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Article

Prognostic Significance of High Survivin Expression in Patients with Gastrointestinal Cancer: A Meta-Analysis

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Abstract: Previous studies on the prognostic impact of survivin expression in gastrointestinal (GI) cancer have yielded inconsistent results. This study was initiated to assess the relationship between survivin expression and overall survival (OS) or disease free survival (DFS) in GI cancer patients. We applied system literature searches on EMBASE, PubMed, Web of science, and the Cochrane library to conduct this up-to-date meta-analysis. Thirty studies with totally 3622 GI cancer patients were collected. The prevalence of high survivin expression in GI cancer was 0.57 (95% CI: 0.51-0.63). High survivin expression was significantly associated with shorter OS (HR 1.57, 95% CI: 1.42-1.74) and DFS (HR 1.38, 95% CI: 1.21-1.58). Subgroup analysis also showed significant association between high survivin expression and poorer OS or DFS in gastric cancer or colorectal cancer. In summary, our study indicated that high survivin expression was related to poor prognosis in GI cancer. Well-designed studies with large sample and more convincing data are needed to confirm our conclusion.

Keywords: survivin; high expression; gastrointestinal cancer; prognostic

1. Introduction

Gastrointestinal (GI) cancer, including gastric cancer and colorectal cancer, is highly aggressive malignancy that constitutes a major risk to public health worldwide, with nearly 2.4 million new cancer patients and 1.4 million deaths in 2012[1]. The Combination of surgery, chemotherapy and radiotherapy remains the standard regimens for GI cancer patients. However, not all patients derive a benefit from these strategies [2]. Thus, novel therapeutic strategy is urgently needed. It is of great clinical value to identify applicable prognostic biomarkers that may not only predict the effectiveness of treatment above but also derive the potential therapeutic drug.

Survivin is the most extensively investigated member of inhibitor of apoptosis proteins family, and it can enhance proliferation, promote angiogenesis and inhibit apoptosis [3,4].

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High survivin expression levels were detectable in various types of malignancies including colorectal cancer [5], glioma[6], breast cancer[7] and gastric cancer[8]. Recently, high survivin expression was found to play a active role in the failure of chemotherapy and radiotherapy [9,10] and predict the poor prognoses in patients with GI cancer in numerous studies [11-14].

However, the results remain controversial and inconsistent. For this reason, we performed an up-to-date systematic analysis to evaluate the potential impact of survivin in the clinical outcome of patients with GI cancer.

2. Results

2.1. Literature search

The flow chart of the literature search was showed in Figure 1. Totally, 532 potentially related articles were selected, and thirty studies were finally included. The majority of removing articles were studies with animals or cell lines or reviews.

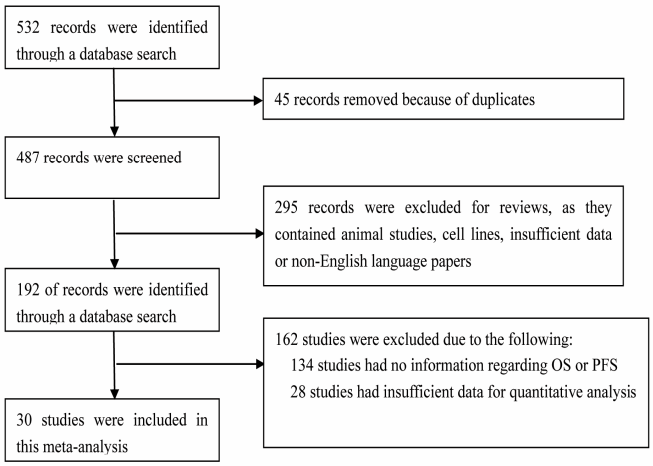

Figure 1. Flow chart representing the process of study selection

2.2. Characteristics of the study

Among the thirty studies, nineteen studies were on colorectal cancer, and eleven studies were on gastric cancer, 3622 patients with GI cancer were finally collected. The fundamental feature of the included studies was shown in Table 1. In addition, OS were extracted from twenty three studies and DFS was extracted from eight studies.

Table 1. Characteristics of included studies

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Cancer Types	Author	Year	No. of Patients	Rate of High Survivin Expression	Definition of High Expression	Quality score
Colorectal Cancer	Kawasaki[19]	1998	171	53.2	Scores 0 and 1 were defined negative, and scores 2 and were defined positive	4
	Sarela[20]	2000	144	61.8	338 base pair PCR product verified to be homologous with Survivin cDNA sequence[21]	4
	Rodel[22]	2002	54	55.6	Final IHC score(values 0-12)≥5	7
	Knutsen[23]	2004	98	51.0	＞25% of staining tumor cells	5
	Hameed[24]	2005	230	63.9	Score≥1 were designated high expression	4
	Ponnelle[25]	2005	46	28.3	＞25% of nuclei staining	4
	Hsiao[26]	2006	41	56.1	NC	6
	Terzi[27]	2008	37	72.9	staining score(value 0-4)＞3	7
	Yie[28]	2008	89	42.7	A fold differerence ＞2.6 is considered	5
	Fang[29]	2009	498	41.0	The intensity of staining was graded 0-3,where grade 2-3 was categorized as high expression of surviving expression	6
	Lee[30]	2009	95	51.0	final IHC scores(values 0-400)≥180	4
	Qi[31]	2009	142	20.4	the IHC grade ++ and +++ were regarded as high expression	4
	Kalliakmanis[32]	2010	77	88.3	＞5% positive cells was defined	5
	Sprenger[33]	2010	116	75.0	final score(values 0-12)＞6	6
	Xiaoyuan[34]	2010	68	54.4	final score(values 0-4)≥2	6
	Xi[35]	2011	61	60.7	＞10% positively stained tumor cell	6
	Jung[36]	2013	193	55.0	＞30% of nuclear staining cell	7
	Kim[37]	2014	188	45.2	more than 90% of nuclear staining cells	4
	Beumer[38]	2014	307	51.5	IHC staining＞median（86.5%）expression	7
Gastric cancer	Okada[39]	2001	133	82.0	NC	8
	Nakamura[40]	2004	42	64.3	A fold difference ＞2 was defined	6
	Lee[41]	2006	106	50.0	staining index(value 0-9)≥4	8
	Yie[42]	2008	55	45.5	A fold differerence ＞2.6 is considered high expression（RT-PCR）	5
	Song[43]	2009	157	40.1	≥10% of the nuclear staining cells	7
	Vallbohmer[44]	2009	30	76.7	grade 2 and 3 was defined high expression	8
	Deng[45]	2010	53	51.7	final score (value 0-12)≥3	6
	Li[46]	2010	65	75.4	final score (value 0-12)≥4	8
	Meng[47]	2012	90	70.0	final histoscores (value 0-12)≥5	9
	Bury[48]	2012	41	73.2	NE	7
	Zhang[49]	2014	195	50.3	≥10% of the nuclear staining cells	5

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2.3. Rate of high survivin expression

The prevalence of high survivin expression in these studies ranged from 20.4% to 88.3%, and it partly reflected the heterogeneity in the criteria for its high expression levels. In the meta-analysis, the prevalence of high survivin expression was 0.57 (95% CI: 0.51-0.63, Figure 2). Subgroup analysis was stratified by colorectal cancer and gastric cancer. The rates of high survivin expression in colorectal cancer and gastric cancer were 0.54 (95%CI: 0.47-0.62) and 0.62 (95%CI: 0.52-0.71), respectively (Supplementary Figures S1-S2).

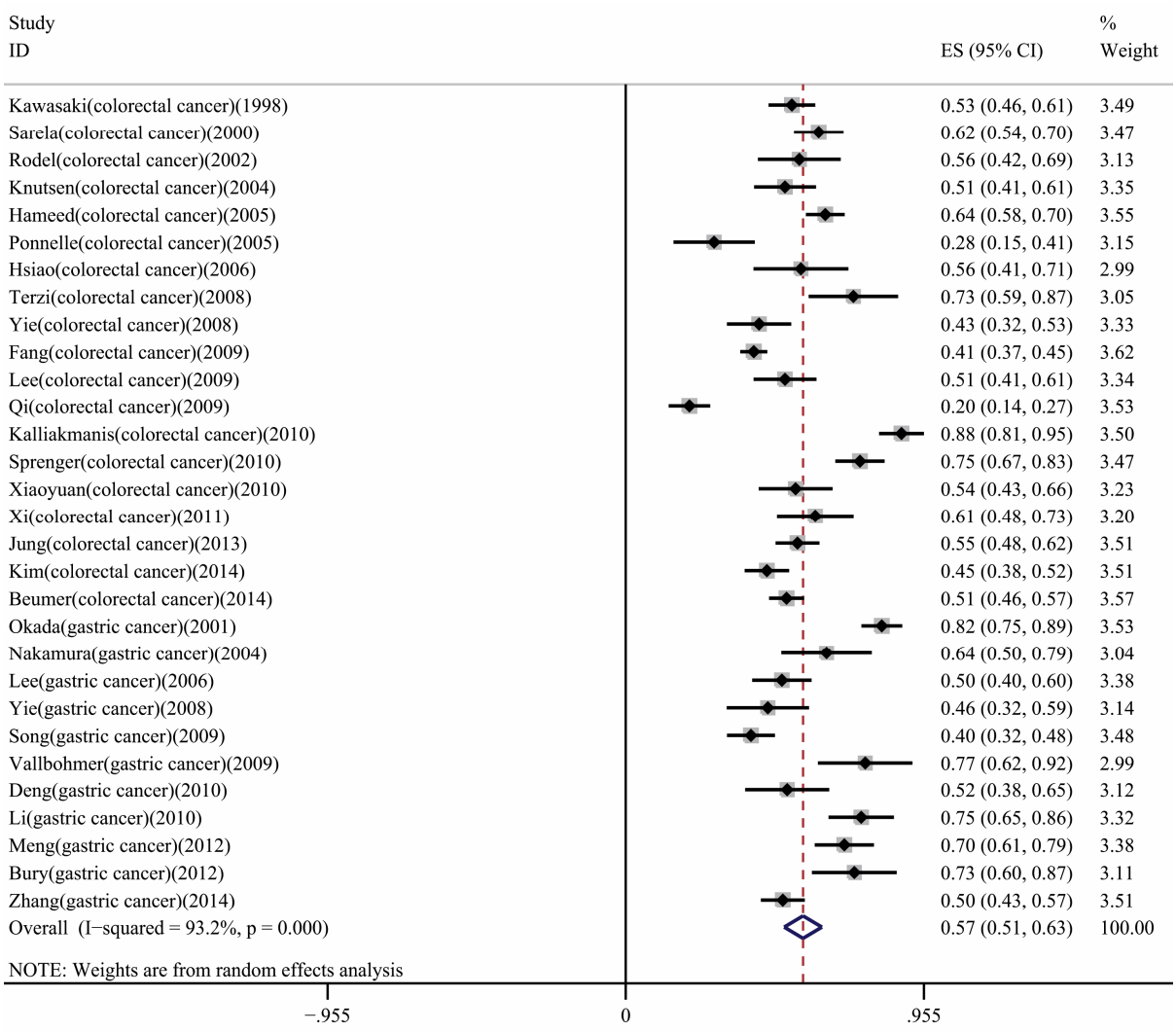

Figure 2. Meta-analysis of the prevalence of high survivin expression.

2.4. Association of survivin with GI cancer prognoses

The pooled OS was utilized to summarize the overall effect of high survivin expression for the twenty three studies. The analysis indicated that the pooled HR was 1.57 (95% CI: 1.42-1.74, Figure 3A) in GI cancer patients. However, the results showed high heterogeneity (I^2 = 57.4%; P＜0.001). In the eight studies reporting DFS, the analysis showed that high survivin expression also contributed to poor DFS (1.38, 95%CI: 1.21-1.58, Figure 3B).

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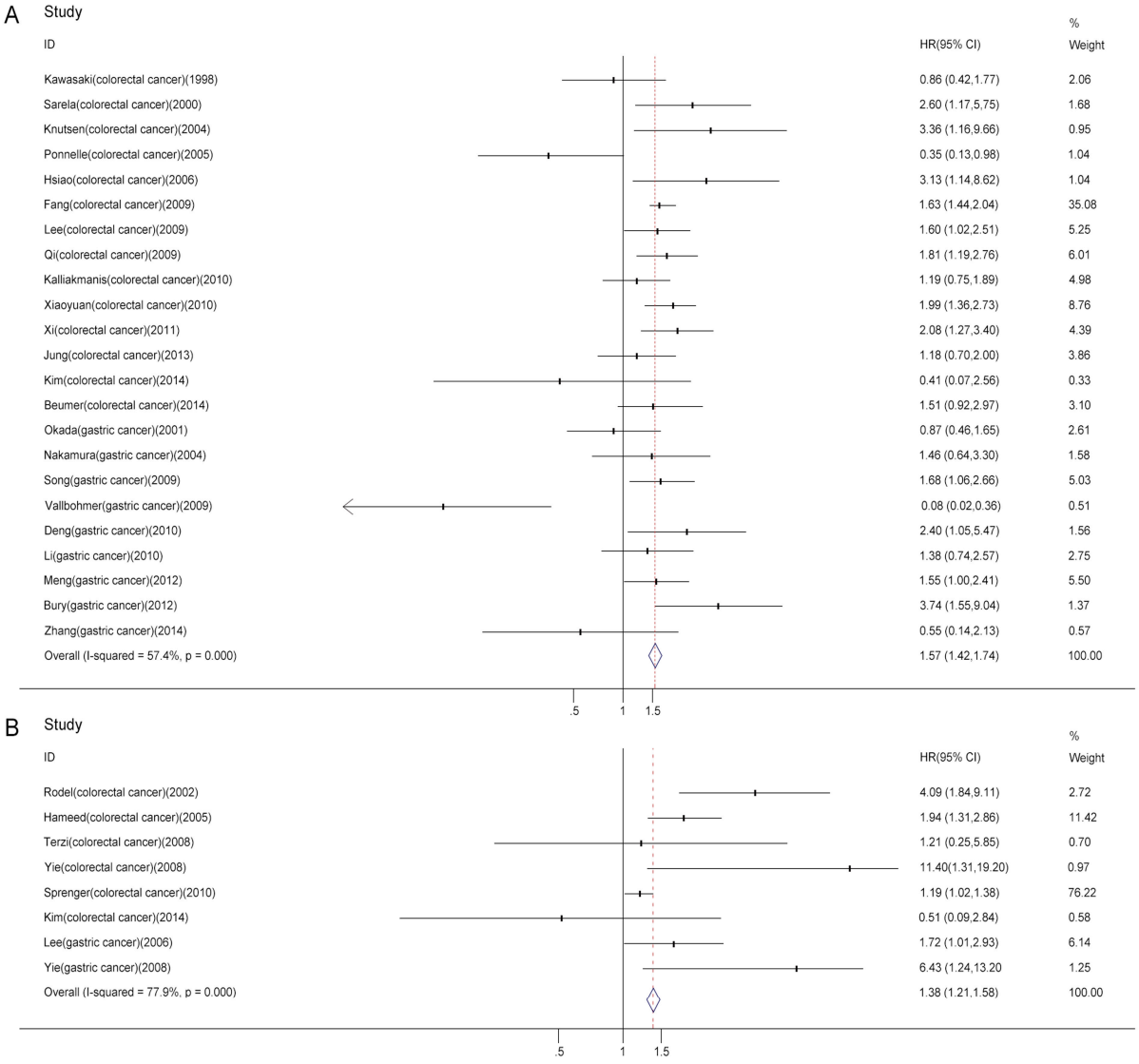

Figure 3: Prognostic value of high survivin expression in GI cancer patients. A. meta-analysis of high survivin expression and OS in GI cancer patients; B. meta-analysis of survivin expression and DFS in GI cancer patients.

In addition we carried out the meta-analysis of high survivin expression and survival in colorectal cancer and gastric cancer. Our results showed that high survivin expression was related to poor OS (HR 1.61, 95% CI: 1.43-1.81, Figure 4A) in colorectal cancer as well as gastric cancer (HR: 1.43, 95% CI: 1.14-1.79, Figure 4B). Further, two pooled results showed that high survivin expression also contributed to shorter DFS (HR: 1.33, 95% CI: 1.16-1.53, Figure 4C) in colorectal cancer and gastric cancer (HR: 2.15, 95% CI: 1.32-3.49, Figure 4D), respectively.

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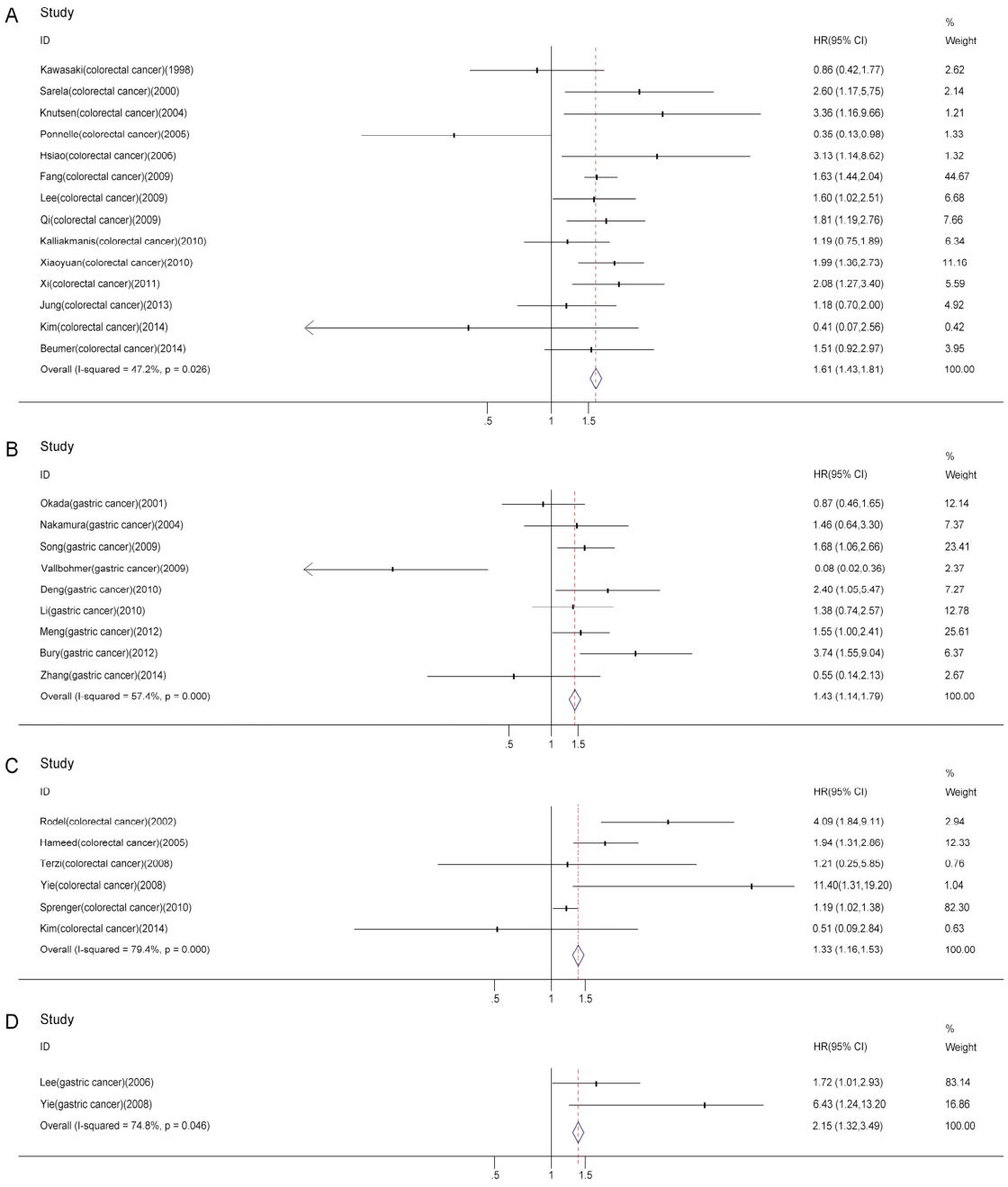

Figure 4: Subgroup analysis of prognostic value of high survivin expression. A. meta-analysis of high survivin expression and OS in colorectal cancer patients; B. meta-analysis of survivin expression and OS in gastric cancer patients; C. meta-analysis of survivin expression and DFS in colorectal cancer patients; D. meta-analysis of survivin expression and DFS in gastric cancer patients.

2.5. Sensitivity and Publication bias

The sensitivity analysis indicated that the results were stable and were not affected when removing one study each time. No obvious asymmetry was found in the chart of the funnel

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plots, suggesting that publication bias was acceptable (Figure 5A and 5C). Begg's funnel plot also indicated no obvious bias (Figure 5B and 5D).

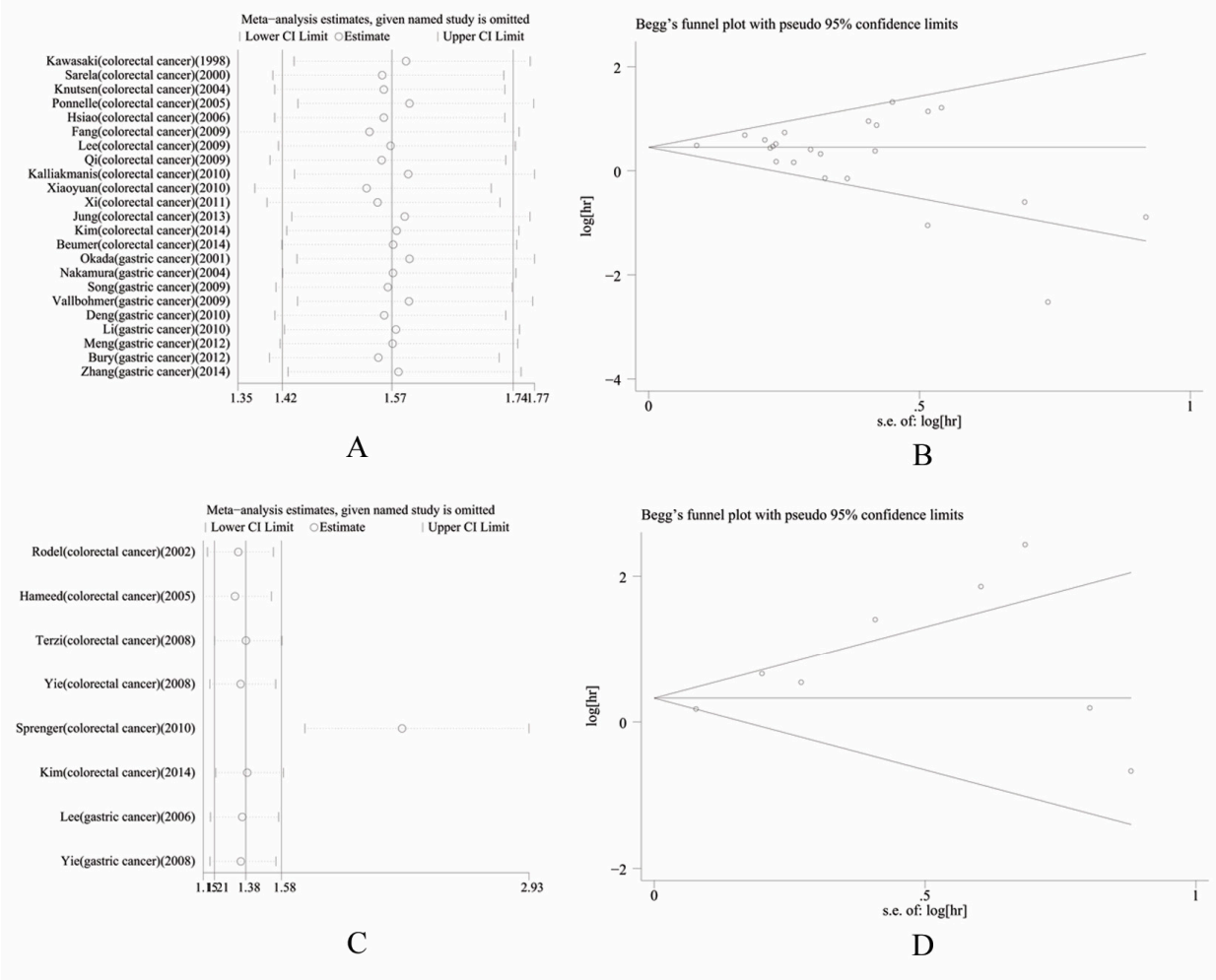

Figure 5: Sensitivity analysis and publication bias for the association between high survivin expression and survival. A. sensitivity analysis of the association between high survivin expression and OS; B. sensitivity analysis of the association between high survivin expression and DFS;C. funnel plot for the association between high survivin expression and OS; D. funnel plot for the association between high survivin expression and DFS.

3. Discussion

The meta-analysis was conducted to assess the potential role of high survivin expression in clinical outcomes in GI cancers patients. Our analysis showed that the overall incidence of high survivin expression was 0.57 in GI cancers patients. Besides, we found that high expression of survivin was the prognostic factor for both OS and DFS. On account of the heterogeneity, we performed the subgroup analysis on gastric cancer and colorectal cancer. Our data also indicated that high survivin expression was significantly related to poor OS and

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DFS. As far as we know, this was the first meta-analysis to investigate the association of high survivin expression and the clinical outcomes in GI cancers patients.

3.1 Survivin as an prognostic biomarker in GI cancer

The current study revealed that high survivin expression was related to poor clinical outcome. Further investigations are necessary to clarify the function of survivin as a biomarker for prognosis in GI cancer patients. The molecular mechanisms involved in the process of survivin contributing to the clinical outcome remains uncertain. Ye et al[50] reported that survivin knockdown by siRNA resulted in the inhibition of colorectal cancer cell invasion and migration by mediating the AKT and the ERK pathways. Fei et al[51] found that survivin transfected by shRNA could activate the extrinsic and intrinsic apoptotic process in SW-620 colon cells. Pandey et al's study[52] showed that survivin inhibition induced enhanced cell death in gastric cells with the 5-fluorouracil (5-FU) treatment. Wang et al[53]revealed that a survivin promoter-regulated oncolytic adenoviral vector has broad-spectrum antitumour properties, and survivin has been closely correlated with an elevated proliferative capacity, an enhanced metastatic capacity, and chemotherapy and radiotherapy resistance in cancer cells. In addition to being a prognostic biomarker, our results are of great value in view of the emergence of new drugs targeting survivin. Currently, several clinical trials targeting survivin at different phases are being developed which will likely benefit patients with certain conditions (Table 2).

3.2. Strengths and limitations of our study

Our results had several important implications. First, our analysis had been enhanced by the involvement of over 3,000 patients in 30 centres. Second, the relationship between high survivin expression and prognosis in GI cancers persisted and remained statistically significant by subgroup analysis. Third, all of the analyses were performed by the fixed effects model or random effects model. Models was applied by the different heterogeneous, which contributed to the validity and reliability of the statistical results.

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Table 2. Studies targeting survivin in cancer

Study	Condition	Phase	Intervention
NCT00108875	Colon Cancer	Phase 1 Phase 2	Survivin peptide vaccine
NCT00573495	Breast Neoplasm	Phase 1	hTERT/SurvivinMulti-Peptide Vaccine
NCT01186328	Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute,Childhood	Phase 1	EZN-3042
NCT01456065	Ovarian Epithelial Cancer	Phase 1	Procure(TERT-mRNA and Survivin-peptide double loaded DCs)
NCT00074230	Melanoma (Skin)	Phase 1 Phase 2	Autologous Dendritic Cells loaded with MAGE-A3, MelanA and Survivin
NCT00664677	Leukemias	Phase 1	Terameprocol (EM-1421)
NCT01416038	Ovarian Cancer Fallopian Tube Cancer Peritoneal Cancer	Phase 1-2	DPX-Survivac low dose cyclophosphamide (oral)
NCT02688686	Non-Small-Cell Lung Cancer With Bone Metastases	Phase 1 Phase 2	genetically modified dendritic cells + cytokine-induced killer
NCT02239861	Colorectal Cancer Gastric Cancer	Phase 1	TAA-Specific CTLs
NCT00415155	Hepatocellular Carcinoma	Phase 1 Phase 2	Drug: LY2181308
NCT00818480	Prostate Cancer Melanoma Non-Hodgkin's Lymphoma	Phase 2	Drug: YM155
NCT01038804	Breast Cancer	Phase 2	Drug: YM155 Drug: Docetaxel
NCT00328588	Lung Cancer	Phase 2	Drug: YM155
NCT00257478	Prostate Cancer	Phase 2	Drug: YM155
NCT00057512	Head and Neck Neoplasms	Phase 1	Drug: M4N
NCT00664586	Refractory Solid Tumors Lymphoma	Phase 1	Drug: Terameprocol (EM-1421)

Our meta analysis had also some limitations as follows. First, our study was a literature-based analysis. It was possible that there may be some degree of publication bias in this area of research. To address this issue, Begg's test was applied. Second, there was statistical heterogeneity among the patients contributing the basic feature of the studies. Accordingly, we further performed a subgroup analysis according to the stratified types of cancers. Third, there was clearly a multitude of confounding factors (test method，definition of high expression, difference between extracting data from Kaplan-Meier curves and raw data ,etc) that made meta-analysis inaccurate.

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4. Materials and Methods

4.1. Identification and Selection of Studies

EMBASE, PubMed, Medline, Cochrane library data and the Web of Science were screened for articles exploring the expression of survivin in GI cancer by two independent investigators. We identified the articles with the following terms: (1)“survivin”or “BIRC5” and (2) “digestive tract” or “gastrointestinal” or “gastric” or “stomach” or “colorectal” or “colon” or “rectal” and (3) “cancer” or “carcinoma” or “tumor” or “neoplasm”. We also collected the reference from the original articles and review papers. Paper published in English was selected only and the ending date was January 31, 2017.

Eligibility criteria were as follows: (1) expression of survivin was conducted using immunohistochemistry or qRT-PCR;(2) association of survivin expression with survival in GI caner; and (3) the hazard ratio (HR) for the overall survival (OS) or disease free survival (DFS) related to survivin expression was reported or could be calculated from the paper. The following studies were excluded :(1) articles about animals or cell lines;(2)studies lacking sufficient data on survival;(3)overlapping samples or duplication of previous publications; and (4)the exclusion of letters to the editor, articles and reviews that were not published in English.

4.2. Data Collection and Synthesis

Data were collected by two independent researchers using predefined variables abstraction forms. The following information was collected: gender, age, tumor type, first author, study location, published year, number of patients, cutoff for considering survivin as being highly expressed and HR with corresponding 95% confidence interval(CI) for OS or DFS. When both multivariate analysis and univariate analysis were used to calculate HR, the data taken from multivariate analysis were selected. When HR was not provided directly, they were estimated using technique published by Tierney [15].

The overall HR was pooled by the random effects model or the fixed effects model, which was determined by the heterogeneity calculated by Chi-square test [16]. When the heterogeneity was high, the former model was used. Otherwise, the fixed effects model was considered. Pooled HR > 1 indicated that high survivin expression contributed to poor OS or DFS in GI cancer patients.

4.3. Quality assessment

The Newcastle Ottawa Scale was applied to evaluate the quality of the studies recruited. The scale is an eight-item system (with a maximum of nine stars) to evaluate a

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study in three aspects: selection, comparability, and outcome. Any disagreements were negotiated between two investigators and reached an agreement finally.

4.4. Statistical Analysis

Data was pooled and analyzed by STATA 10.0 (Stata Corporation, Texas, USA). For the rate of high survivin expression, we combined the incidences and 95%CI. The relationship between survivin expression and the survival such as OS and DFS were estimated using HR. In our study, the HR with corresponding 95%CI was preferably extracted from the article and calculated by the technique mentioned above. The publication bias was visually checked by funnel plots, and was further assessed using Begg's test [17,18]. The sensitivity test was evaluated by deleting one study each time. The statistical significance was defined as $P<0.05$ and all statistical tests were two-sided.

5. Conclusions

Based on our study, it was found that high survivin expression was associated with poor prognosis in terms of OS and DFS, which indicates that developing the strategies targeting survivin could be a promising therapeutic treatment for GI cancer patients.

Supplementary Materials: Supplementary materials can be found at www.mdpi.com/link.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent Informed consent was obtained from all individual participants included in the study.

Author Contributions: P.X., C.L. and J.X. conceived and designed the meta-analysis. P.X., Q.L. and J.L. performed the analysis. P.X., D.Z., Z.N. and M.J. analyzed the data. P.X., J.L., Y.W. and W.T. wrote the manuscript. Others: P.X., J.L. and Q.L. contributed equally to this paper.

Conflicts of Interest: The authors declare that they have no conflict of interest.

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