The Prognostic Value of Survivin Expression in Patients with Colorectal Carcinoma: A Meta-analysis

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Received April 12, 2013; accepted July 1, 2013

Objective: The prognostic role of survivin in colorectal carcinoma remains controversial. This meta-analysis aimed to explore the association between survivin expression and survival outcomes in patients with colorectal carcinoma.

Methods: A comprehensive literature search for relevant studies published up to April 2013 was performed using PubMed, MEDLINE and ISI Web of Science. Only articles in which survivin was detected by immunohistochemical staining were included. This meta-analysis was done using STATA and Review Manager.

Results: A total of 1784 patients from 14 studies were included in the analysis. Our results showed that survivin overexpression in patients with colorectal carcinoma was significantly associated with poor overall survival (hazard ratio, 1.505; 95% confidence interval, 1.197–1.893; *P* = 0.000) and disease-free survival (hazard ratio, 2.323; 95% confidence interval, 1.687–3.199; *P* = 0.000). The results indicated that a significant relationship between survivin expression and overall survival was also exhibited in studies with an Asian country (hazard ratio, 1.684; 95% confidence interval, 1.477–1.921), patient number >100 (hazard ratio, 1.604; 95% confidence interval, 1.371–1.877), the cut-off level <50% (hazard ratio, 1.449; 95% confidence interval, 1.045–2.010), the percentage of survivin overexpression >50% (hazard ratio, 1.528; 95% confidence interval, 1.056–2.211) and the hazard ratio estimated (hazard ratio, 1.643; 95% confidence interval, 1.262–2.139). Moreover, upregulation of survivin was associated with stages (III/IV vs. I/II: odds ratio, 1.08; 95% confidence interval, 0.80–1.46), the depth of invasion (T3/T4 vs. T1/T2: odds ratio, 1.79; 95% confidence interval, 0.67–4.74), lymph node metastasis (positive vs. negative: odds ratio, 1.49; 95% confidence interval, 0.99–2.26), distant metastasis (positive vs. negative: odds ratio, 2.37; 95% confidence interval, 0.99–5.72) and grade of differentiation (well/moderate vs. poor: odds ratio, 1.02; 95% confidence interval, 0.43–2.41), but without significance.

Conclusion: The present meta-analysis indicated that upregulation of survivin was associated with poor prognosis in patients with colorectal carcinoma.

Key words: survivin – prognosis – colorectal carcinoma – immunohistochemical – meta-analysis

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies and the third most common cause of cancer-related deaths worldwide (1,2). Treatment advances such as standardized technique of total mesorectal excision, preoperative radiotherapy and adjuvant chemotherapy have reduced the earlier high local recurrence rates and have improved the...
survival in patients (3). However, a great number of patients who underwent apparently curative surgery develop local recurrences or distant metastases leading to shorter survival (4). Identification of factors that affect tumor aggressiveness and predict a more accurate prognosis is required.

Survivin, an inhibitor of apoptosis protein with a molecular weight of ≈16.3 kDa, is considered to play an important role in cell proliferation, angiogenesis and inhibition of apoptosis (5–8). In addition, survivin is involved in the resistance of tumor cells to both chemotherapy and radiotherapy (9). Furthermore, aggressive tumor behavior and worse clinical outcome have recently been linked to high levels of survivin (10), leading several authors to conclude that an important relationship exists between survivin and prognosis of CRC (11–14). However, conflicting results were observed in other studies regarding the ability of survivin to predict prognosis in CRC (15–17). Therefore, in this study, we sought to conduct a meta-analysis to estimate the prognostic importance of elevated survivin expression in survival among patients with CRC.

PATIENTS AND METHODS

SEARCH STRATEGY

We searched Medline, PubMed, Embase and the Web of Science using the following search terms: (survivin and (colorectal or colon or rectal) and (cancer or carcinoma or tumor) and ‘prognosis’). The last search was updated in April 2013. To expand our search, references of the retrieved articles were also screened for additional studies.

STUDY SELECTION

Two independent reviewers assessed the eligibility of studies. Abstracts of all candidate articles were read. Articles that could not be categorized based on the title and abstract alone were retrieved for a full-text review. These articles were independently read and checked for the inclusion criteria. Disagreements were resolved through consensus with a third reviewer. Primary studies that reported data required for meta-analysis were identified and included.

STUDY INCLUSION/EXCLUSION CRITERIA

The inclusion criteria for primary studies were as follows: (i) proven diagnosis of CRC in humans, (ii) survivin evaluation using immunohistochemistry (IHC) and (iii) correlation of survivin with overall survival (OS) or disease-free survival (DFS). There was no pre-specified sample size or follow-up period used to determine the study inclusion. Studies written only in English were included. Conference abstracts were not in the scope of our analysis because of the limited data reported in them. Studies not directly reporting hazard ratios (HRs) were allowed if data were available for statistical estimation. When more than one of the same patient populations was included in several publications, only the most recent or complete study was used to avoid duplication of information.

QUALITY ASSESSMENT

Quality assessment was performed in each of the acceptable studies by two reviewers independently using the Newcastle–Ottawa Quality Assessment Scale for cohort studies (Table 1). This scale is an eight-item instrument that allows for assessment of patient population and selection, study comparability, follow-up and outcome of interest. A star system of the

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<td>(i) Representativeness of the exposed cohort</td>
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<td>(a) Truly representative of the average ‘CRC patient’ in the community (★)</td>
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<td>(b) Somewhat representative of the average ‘CRC patient’ in the community (☆)</td>
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<td>(c) Selected group of users (e.g. nurses and volunteers)</td>
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<td>(d) No description of the derivation of the cohort</td>
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<td>(ii) Selection of the non-exposed cohort</td>
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<td>(a) Drawn from the same community as the exposed cohort (★)</td>
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<td>(b) Drawn from a different source</td>
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<td>(c) No description of the derivation of the non-exposed cohort</td>
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<td>(iii) Ascertainment of exposure</td>
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<td>(a) Secure record (e.g. surgical records) (★)</td>
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<td>(b) Structured interview (★)</td>
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<td>(c) Written self-report</td>
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<td>(i) Comparability of cohorts on the basis of the design or analysis</td>
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<td>(a) Study controls for ‘metastasis or micrometastasis’ (★)</td>
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<td>(b) Study controls for any additional factor (☆)</td>
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<td>Outcome</td>
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<td>(a) Independent blind assessment (★)</td>
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<td>(b) Record linkage (★)</td>
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<td>(c) Self-report</td>
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<td>(ii) Was follow-up long enough for outcomes to occur?</td>
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<td>(a) Yes (‘2 years’) (★)</td>
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<td>(b) No</td>
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<td>(iii) Adequacy of follow-up of cohorts</td>
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<td>(a) Complete follow-up - all subjects accounted for (★)</td>
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<td>(b) Subjects lost to follow-up unlikely to introduce bias - small number lost ‘25%’ follow up, or description of those lost (★)</td>
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<td>(c) Follow-up rate &lt; ‘75%’ and no description of those lost</td>
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<td>(d) No statement</td>
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A study can be awarded a maximum of one star (★) for each numbered item in the selection and outcome categories. A maximum of two stars can be given in Comparability. Underlined and quoted phrases are provided in the scale to allow for adjustment to particular studies.

CRC, colorectal carcinoma.
Newcastle–Ottawa Scale (NOS) (range zero to nine stars) has been developed for evaluation. The highest value for quality assessment was nine stars. Any discrepancies were resolved by a consensus reviewer.

**DATA EXTRACTION**

Two investigators extracted data from eligible studies independently, discussed discrepancies and reached consensus for all items. The following information was extracted from each article: (i) basic information from papers, such as first author’s name, year of publication and country; (ii) tumor data such as tumor–node–metastasis stage; (iii) variables such as the number of patients analyzed, cut-off value of survivin levels and district of the patients. The primary data included HR and 95% confidence interval (CI) of OS and DFS.

**STATISTICAL ANALYSIS**

The primary outcome for analysis was survival in patients with high survivin values when compared with those with low survivin values. When HRs were not reported in an article, they were calculated to use established methods reported by Parmar et al. (18). Forrest plots were undertaken to evaluate the heterogeneity of combined HRs. Statistical assessment was performed using a $\chi^2$-based test of homogeneity and evaluation of the inconsistency index ($I^2$) statistic. Heterogeneity was defined as $P < 0.10$ or $I^2 > 50\%$ (19). When heterogeneity was judged between primary studies, a random-effects model was used for pooled analyses. If not, a fixed-effects model was used (20). Subgroup analyses by stratifying on the country, number of patients, stage, cut-off value, the percentage of patients with survivin overexpression and HR estimation were conducted. Odds ratios (ORs) and their 95% CIs were combined to estimate the correlation between survivin high expression and clinicopathological features (stage, the depth of invasion, lymph node metastasis, distant metastasis and grade of differentiation). An observed HR or OR > 1 implied a worse prognosis for the group with upregulated survivin expression and would be considered to be statistically significant if the 95% CI did not overlap 1. Egger’s test was performed to test for publication bias (21).

Analyses were carried out using STATA and Review Manager. The statistically significant test was determined by a $P$ value of >0.05.

**RESULTS**

**STUDY IDENTIFICATION AND ELIGIBILITY**

An electronic search yielded 79 articles, of which 43 were excluded on the basis of their abstracts. We then screened the remaining 36 articles in full text. Upon further review, 11 articles were eliminated due to no survival data and 9 articles were eliminated due to inadequate data for calculation. We also excluded one study analyzing mRNA of survivin by quantitative real-time reverse transcription and one duplicate study. The selection process and reasons for exclusion have been summarized in Fig. 1. From the 14 studies that were included (11–13,15,16,22–30), a total of 1784 patients were analyzed. The characteristics of the selected studies are presented in Table 2.

**QUALITY ASSESSMENT**

Quality assessment using the NOS was performed on all 14 studies included for meta-analysis. Of note, there was no study attempting to control for important prognostic factors that may have confounded the association of high survivin with survival. The NOS scores of 1–3, 4–6 and 7–9 were defined as low-, intermediate- and high-quality studies, respectively. Our NOS results showed that the median overall score was 5.5 (range 4–7), which indicated that the quality of included trials was acceptable.

**ASSOCIATION BETWEEN SURVIVIN AND OS**

The pooled HR for OS showed that the survivin level was significantly associated with OS (HR, 1.505; 95% CI, 1.197–1.893; $P = 0.000$). There was significant heterogeneity ($P = 0.024$, $I^2 = 56.5\%$, $\chi^2 = 16.08$), and the pooled HR for OS was calculated by using the random-effects model (Fig. 2).

We also performed subgroup analysis by country, number of patients, stage, cut-off value, the percentage of patients with survivin upregulation and HR estimation. The results indicated that a significant relationship between survivin overexpression and OS was also exhibited in studies with an Asian country (HR, 1.684; 95% CI, 1.477–1.921), patient number $>100$ (HR, 1.604; 95% CI, 1.371–1.877), the cut-off level $<50\%$ (HR 1.449; 95% CI, 1.045–2.010), the percentage of survivin overexpression $>50\%$ (HR 1.528; 95% CI, 1.056–2.211) and the HR estimated (HR 1.643; 95% CI, 1.262–2.139) (Table 3).

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**Figure 1.** Flow chart of the meta-analysis.
ASSOCIATION BETWEEN SURVIVIN AND DFS

The pooled HR for DFS showed that the survivin level was significantly associated with DFS (HR, 2.323; 95% CI, 1.687–3.199; \( P = 0.000 \)). No significant heterogeneity was found \(( P = 0.333, I^2 = 12.8\%, \chi^2 = 4.59 \)) , and the pooled HR for DFS was calculated by using the fixed-effects model (Fig. 3).

CORRELATION BETWEEN SURVIVIN EXPRESSION AND CLINICOPATHOLOGICAL CHARACTERISTICS

As shown in Table 4, survivin expression was associated with stages (III/IV vs. I/II: OR, 1.08; 95% CI, 0.80–1.46), the depth of invasion (T3/T4 vs. T1/T2: OR, 1.79; 95% CI, 0.67–4.74), lymph node metastasis (positive vs. negative: OR, 1.49; 95% CI, 0.99–2.26), distant metastasis (positive vs. negative:
OR, 2.37; 95% CI, 0.99–5.72) and grade of differentiation (well/moderate vs. poor: OR, 1.02; 95% CI, 0.43–2.41), but without significance. Significant heterogeneity existed in the meta-analysis of the association between survivin and the depth of invasion ($I^2 = 64\%$, $P = 0.1$) and grade of differentiation ($I^2 = 61\%$, $P = 0.03$), whereas analysis of other
histological features exhibited no inter-study heterogeneity ($I^2 = 0–48\%$).

**PUBLICATION BIAS**

As we had taken a number of steps in the study design to minimize the potential for publication bias, such as, the search strategy, was extensive, papers were selected strictly according to the inclusion criteria, and publication bias was detected by several methods. No significant publication bias was found in the analysis of OS (Begg’s test, $P = 0.063$; Egger’s test, $P = 0.172$) and DFS (Begg’s test, $P = 1$; Egger’s test, $P = 0.421$).

**DISCUSSION**

Up to date, attention has been drawn at a meta-analytical level on the prognostic marker, and potential roles of survivin overexpression have been postulated in various types of cancers, such as lung cancer (31), esophageal squamous cell carcinoma (32), bladder (33) and breast cancers (34). The previous meta-analysis demonstrated that survivin positivity was associated with reduced survival in lung cancer (31) and esophageal squamous cell carcinoma (32). This highlights that survivin may play an important role in cancer prognosis.

This meta-analysis aimed to examine the association between survivin overexpression and survival and clinicopathological characteristics of CRC. Our analysis combined the outcomes of 1784 CRC patients from 14 individual studies, indicating that survivin upregulation significantly predicted poor OS and DFS. Further, there seems to be a correlation between survivin overexpression and stages, the depth of invasion, lymph node metastasis, distant metastasis and grade of differentiation. These results might be important for prognosis and treatment of CRC, in addition to improving the understanding of CRC biology. Identification of prognostic factors helps us to distinguish high-risk groups of patients who need specific therapy, and may be of potential benefit in the development of anticancer therapies to improve clinical outcomes.

In this systematic review, we had dealt with a number of heterogeneity problems. Heterogeneity is a potential problem to affect meta-analysis results. First, we chose studies only performing immunohistochemical staining to reduce heterogeneity as much as possible. However, differences in the techniques used to detect survivin expression, such as the choice of antibody and dilutions of antibody, led to a potential bias, because the sensitivity of the IHC may rely on the antibody concentration. It is impossible to perform subgroup analysis to explore this technical problem, because the small groups of studies used the same antibody. In addition, we found that different cut-offs for survivin overexpression in tissues (5–25%, scores 0–180) were used in the included studies. So far, no optimal threshold has been defined, and the cut-off defining CRC with survivin overexpression is arbitrary. Accordingly, it is very important to use the same antibody, protocol and criteria for evaluation between different laboratories to detect the biological makers. Besides, another potential source of bias might be associated with the approach of extrapolating the HRs. If the HRs were not directly reported in the studies, we calculated them from the survival curves, assuming that censored observations were identically distributed. Two independent authors conducted the reading of the survival rates on the survival curves; however, this approach did not completely eliminate inaccuracy during the extraction of the survival rates, indicating that the estimated HR might thus be less reliable than the HR obtained directly from the published statistics.

One of the strengths of the present meta-analysis is that we analyzed survivin expression and OS, DFS and the clinicopathological parameters in CRC which made our analysis more extensive and valid. Furthermore, the results from the random-effects model were consistent with those from the fixed-effects model, which indicated that the statistical results were robust. Besides, Begg’s and Egger’s tests did not show any publication bias, indicating that the results of the present meta-analysis were not biased. Finally, all the scores of study quality assessed by the Newcastle–Ottawa quality assessment scale were $\geq 4$, indicating that our results were more convincing. But our meta-analysis is still far from perfect. Some limitations need to be carefully considered when interpreting the
results. First, significant heterogeneity among included studies existed indeed. Second, the potential risk bias was a concern. This meta-analysis relied on the published trials rather than the individual patient data (IPD). As positive results were more likely to be published than the negative ones, the meta-analyses based on the published data tend to overestimate the predictive effects of survivin compared with IPD analyses. As a result, we tried to collect all relevant information; but some missing data were still unavoidable. Third, original studies included in our analyses were all retrospective studies, providing a lower level of evidence. Fourth, most of the patients in our research were from Asia, which raises a question about the external validity of results and applicability to the patients from western countries. Finally, this study was constrained to studies published in English language and excluded conference abstracts. Although we detected no evidence of publication bias, it was difficult to completely rule out this possibility.

In conclusion, this meta-analysis, for the first time, demonstrated that increased survivin expression was significantly associated with poor OS and DFS in CRC. However, one should be cautious when interpreting these results due to the limitations of our studies. Further high-quality studies are still needed to confirm these results.

Authors’ contribution
Yao Yang and Huang Yujing were responsible for the study design, article drafting and data analysis. Wei-Xiang Qi and Ai-Na He were responsible for the study concept, interpretation of data and critical appraisal. Zan Shen and Yuan-Jue Sun were responsible for revision of the article and critical appraisal.

Funding
The study was supported by grants from the National Natural Science Foundation of China (81001191) and Science and Technology Commission of Shanghai (10PJ1408300).

Conflict of interest statement
None declared.

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