

Meta-analysis: prognostic value of survivin in patients with pancreatic cancer

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Abstract Objective: The aim of the study was to conduct a systematic review of the literature evaluating survivin expression in pancreatic carcinoma as a prognostic indicator. **Methods:** The relevant literatures were searched using PubMed, EMBASE, and Chinese Biomedicine Databases. A meta-analysis of the association between survivin expression and overall survival in patients with pancreatic cancer was performed. Studies were pooled and summary hazard ratios (HRs) were calculated. Subgroup analysis according to the location of survivin expression was also performed. **Results:** Seven eligible studies with a total of 448 patients were included in this study. Combined HR suggested that survivin expression had an unfavorable impact on survival of pancreatic cancer patients (HR = 1.65, 95% CI: 1.02–2.68). When stratified according to the location of survivin expression, the combined HR showed that expression in the cytoplasm was significantly associated with poor prognosis of pancreatic cancer patients (HR = 2.09, 95% CI: 1.29–3.40). In contrast, survivin expression in the nucleus was not significantly associated with poor prognosis (HR = 0.83, 95% CI: 0.24–2.81), and the heterogeneity was highly significant ($I^2 = 87.2\%$, $P = 0.005$). **Conclusion:** Survivin expression was associated with a poor prognosis in patients with pancreatic cancer. Cytoplasmic expression of survivin may be a prognostic factor for pancreatic cancer patients. Based on the current obtained data, there was no evidence that survivin expression in the nucleus had a significant impact on patients' overall survival.

Key words survivin; pancreatic cancer; meta-analysis

Pancreatic cancer is one of the most aggressive malignant tumors [1]. In over 80% of patients, pancreatic cancer may be unresectable at the time of diagnosis [2]. Despite the considerable costs [3], the overall survival remains poor among patients with early stage disease [4–5]. Currently, the prognostic system routinely employed for the management of pancreatic cancer is based on the International Union Against Cancer (UICC) tumor-node metastasis (TNM) staging system. However, often this staging system cannot accurately predict the prognosis of cancers. Molecular biological prognostic factors may allow a more accurate prediction of clinical outcome and also reveal novel predictive factors and therapeutic targets [6]. A lot of studies have evaluated molecular prognostic markers that have an association with some clinical outcome in pancreatic cancers [7–8]. Of these, survivin, which is considered a very important prognostic marker, has been widely investigated.

Survivin is also called baculoviral inhibitor of apoptosis repeat containing 5 (BIRC5). It is a member of the inhibitor of apoptosis (IAP) family. The IAP family is one of the most cancer-specific proteins identified to date. This

family is upregulated in almost all human tumors. Studies have shown that survivin has the ability to inhibit apoptosis, enhance proliferation and promote angiogenesis [9–11]. It is highly expressed in most human tumors and fetal tissues, but it is undetectable in most terminally differentiated cells [12]. Because of the larger difference in expression between normal and malignant tissues and its causal role in cancer development, survivin is currently attracting more attention as a prognostic indicator for cancer.

The expression of survivin is thought to be a promising prognostic indicator. It is often associated with a worse overall survival of patients with gastric, lung, esophageal and breast cancers, and the associations have been confirmed by meta-analysis [13–16]. However, evidence regarding the prognostic value of survivin regarding overall survival in pancreatic cancer remains unclear. Two systematic reviews [17–18] have been reported by Ansari and Jamieson, and both of the systematic reviews provided a systematic summary of prognostic markers (including survivin) in patients with pancreatic cancer. In the article by Ansari [17], a systematic review was performed without a meta-analysis and no survival data were analyzed. Although a meta-analysis was performed by Jamieson [18], only two studies concerning survivin were included. We

performed this systematic review of the literatures with a meta-analysis including a larger number of studies.

Methodology

Literature search

Studies were identified via an electronic search of PubMed, EMBASE and Chinese Biomedicine Databases using the following keywords: pancreatic cancer or pancreatic carcinoma, BIRC5 or baculoviral inhibitor of apoptosis repeat-containing 5 or survivin. The search ended on July 3, 2013. The references of articles and reviews were manually searched for additional studies. We also hand-searched the journals that published articles that were most relevant to this review.

Inclusion and exclusion criteria

We used the complete databases from the published studies about the prognostic value of survivin in patients with pancreatic cancer. There was no language restriction for the published papers. The inclusion criteria included the following: (1) the studies measured survivin expression in pancreatic cancer using immunohistochemistry (IHC), reverse transcription-polymerase chain reaction (RT-PCR) or fluorescence *in situ* hybridization (FISH), and so on; (2) the studies compared overall survival between different expressions of survivin in pancreatic cancer; (3) the studies reported the hazard ratio (HR) and 95% confidence interval (CI) for overall survival according to survivin status, or values could be calculated from the provided data; (4) the prognostic effect was determined by mortality of the patients; (5) when the same author or group reported results obtained from the same patient population in more than one article, the most recent report or the most informative one was included.

The exclusion criteria were as follows: (1) letters, reviews, case reports, conference abstracts, editorials, and expert opinion; (2) articles in which no information of overall survival were given, or HR about overall survival from the given information could not be computed; (3) articles in which the prognostic effect was determined by recurrence of pancreatic cancer; (4) articles regarding the prognosis of pancreatic endocrine tumors.

Data extraction

Two investigators (Liu JL and Zhang XJ) reviewed all of the studies that met inclusion and exclusion criteria. Data were extracted independently by the two investigators (Liu JL and Yang SG) using a data extraction sheet. The extracted data included the first author's name, year of publication, source of patients, language, number of

patients, treatment received, assay method, location of expression and survival data. Any disagreements were resolved by a meeting with Dong JH.

Assessment of study quality

Study quality was assessed independently by two investigators (Liu JL and Zhang Z) according to Newcastle-Ottawa Quality Assessment Scale [19]. Briefly, the overall star assessed three main categories on the following: (1) selection of cohort; (2) comparability of cohort; (3) ascertainment of outcome. A study could be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars could be given for comparability. The total number of stars was determined, with more stars reflecting a better methodological quality. A study could be awarded a maximum of nine stars.

Statistical analysis

HR and 95% CI were used to estimate the impact of survivin expression on survival. A combined HR > 1 implied a worse survival for the group with survivin expression. This pejorative impact of survivin on survival was considered statistically significant if the 95% CI for the combined HR did not overlap 1. If a direct report of HR and 95% CI was not available, the estimated value was derived indirectly from Kaplan-Meier curves using the methods described by Tierney [20]. Kaplan-Meier curves were read by Engauge Digitizer Version 4.1 (<http://digitizer.sourceforge.net/>), then the survival data determined from the Kaplan-Meier curves were entered in the spreadsheet appended to Tierney's paper [20]. For example, the study by Sun [21] did not provide the HR value in the original article; therefore, we determined the HR value from the Kaplan-Meier curve using Tierney's method (Fig. 1). The survival curves we obtained using Tierney's method were similar to the original graphs. This task was performed by two independent investigators (Liu JL and Zhang Z) to reduce inaccuracy in the extracted survival rates.

To assess heterogeneity among the studies, we used the Cochran Q and I^2 statistics. For the Q statistic, a P value < 0.10 was considered statistically significant for heterogeneity [22]. Then, the random-effects model was calculated according to the DerSimonian-Laird method [23]. Otherwise, the fixed-effects model (Mantel-Haenszel method) was used. For I^2 , a value > 50% was considered a measure of severe heterogeneity [24]. The final conclusion should be made with discretion. Publication bias was tested by Egger's test. All statistical analyses were performed by Stata 12.0. A significant two-way P value for comparison was defined as $P < 0.05$.

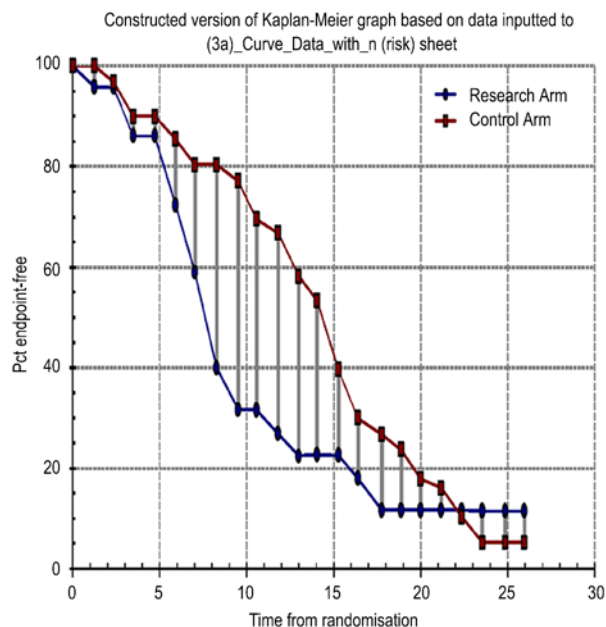


Fig. 1 Survival data by Tierney's method based on Kaplan-Meier curve from Sun's study. It was similar to the original graph

Results

Literature selection and characteristics

A total of 378 potentially relevant citations were retrieved after initial databases search. Although an additional 23 studies were found from the references of articles and reviews or by hand-search of the journals, they were all duplicates of studies from the database search. The title and abstract of the relevant articles were read by the two authors (Liu JL and Yang SG) independently. A total of 359 citations were excluded from analysis after the first screening based on abstracts or titles, resulting in 19 articles for full-text review. After carefully reading the full-text articles, 12 studies were excluded. Of these, 8 studies were excluded because they were reviews or studies about the correlation with clinicopathological vari-

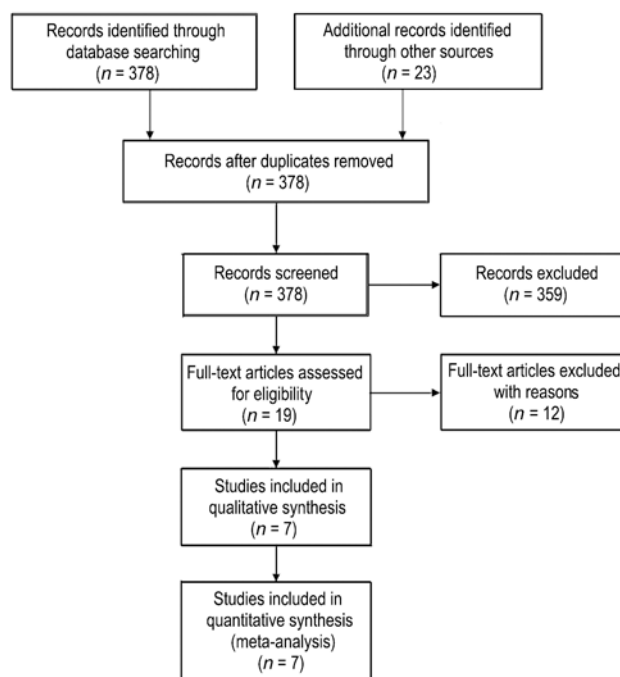


Fig. 2 Flow diagram of study selection

ables instead of survival. Two studies [25–26] were excluded due to insufficient survival data. Two studies [27–28] were excluded because they dealt with the prognosis of pancreatic endocrine tumors. As a result, 7 eligible studies [21, 29–34] were included in the qualitative synthesis, and a final meta-analysis of 448 patients from the 7 studies was performed (Fig. 2).

Characteristics of the included studies

The basic characteristics of the 7 studies were summarized in Table 1. Briefly, study sample sizes ranged from 41 to 118. All of the pancreatic cancer patients in the 7 studies underwent R0 or R1 resection. Three studies were conducted in Chinese populations, while the remaining 4 were conducted in Japanese [29], American [33],

Table 1 Characteristics and results of the included studies

| First author | Year | NOS | Source | Language | N. of P. | Curative Rec. | Method | Location | HR estimate | HR | 95% CI |
|----------------|------|-----|---------|----------|----------|---------------|--------|----------|-------------|------|------------|
| Kami K [29] | 2004 | 8 | Japan | English | 47 | Yes | IHC | Cyt. | HR | 9.26 | 2.40–35.71 |
| Sarela AI [30] | 2002 | 8 | UK | English | 41 | Yes | IHC | Cyt. | HR | 3.33 | 0.56–20.00 |
| Sun HC [31] | 2007 | 8 | China | English | 58 | Yes | IHC | Cyt. | Sur. curve | 1.18 | 0.61–2.28 |
| Jia FX [34] | 2011 | 7 | China | Chinese | 63 | Yes | IHC | Cyt. | HR | 4.39 | 1.22–15.87 |
| Sun JJ [21] | 2012 | 7 | China | Chinese | 54 | Yes | IHC | Cyt. | Sur. curve | 1.49 | 0.82–2.72 |
| Tonini G [32] | 2005 | 9 | Italy | English | 67 | Yes | IHC | Cyt. | HR | 1.80 | 1.11–2.91 |
| Xie H [33] | 2013 | 9 | America | English | 118 | Yes | IHC | Nu. | HR | 0.43 | 0.21–0.90 |
| | | | | | | | | Nu. | HR | 1.50 | 0.90–2.40 |

NOS, Newcastle-Ottawa Quality Assessment Scale; N. of P., number of patients; Curative Rec., curative resection; HR, hazard ratio; 95% CI, 95% confidence interval; IHC, immunohistochemistry; Cyt., cytoplasm; Nu., nucleus; Sur. curve, survival curve

Italian [32] and British [30] populations. All of the studies investigated survivin expression using IHC in pancreatic cancer tissues. Two studies [29, 34] characterized survivin as an indicator of poor prognosis, and four [21, 30–31, 33] studies reported no significant impact on overall survival. In addition, one study [32] reported survivin nuclear staining as an indicator of good prognosis while cytoplasmic staining was an indicator of poor prognosis.

Methodological quality of the studies

Two authors independently extracted data and assessed the methodological quality of the included studies using the Newcastle-Ottawa Quality Assessment Scale. The scores were shown in Table 1. All the studies included in our meta-analysis had high methodological qualities (> 5 stars on the Newcastle-Ottawa Scale).

Results of meta-analysis

Overall, the pooled HR for all evaluable studies on survivin expression in cancer was 1.65 (95% CI: 1.02–2.68) (Fig. 3). This indicated that survivin expression was significantly associated with worse overall survival of pancreatic cancer patients. To investigate the relationship between survivin subcellular location and overall

survival further, a subgroup analysis according to the location of survivin expression was performed. Six studies [21, 29–32, 34], which identified survivin in the cytoplasm in 330 patients, were used for the subgroup analysis. Due to the heterogeneity ($I^2 = 49.6\%$, $P = 0.078$), a random effect model was accepted. The combined HR was 2.09 (95% CI: 1.29–3.40), which demonstrated that expression of survivin in the cytoplasm was significantly associated with poor prognosis of pancreatic cancer patients (Fig. 4). Two studies [32–33] identified survivin expression in the nucleus in 185 patients. Because of significant heterogeneity ($I^2 = 87.2\%$, $P = 0.005$), a random effect model was adopted. The combined HR was 0.83 (95% CI: 0.24–2.81), which illustrated that survivin expression in the nucleus was not significantly associated with overall survival of pancreatic cancer patients. However, the heterogeneity was highly significant ($I^2 > 50\%$); therefore, the result should be accepted with discretion.

Assessment of heterogeneity and sensitivity analysis

Although the combined HR showed that the expression of survivin had an inverse effect on survival in pancreatic cancer, highly significant heterogeneity was de-

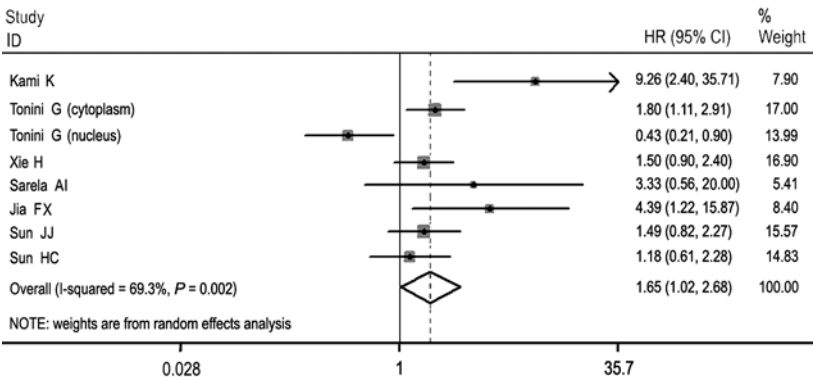


Fig. 3 Forest plot of hazard ratio (HR) for overall survival of pancreatic cancer patients. Survivin expression was significantly associated with worse overall survival of pancreatic cancer patients with highly significant heterogeneity

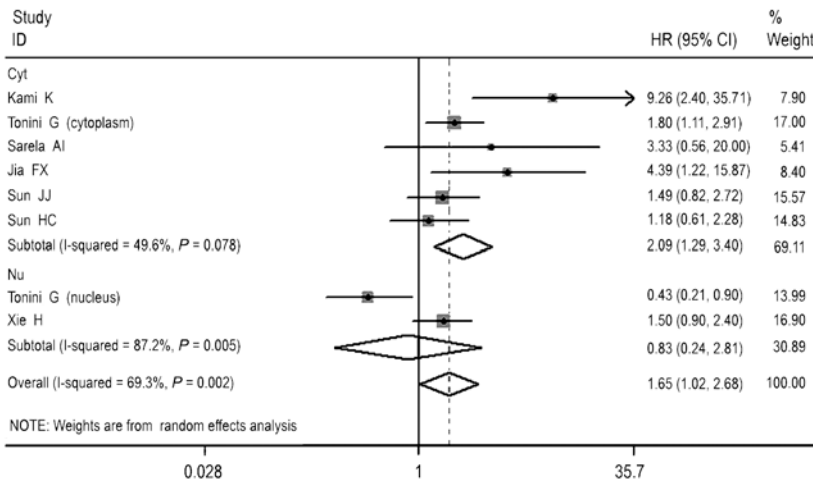


Fig. 4 Forest plot of subgroup analysis stratified by survivin subcellular location. Positive expression in the cytoplasm was significantly associated with poor prognosis, while nuclear expression was not significantly associated with overall survival

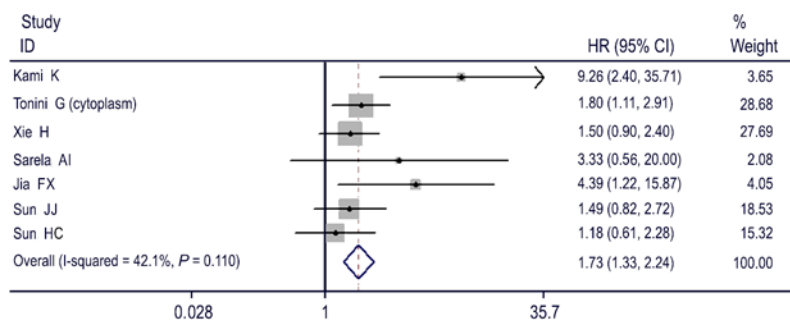


Fig. 5 Forest plot of hazard ratio (HR) after excluding the data of nuclear survivin expression from the study by Tonini G. Heterogeneity decreased significantly. The correlation between survivin expression and overall survival did not change after exclusion of the study

tected when all the 7 studies were pooled ($I^2 = 69.3\%$, $P = 0.002$). We determined the source of heterogeneity from the forest plot (Fig. 3). One study^[32] examined the association of nuclear and cytoplasmic survivin staining with the overall survival in patients with pancreatic cancer. In this study, the authors reported nuclear survivin expression as an indicator of good prognosis and cytoplasmic expression as a poor prognosis. After excluding the data regarding nuclear survivin expression from this study, the heterogeneity in the I^2 statistics dropped significantly ($I^2 = 42.1\%$). For the Q statistic, the P value increased to 0.11; therefore, the fixed-effects model was used (Fig. 5). After excluding the data by Tonini G regarding nuclear survivin expression, the combined HR of the overall survival studies was 1.73 (95% CI: 1.33–2.24). The final conclusion did not change after exclusion of the study, indicating the robustness of this meta-analysis.

Publication bias

Publication bias may exist when non-significant findings remained unpublished, thus artificially inflating the apparent magnitude of an effect. To test the publication bias, we performed Egger's test. No significant funnel plot asymmetry was found in any of the studies, with $P = 0.315$ in the Egger's test (Fig. 6). Therefore, no evidence of publication bias was detected.

Discussion

Survivin as a prognostic biomarker in malignancies has generated significant interest. However, the conclusions from published researches regarding its prognostic value for different cancers are controversial. Survivin expression is an unfavorable prognostic indicator in esophageal, lung and gastric cancers^[13–15]. Many studies have investigated the prognostic value of survivin in pancreatic cancer, but the sample sizes have been small. In addition, reports about prognostic significance of survivin in pancreatic cancer are controversial. In his systematic review, Ansari^[17] reported that prognostic data for expression of survivin were conflicting, but he did not provide a meta-analysis. Although a meta-analysis was performed by Jamieson^[18],

only two studies^[29, 32] were included, and one^[29] of these studies extracted the HR value as a favorable prognostic indicator, which was not in agreement with the conclusion of the original article. We included more studies and performed a meta-analysis to evaluate the role of survivin in the prognosis of pancreatic cancer.

In all included studies, survivin expression was detected by IHC. The specimens were pancreatic cancer tissues. By meta-analysis of the 7 studies, we determined that survivin was an indicator for poor prognosis in pancreatic cancer. We can explain this result by survivin's ability to inhibit apoptosis, promote proliferation, and enhance angiogenesis. Because of its involvement in these processes, survivin is likely to be involved in tumor progression and increased levels would be expected to predict a poor prognosis. As a prognostic factor of pancreatic cancer, survivin may aid in a more accurate prediction of clinical outcome and may also be a novel therapeutic target.

The subcellular distribution of survivin appears to alter during progression through the cell cycle. For example, survivin was associated with the microtubule organization center during interphase, and centrosomes and mitotic spindles during metaphase, but relocated to

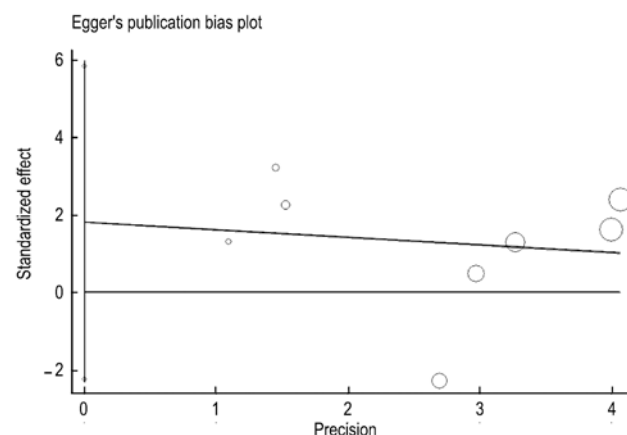


Fig. 6 Funnel plots of Egger's test were used to detect publication bias on overall estimate. Studies were distributed symmetrically, with $P = 0.315$ in the Egger's test, indicating that there was no publication in the meta-analysis

midbodies in late telophase [35–36]. To investigate the relationship between the subcellular location of survivin and overall survival, we performed a subgroup analysis using 6 studies [21, 29–32, 34] in which survivin was located in the cytoplasm. The results showed that survivin expression in the cytoplasm was closely associated with poor prognosis of patients with pancreatic cancer. However, when we performed a subgroup analysis on two studies in which survivin expression was found in nucleus, the results showed no significant impact on patients' overall survival; however, the heterogeneity was highly significant ($I^2 > 50\%$). The different roles of survivin for prognosis based on different locations may indicate that the cell cycle phase of the tumor cells may contribute to the prognosis of pancreatic cancer. While the results may also relate to varying specificity of the antibodies used in IHC, further work is necessary to establish whether different locations of survivin are associated with different prognosis of pancreatic cancer.

We included 7 studies based on the inclusion criteria. We found highly significant heterogeneity when all the 7 studies were pooled. From the forest plot, we identified the study by Tonini [32] as the source of heterogeneity. In the study by Tonini, nuclear survivin staining was reported as a favorable prognostic indicator for patients with pancreatic cancer. To test the robustness of this meta-analysis, we performed a sensitivity analysis by excluding the HR value of survivin nuclear staining reported by Tonini. The final conclusion did not change after the exclusion. This indicates that the outcome of the meta-analysis is stable and convincing.

This meta-analysis has a larger sample size to obtain a relatively convincing conclusion. However, some limitations of this review must be addressed.

First, our meta-analysis had heterogeneity problems. It is possible that the results of the meta-analysis could have been influenced by the heterogeneity. Therefore, we performed a sensitivity analysis and subgroup analysis to decrease the heterogeneity.

Second, all included studies used the IHC method. It is not a precise method because the results are still highly dependent on a variety of methodological factors, such as storage time, fixation method of paraffin-embedded tissues, different primary antibodies, the revelation protocols, and different levels of positive [37].

Another potential source of bias is related to the method used to extrapolate the HR. If the HR was not reported in a study, it was calculated from the data included in the article or extrapolated from the survival curves. The method of extrapolating HR from survival curves seemed to be less reliable than obtaining the HR value from published statistics because this strategy did not completely eliminate inaccuracy in the extracted survival rates.

Finally, we did not take into account unpublished arti-

cles and abstracts. In addition, of the 378 studies gathered, 2 studies [25–26] were not included in the meta-analysis due to insufficient survival data. Because of these limitations, the pooled HRs calculated in our meta-analysis may be overestimated, and the strength of this study may be weakened.

Conclusions

This systematic review and meta-analysis indicate that survivin expression is associated with a poor prognosis in patients with pancreatic cancer. Cytoplasmic expression of survivin may be regarded as a prognostic factor for pancreatic cancer patients. In contrast, there was no evidence that nuclear survivin expression had a significant impact on patients' overall survival. Our conclusions should be confirmed by an adequately designed prospective study, and the exact role of survivin expression needs to be determined by an appropriate multivariate analysis that takes into account the classic well-defined prognostic factors for pancreatic cancer and particularly its subcellular location should be carefully considered.

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