” or “tumor” or “neoplasm” or “carcinoma,” and “prognosis” or “survival”. Only the human studies of solid tumor were selected. Totally 1436 articles were retrieved.

The eligible articles must to meet all the following inclusion criteria: the association between IGFBP7 expression and OS were investigated in solid tumor, the hazard ratios (HR) and corresponding 95% confidence intervals (CI) could obtained or estimated by the published data, and the original studies must be a English language publication. Excluded refer to the following criteria: overlapped data or duplicate studies, studies were book, letter, conference abstract or reviews, studies about basic research or animal experiments which did not reported available data. Two investigators (HH and XJ) independently evaluated the eligible articles, any divergences were resolved by discussion with a third assessor (CB).

Data extraction and quality assessment

Two independent investigators (XJ and LL) carefully extracted the data and clinical information from each eligible publication: author’s name, year of published, original country, tumor type, number of patients, gender, median age, detection means, cut-off value of IGFBP7, follow-up time, OS, and NOS scores. The HR and 95% CI were extracted from the original data or Kaplan-Meier curves. The Newcastle-Ottawa Scale (NOS) [20] was performed to detect the quality of each eligible articles. Only NOS score ≥ 6 was considered as high quality publication.

Statistical analysis

HR and 95% CI were obtained from the included articles or extracted through Kaplan-Meier method according to Tierney’s method.[21] Next, those data were analyzed by RevMan 5.3 analysis software (Cochrane Collaboration, Copenhagen, Denmark). Statistical heterogeneity was evaluated using Higgin’s

I^2 statistics and Cochran's Q test.[22, 23] Fixed-effects model (Mantel-Haenszel) was performed when $I^2 < 50\%$ and $P > 0.05$. In addition, random-effects model (DerSimonian and Laird) was conducted when $I^2 \geq 50\%$ and $P \leq 0.05$. Besides, Subgroup analysis was applied to detect the heterogeneity source. Begg's funnel plot and Egger's test also conducted to evaluate the publication bias risk though STATA 12.0 software. The statistical significance was considered as $P < 0.05$.

Results

Study characteristics

A flow diagram about the article selection process were shown (Figure 1).

Firstly, there are 1436 potential articles were retrieved in Web of Science, PubMed and Embase. According to the inclusion criteria described above, finally, 7 eligible publications were identified in the present study. The general characteristic of 7 eligible articles were shown in Table 1. Totally, 1305 solid tumor patients were included, which refer to three countries (People's Republic of China, Japan, Korea). In addition, this study analyzed six types of solid tumors: two gastric cancer,[13, 14] cholangiocarcinoma,[15] human glioma,[16] pancreatic ductal adenocarcinoma,[17] hepatocellular carcinoma,[18] and colorectal cancer.[19] OS rate is a crucial indicator for clinical observation of cancer prognosis. Thus, this study was conducted to analyze OS. Furthermore, all involved studies got more than 6 quality score in NOS assessment (Table 2).

Overall survival (univariate analysis)

The comprehensive analysis of 6 univariate analysis published data indicated that low IGFBP7 expression was associated with worse OS of solid tumors (HR = 0.60; 95% CI, 0.54–0.66, $P < 0.001$). It reported no significant heterogeneity ($I^2 = 44\%$, $P = 0.11$), so we use a fixed-effects model (Figure 2). Then, a subgroup analysis was conducted to analysis by cancer type, which indicated a negative outcome of low IGFBP7 expression on OS in patients with digestive system cancer (HR = 0.60; 95% CI, 0.53–0.66, $P < 0.001$) (Figure 3A), and other system cancer (HR = 0.61; 95% CI, 0.39–0.95, $P = 0.03$) (Figure 3B). Consistently, the subgroup analysis by country revealed an association between IGFBP7 downregulation and unfavorable prognosis on OS in Chinese patient with solid tumors (HR = 0.57; 95% CI, 0.43–0.74, $P < 0.001$) (Figure 3C), and other country (HR = 0.55; 95% CI, 0.38–0.80, $P = 0.002$) (Figure 3D). Besides, all of the pooled HR are shown in Table 3.

Overall survival (multivariate analysis)

The pooled analysis of 6 multivariate analysis results demonstrated that IGFBP7 downregulation was associated with worse survival outcome in solid tumor patients (HR = 0.57; 95% CI, 0.50–0.64, $P < 0.001$). It suggested no significant heterogeneity ($I^2 = 1\%$, $P = 0.41$), so we perform a fixed-effects model (Figure

4). In addition, a subgroup analysis was conducted to analysis by cancer type, which suggested low-level expression of IGFBP7 was correlated strongly with poor OS in patients with digestive system cancer (HR = 0.56; 95% CI, 0.49–0.64, $P < 0.001$) (Figure 5A), and other system cancer (HR = 0.62; 95% CI, 0.40–0.96, $P = 0.03$) (Figure 5B). Similarity, the subgroup analysis by country indicated a negative outcome of low IGFBP7 expression on OS in Chinese patient with solid tumors (HR = 0.57; 95% CI, 0.50–0.65, $P < 0.001$) (Figure 5C), and other country (HR = 0.55; 95% CI, 0.39–0.77, $P < 0.001$) (Figure 5D).

Publication bias

In this meta-analysis, the potential publication bias was evaluated through Begg's funnel plot and Egger's test. The results for univariate analysis ($P = 0.261$) (Figure 6A) and multivariate analysis ($P = 0.791$) (Figure 6B) showed that significant publication bias did not exist.

Discussion

Human solid tumor as the most common malignant cancer leading a high cancer-related deaths in worldwide.[24, 25] Therefore, to identifying effective biomarkers for the prognostic prediction and therapeutic target of human solid tumors are clearly needed.

Previous studies have indicated that insulin-like growth factor (IGF) signaling pathway is a finely tuned network formed by IGFs, their receptors and IGFBPs, which play a crucial role in regulating cancer cells proliferation, differentiation and apoptosis.[26] IGFBP7 have been reported to be involved in both IGF-dependent and IGF-independent pathways.[1, 27] Heesch *et al.*[28] demonstrated that aberrant IGFBP7 expression was correlated with DNA methylation in acute leukemia. Consistently, the absence of IGFBP7 expression in colon cancer was associated with its methylation.[29] Interestingly, DNA methylation play a important role in clinical detected, which may lead to biomarkers for early detection, prognosis and therapeutic monitoring. Moreover, a published study suggested that downregulate the expression of IGFBP7 was significant correlation with chemotherapeutic drug resistance in hepatocellular carcinoma.[30] Subsequently, Okamura *et al.*[31] indicated that the transcriptional level of IGFBP7 was reduced in cisplatin-resistant human non-small cell lung cancer cells and knock-down of IGFBP7 increased cellular resistance to cisplatin. Verhagen *et al.*[32] suggested that increase expression of IGFBP7 results in enhanced sensitivity to chemotherapy-induced cell death in acute myeloid leukemia. Additionally, in several cancers mouse models treat with recombinant IGFBP7 shown effective cancer inhibition.[33, 34] Taken together, it seems noteworthy that IGFBP7 might be a novel therapeutic target in human solid tumors.

Accumulating research reported that the expression level of IGFBP7 has a crucial impact on clinical outcome. It has been shown that IGFBP7 play a negative effect on the growth of cancer cells and high expression of IGFBP7 correlated with favorable prognosis in colorectal cancer.[19] Tomimaru *et al.*[18] demonstrated that downregulation of IGFBP7 was significantly associated with both tumor progression and poor OS in hepatocellular carcinoma. Furthermore, in gastric cancer patients, silenced of IGFBP7

markedly correlated with worse clinical prognosis.[13] These evidences indicate that IGFBP7 play a key role in tumor microenvironment and significantly associated with clinical prognosis in cancer patients. Therefore, we aim to investigate the prognostic role of IGFBP7 in patients with solid tumor through this comprehensive meta-analysis.

In this analysis, we comprehensively evaluated the survival data of 1305 solid tumor patients. These meta-analysis results suggest that low-expression of IGFBP7 was statistically significant associated with worse OS both in multivariate analysis and univariate analysis. As for subgroup analysis, the results showed that downregulation of IGFBP7 was also strongly correlated with poor OS in digestive system cancers and human glioma. These evidences highlight the potential role of IGFBP7 to be a crucial prognostic marker and therapeutic target for solid tumors. However, the clinical feature and therapeutic outcome of IGFBP7 need to further confirmed.

There are several limitations may exist in this meta-analysis. On one hand, some publication bias and selection bias are unavoidable because of only English language published articles were selected. On the other hand, it was inconsistent in the method for detection of IGFBP7 expression. In addition, there are some data were indirectly extracted from Kaplan–Meier curves. More multicenter prospective studies are required to further confirm the prognostic and clinicopathological significances of IGFBP7 expression in human solid tumors.

Conclusions

In conclusion, low-expression of IGFBP7 was correlated strongly with worse OS, which indicated that IGFBP7 might be a new biomarker for prognosis prediction and a promising therapeutic target in solid tumors.

Declarations

List of abbreviations

CI = confidence interval, HR = hazard ratio, IGF = insulin-like growth factor, IGFBP7 = insulin-like growth factor binding protein 7, IGFBP-rP1 = insulin-like growth factor binding protein-related protein-1, IHC = immunohistochemistry, IV = inverse variance, M = multivariate analysis, No = number, NOS = Newcastle-Ottawa, NR = not reported, OS = overall survival, SE = standard error, U = univariate analysis.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets used in the present study are available from the corresponding author upon reasonable request.

Competing interests

Not competing interests.

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Authors contributors

CB and HZ designed and performed the study. HH and XJ carried out the literature selection criteria and developed the literature search. XJ and LL extracted the original data. YW, ZZ and LJ performed the statistical analysis. ZJ and HH processed related figures and tables. CB and HZ drafted the manuscript. All authors read and approved this final manuscript.

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Tables

Due to technical limitations, Tables 1 - 3 are only available for download from the Supplementary Files section.

Figures

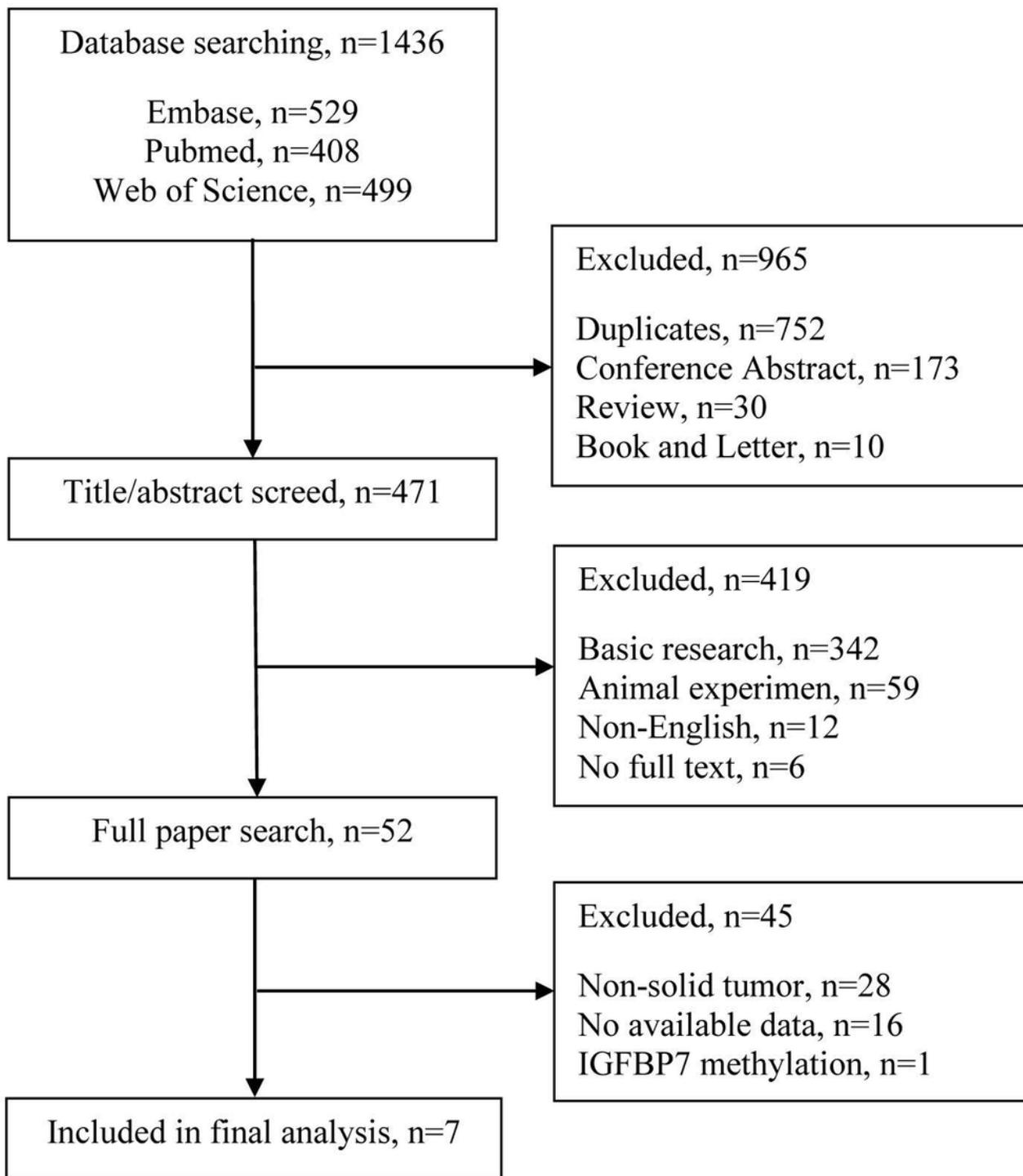


Figure 1

Flow diagram about the steps of literature selection.

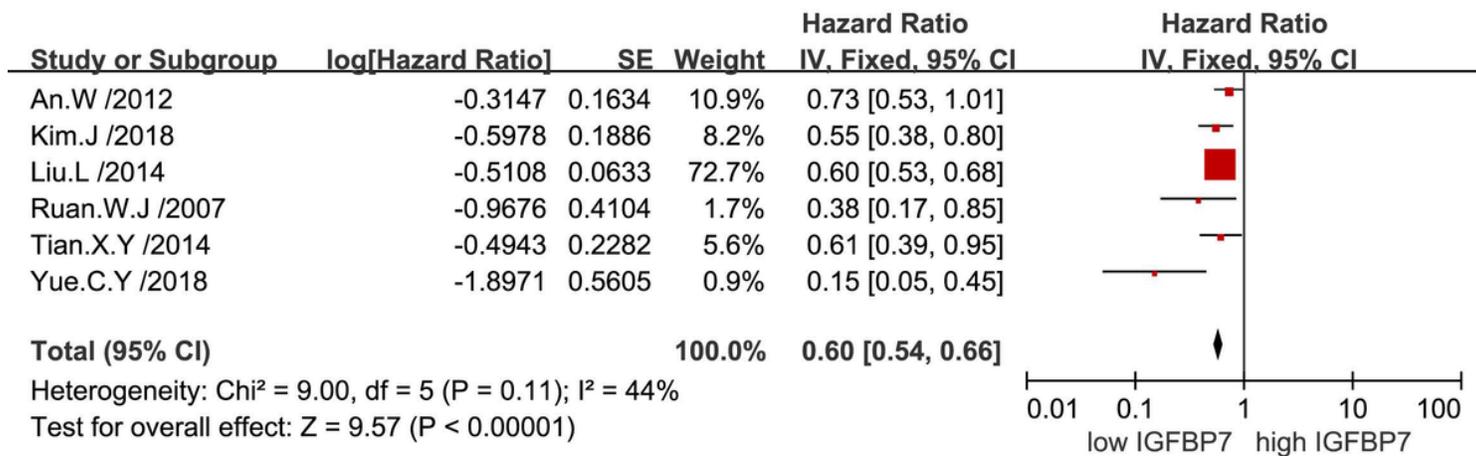


Figure 2

Forest plots showing the relationship between IGFBP7 and OS (univariate).

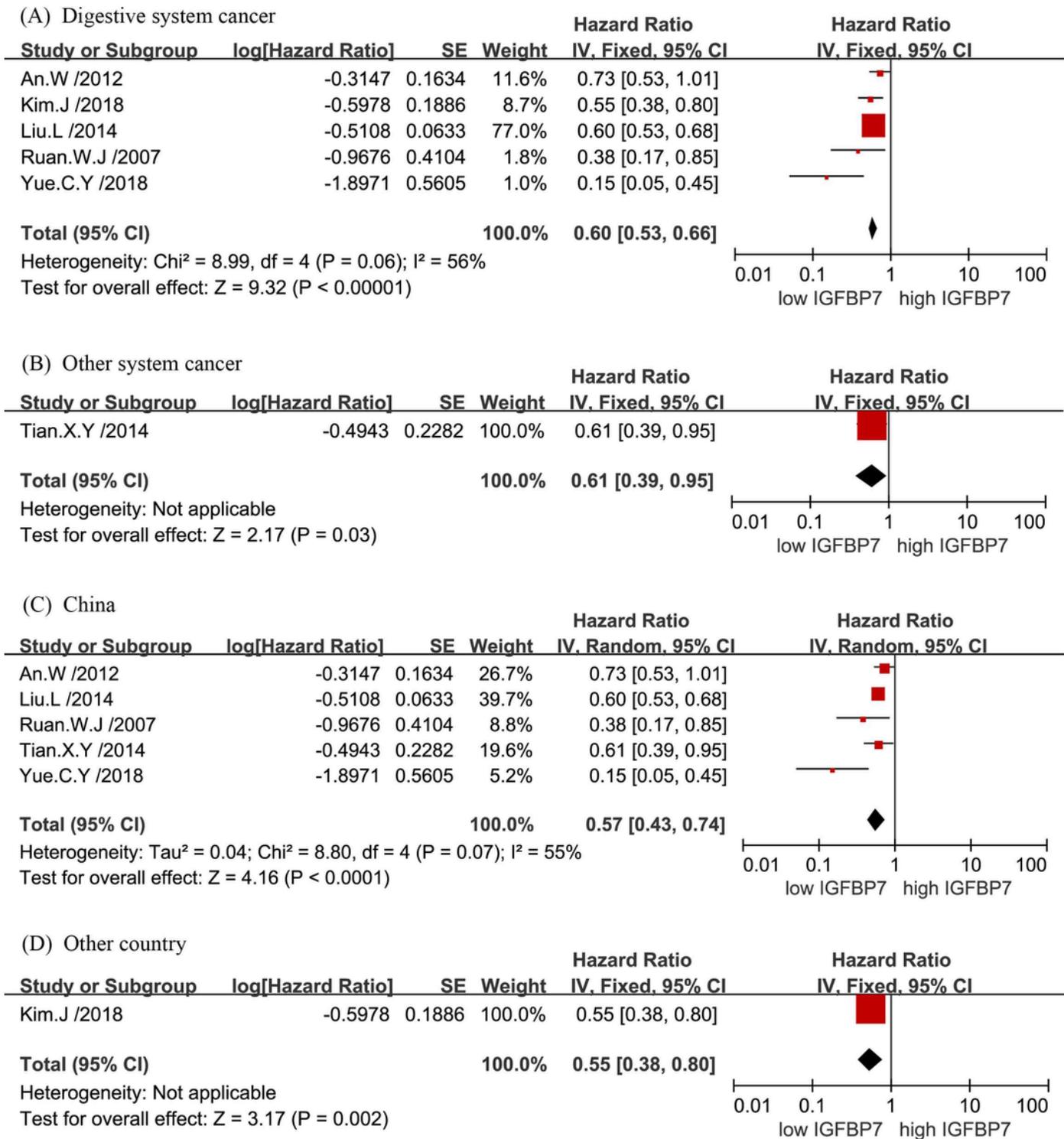


Figure 3

Subgroup analysis of OS (univariate) according to IGFBP7 expression.

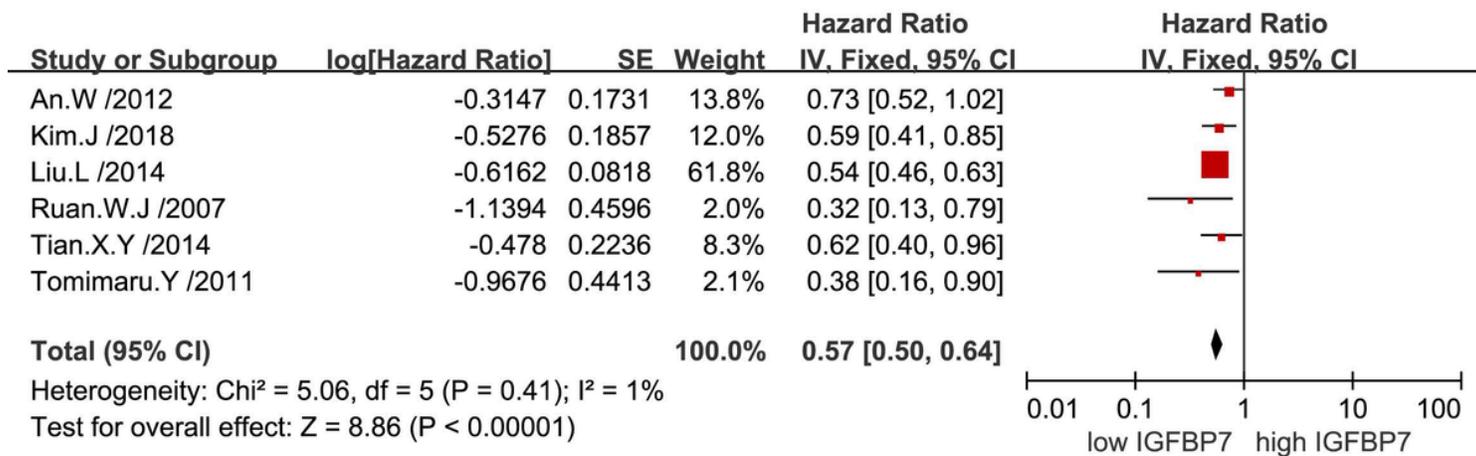
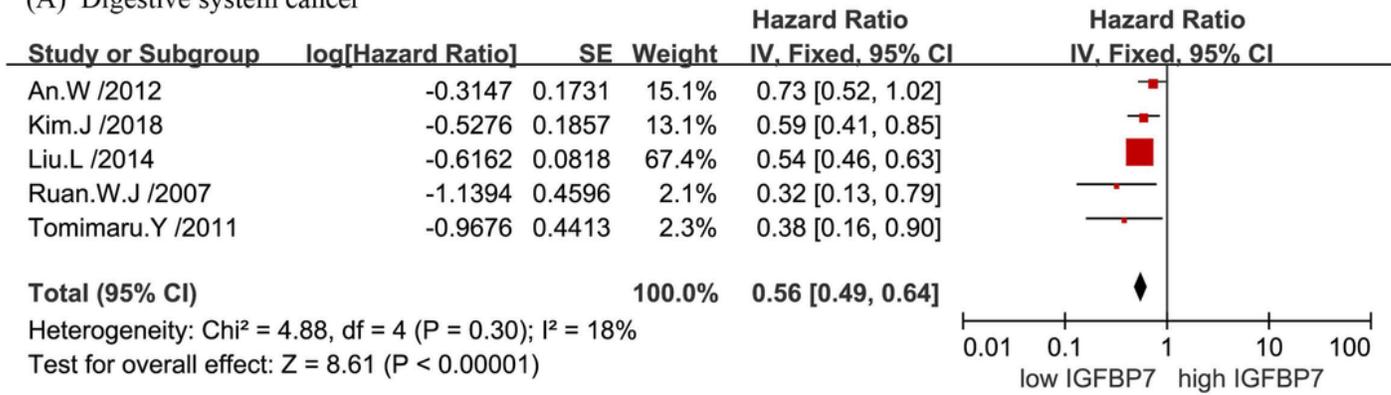


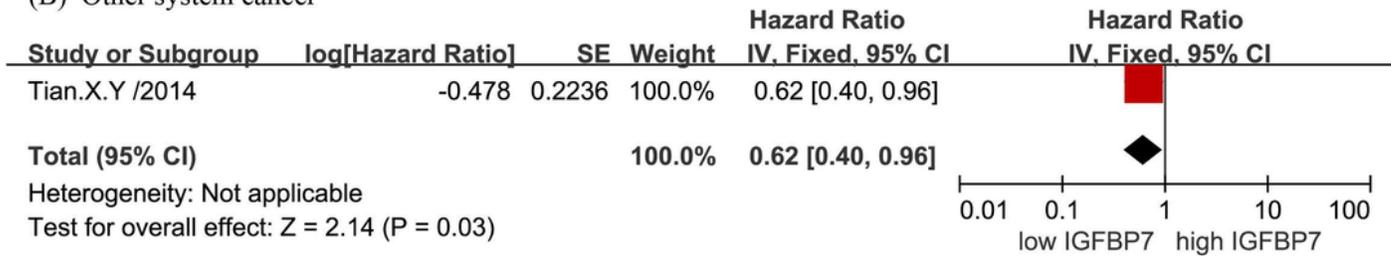
Figure 4

Forest plots showing the relationship between IGFBP7 and OS (multivariate).

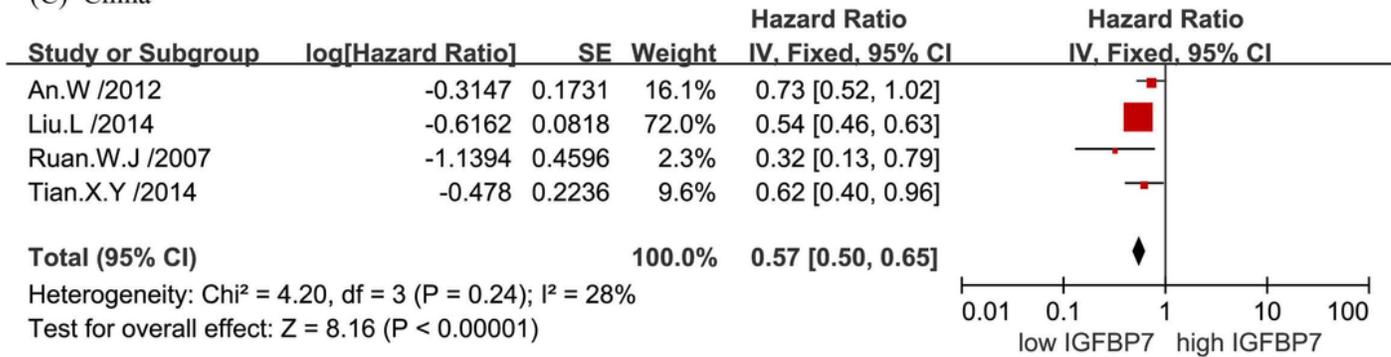
(A) Digestive system cancer



(B) Other system cancer



(C) China



(D) Other countries

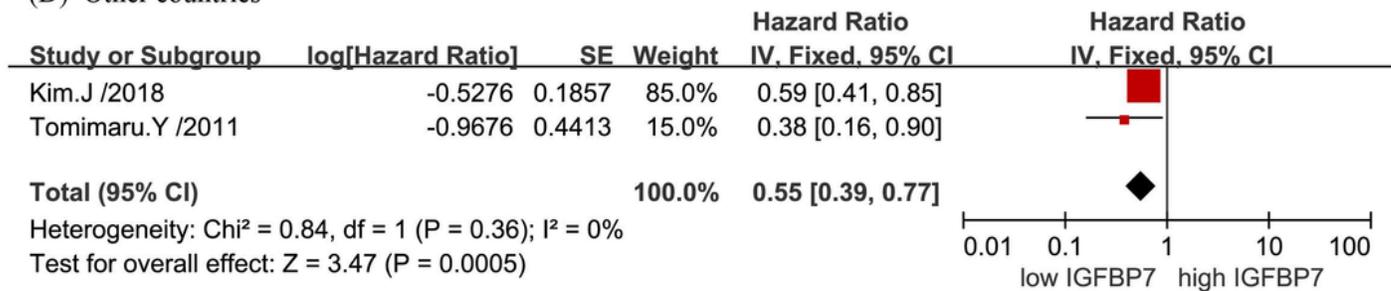


Figure 5

Subgroup analysis of OS (multivariate) according to IGFBP7 expression.

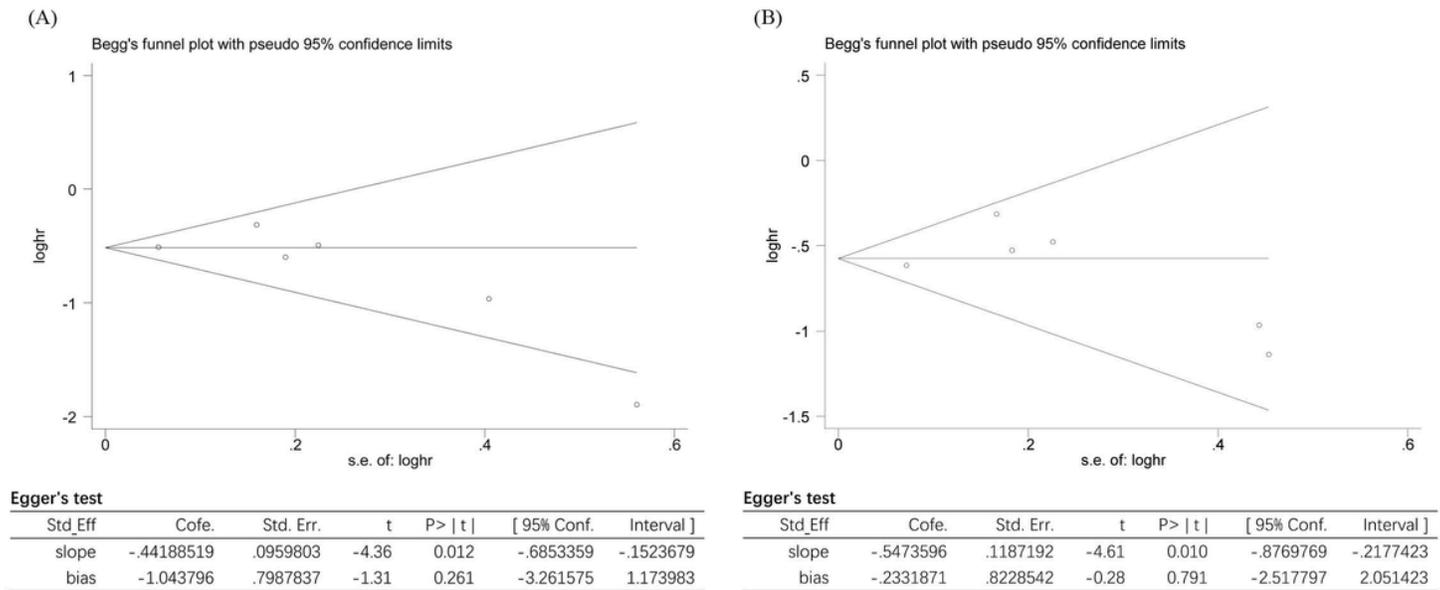


Figure 6

Funnel plot to the evaluation of potential publication bias for OS with univariate analysis (A) and multivariate analysis (B).

Supplementary Files

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