High expression of anti-apoptotic protein Bcl-2 is a good prognostic factor in colorectal cancer: Result of a meta-analysis

Qi Huang, Shu Li, Pu Cheng, Mei Deng, Xin He, Zhen Wang, Cheng-Hui Yang, Xiao-Ying Zhao, Jian Huang

Qi Huang, Pu Cheng, Mei Deng, Zhen Wang, Cheng-Hui Yang, Jian Huang, Department of Surgical Oncology, the Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang University, Hangzhou 310009, Zhejiang Province, China
Shu Li, Xin He, Xiao-Ying Zhao, Department of Hematology, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, Zhejiang Province, China

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Correspondence to: Jian Huang, MD, PhD, Professor, Department of Surgical Oncology, the Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang University, Jiefang88 Road, Hangzhou 310009, Zhejiang Province, China. dhhuangjian@zju.edu.cn
Telephone: +86-571-87784642
Fax: +86-571-87784642
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Abstract

AIM
To systematically evaluate the prognostic-predictive capability of Bcl-2 in colorectal cancer (CRC).

METHODS
A systematic literature search was conducted using PubMed, Web of Science and EMBASE databases. Any eligible study must meet the following criteria: (1) bcl-2 expression was evaluated in human CRC tissues by immunohistochemistry; (2) assessment of the relationships between bcl-2 expression and overall survival (OS), disease free survival (DFS), recurrent free survival (RFS) or clinic-pathological characteristics of CRC was included; (3) sufficient information was provided to estimate the hazard ratio (HR) or odds ratio and their 95% confidence intervals (CIs); and (4) the study was published in English. The impact of Bcl-2 expression on survival of CRC patients were evaluated through this meta-analysis.

RESULTS
A total of 40 eligible articles involving 7658 patients were enrolled in our final analysis. We drew the conclusion that Bcl-2 high expression was significantly correlated with favorable OS (pooled HR = 0.69, 95%CI: 0.55-0.87, P = 0.002) and better DFS/RFS (pooled HR = 0.65, 95%CI: 0.50-0.85, P = 0.001). Additionally, the subgroup analysis suggested that Bcl-2 overexpression was significantly associated with
No consensus is available in the literature. Nonetheless, data obtained by different researchers were often in disagreement. An increasing body of evidence from many studies indicates that Bcl-2 expression may be associated with favorable OS and better DFS/RFS. Hence, we propose that Bcl-2 may be a valuable prognostic-predictive marker in CRC.

Key words: Bcl-2; Colorectal cancer; Meta-analysis; Prognostic; Apoptotic

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Core tip: No consensus is available in the literature about the prognostic value of Bcl-2 expression in patients with colorectal cancer (CRC). This is the first systematic review and meta-analysis indicating that Bcl-2 is a good prognostic factor in CRC. We investigated the relation in terms of overall survival, disease free survival/recurrent free survival, number of patients, nations, therapy methods, pathological grade.

INTRODUCTION

Bcl-2 family proteins are key regulators of apoptosis whose dysregulation can cause various pathological consequences including the development of cancer. The anti-apoptotic protein Bcl-2 (B-cell lymphoma-2) is an important member of the Bcl-2 family which controls the release of proapoptotic factors responsible for the activation of caspases by stabilizing the mitochondrial outer membrane.

Colorectal cancer (CRC) is one of the most common malignancies worldwide. Despite the great progress made in clinical treatment, the morbidity and mortality of CRC remains high. Aberrant expression of Bcl-2 has been implicated in several cancer types including CRC. Nonetheless, data obtained by different researchers were often in disagreement.

An increasing body of evidence from many studies indicates that Bcl-2 expression may be associated with prognosis in malignancies including CRC. Expression of Bcl-2 has been found to correlate with favorable clinicopathologic parameters and better prognosis by many investigators. In contrast, some groups demonstrated that Bcl-2 was a poor prognostic for cancer patients. And there are others who found no prognostic significance of Bcl-2 expression in CRC. Thus, neither the function nor the prognostic value of Bcl-2 expression in patients with CRC is clear to us.

Herein, we carried out this meta-analysis to explore the reason for present contradictory observations and determine the prognostic value of Bcl-2 in patients with CRC.

MATERIALS AND METHODS

Literature search

We identified relevant articles by conducting searches in the PubMed, Web of Science and EMBASE databases using the following terms and all possible combinations: “Bcl-2”, “colorectal carcinoma”, “CRC”, “colon cancer”, “rectal cancer”. More than this, we examined the references to identify additional eligible studies. The reviews and bibliographies were also retrieved to discern other relevant articles. The most recent search update was October 15, 2016. After excluding non-related articles through browsing the titles and abstracts of the listed studies, full-text viewing of resting studies was performed. The largest population size study was chosen to avoid duplicate analysis when patients overlap partly or entirely.

Inclusion criteria

The eligible studies included in our meta-analysis must meet the following requirements: (1) bcl-2 expression was evaluated in human CRC tissues by immunohistochemistry (IHC); (2) assessment of the relationships between bcl-2 expression and overall survival (OS), disease free survival (DFS), recurrent free survival (RFS) or clinic-pathological characteristics of CRC was included; (3) sufficient information was provided to estimate the hazard ratio (HR) or odds ratio (OR) and their 95% confidence intervals (CIs); and (4) the study was published in English.

Exclusion criteria

The articles were excluded from our analysis if they have the following characteristics: (1) letters, reviews, case reports, and conference abstracts without original data; (2) lack of necessary data or survival curves to calculate HRs, ORs or the corresponding 95%CIs; and (3) overlapping studies.

Data extraction and assessment of study quality

Data extraction and quality assessment were conducted independently by two primary investigators (Qi H and Shu L) using a standardized form. Discrepancies were arbitrated by a third reviewer. The following characteristics were retrieved: first author’s name,
year of publication, country of patients' origin, tumor location, number of patients, age of patients, tumor stage, treatment state before surgery, follow-up time, research technique used, antibody source and dilution, cut-off value, survival data and clinical-pathological data. The quality of each study was tested according to the Newcastle-Ottawa quality assessment scale (NOS).

Statistical analysis
All statistical analysis was performed using the STATA 12.0 software (Stata Corporation, Collage Station, TX, United States). We calculated the pooled HRs and the 95%CIs of all included articles. OS, DFS and RFS were all included in our outcome analysis. We used the raw data directly if HRs and their corresponding 95%CIs were described in the literature. Otherwise, they were extracted from Kaplan-Meier curves published in the article read by Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/) according to the methods described by Parmar et al.[17]. At the same time, we also explored the correlation between Bcl-2 expression and clinical-pathological parameters of CRC such as tumor location, tumor grade, Ducks’ stage and lymph node metastasis combining the ORs and their 95%CIs. A value of HR > 1 implies a worse prognosis of survival in patients who overexpressed Bcl-2, while a value of OR < 1 indicates an unfavorable parameters in those high Bcl-2 expression patients. The association between Bcl-2 and survival or clinical-pathological factors was considered statistically significant if the 95%CI did not span across 1. The heterogeneity among articles included in this meta-analysis was evaluated by χ²-based Q statistical test according to Peto’s method.[18] The inconsistency index (I²) ranged from 0% to 100% was used to quantify the proportion of the total variation.[19] A P-value for the Q-test was presented to assess the heterogeneity among the studies. We chose the random-effects model (the DerSimonian and Laird method) when P < 0.10. Otherwise, the fixed-effects model (the Mantel-Haenszel method) was applied.[19,20] Begg's test was used to determine the potential publication bias when P < 0.05. Statistical significant was defined as P < 0.05.

RESULTS

Literature search and study description
We identified 2274 relevant articles upon screening the keywords from several databases and a total of 40 eligible studies were finally selected to explore the relationship between Bcl-2 expression and CRC patients’ survival using the strategy depicted in Figure 1.[6-10,12-16,21-50]. The detailed clinical features of each record were shown in Table 1, which enrolled an overall of 7658 CRC patients in this analysis published ranging from 1995 to 2016. Among the 40 studies, 6 studies were conducted in Italy, 5 in Greece, 4 each in China and United Kingdom, 2 each in Netherlands, Sweden, United States, Canada, Finland and Germany, 1 each in Romania, Switzerland, Brazil, South Korea, Ireland, Japan, Australia, India and Austria. As to the prognostic analysis, 34 studies evaluated the correlation between Bcl-2 expression and patients’ OS while 13 articles reported the data of Bcl-2 related DFS or RFS.

In OS analysis, 22 of the included articles enrolled more than 100 patients and 12 manuscripts recruited less than 100 patients. Patients from 7 studies received treatment such as radiotherapy, chemotherapy or endocrine therapy before surgery while other 18 studies were not the case, another 9 articles did not provide therapy strategy before surgery.

Methodological quality of selected studies
Each of the 40 eligible studies included in our meta-analysis underwent quality evaluation according to the Newcastle-Ottawa Scale (NOS). NOS scores were judged on eight items of the methodology that categorized into three sections: selection, comparability, exposure and outcome. The quality score of enrolled studies ranged from 5 to 8 with a mean score of 6.5. Eighteen studies scored 7 or more in methodological assessment were defined as high quality (Table 1).

Correlation between Bcl-2 high expression and increased OS or DFS/RFS in CRC
34 studies were included in the analysis to evaluate the association between Bcl-2 high expression and OS. The pooled hazard ratio (HR) for OS was 0.69 (95%CI: 0.55-0.87, Z = 3.14, P = 0.002). A statistical heterogeneity (I² = 80.0%, P < 0.001) was observed based on the random-effects model (Figure 2A). A meta-analysis on 13 studies was performed to analyze the correlation between Bcl-2 and DFS/RFS. The pooled HR for DFS/RFS was 0.65 (95%CI: 0.50-0.85, Z = 3.19, P = 0.001), accompanied with considerable heterogeneity (I² = 59.0%, P = 0.004) (Figure 2B). These results indicate that high level expression of Bcl-2 is significantly associated with decreased mortality risk in CRC patients and Bcl-2 may be an independent prognostic factor in CRC.

Subgroup analysis and sensitivity analysis of the correlation between Bcl-2 high expression and OS in CRC
To address the heterogeneity in OS, we performed subgroup analysis on the number of patients involved in the study, the origin country of patients, the treatment situation before surgery and the NOS score (Table 2). We found that a significant relationship between high expression of Bcl-2 and OS was exhibited in subgroup with number of patients more than 100 (HR = 0.684, 95%CI: 0.54-0.866, P = 0.002) (Figure 3A) and subgroup with origin country of Europe and America (HR = 0.691, 95%CI: 0.553-0.864, P = 0.001) (Figure 3B). Additionally, Bcl-2 overexpression showed
Table 1 Main characteristics of the studies included in the meta-analysis

| Ref. | Year | Country | Tumor location | Patient(P/N) | Age | Stage | Treatment before surgery | Follow-up time | Detection method | Antibody source | Antibody dilution | Cut off value | HR(95%CI) estimation | Quality Score |
|------|------|---------|----------------|--------------|-----|-------|---------------------------|----------------|----------------|----------------|------------------|-------------|---------------------|--------------|
| Cai et al. | 2016 | China | Colon and rectum | 117(34/83) | 52.0 yr | I-IV | No | NA | IHC | Thermo Scientific | 1:50 | > 10% | OS = 0.7 (0.34-1.45) | Multivariate |
| Melincovic i et al. | 2016 | Romania | Colon | 31(12/19) | 63 ± 11.7 yr | A-D (Ducks) | Yes | NA | TMA/IHC | 1:100 | > 5% | OS = 0.21 (0.02-1.71) | Multivariate |
| Huang et al.2015 | 2015 | China | Colon and rectum | 390(85/105) | NA | A-D (Ducks) | No | 986 d | IHC | Genetex | NA | OS = 1.32 (1.21-3.3) | Multivariate |
| Balzotto et al.2015 | 2015 | Italy | Colon and rectum | 321 (153/168) | < 85 yr | I-III | No | NA | IHC | Dako | 1:50 | > 5% | OS = 0.87 (0.51-1.48) | Multivariate |
| Belt et al.2014 | 2014 | Netherlands | Colon | 160 (81/76) | 72.4 yr | I-IV | Yes | T1-4, N1-2, M0 | IHC | Dako | 1:50 | Score ≥ 1 | DFS = 0.971 | Multivariate |
| Fucini et al.2012 | 2012 | Italy | Rectum | 66 (27/39) | 67 ± 9 yr | II-III | Yes | NA | IHC | Dako | 1:50 | > 10% | OS = 1.8 (1.45-5.65) | Multivariate |
| Xu et al.2009 | 2009 | China | Colon and rectum | 119 (33/86) | 57 yr | I-IV | No | 95 mo | IHC | Dako | 1:50 | > 10% | OS = 3.06 (1.21-7.71) | Multivariate |
| Zlobec et al.2008 | 2008 | Switzerland | Colon and rectum | 1420 (NA) | NA | II-III | No | 105.5 ± 39.6 mo | IHC | Dako | 1:50 | > 10% | OS = 1.15 (0.94-1.39) | Multivariate |
| Torsello et al.2008 | 2008 | Italy | Colon and rectum | 1340 (650/690) | NA | A-D (Ducks) | Yes | 5 yr | IHC | Dako | 1:50 | > 10% | OS = 0.221 (0.105-0.464) | Multivariate |
| Cahlin et al.2008 | 2008 | Sweden | Colon | 22 (NA) | 75 ± 9 yr | A-D (Ducks) | No | 68 mo | IHC | Santa Cruz Biotechnology | 1:40 | > 5% | OS = 1.43 (1-2.06) | Multivariate |
| Tsamandas et al.2007 | 2007 | Greece | Rectum | 28 (17/11) | 64 yr | I-IV | No | 47.19 ± 6.2 mo | IHC | Dako | 0.25 µg/mL | NA | OS = 0.032 (0.007-0.158) | Multivariate |
| Meleth et al.2007 | 2007 | United Kingdom | Colon and rectum | 491 (NA) | NA | I-IV | No | 5 yr | IHC | NA | NA | Score ≥ 0.5 | OS = 0.67 (0.493-0.92) | Multivariate |
| Zavrides et al.2006 | 2006 | Greece | Colon and rectum | 100 (27/73) | NA | I and II | No | 7 yr | Biogenex | 1:10 | > 5% | OS = 0.273 (0.139-0.534) | Multivariate |
| Georgiou et al.2006 | 2006 | Greece | Colon and rectum | 170 (64/106) | NA | B and C (Ducks) | No | 45 mo | IHC | Dako | 1:80 | > 10% | OS = 0.56 (0.326-1.031) | Multivariate |
| Chadha et al.2005 | 2005 | United States | Colon and rectum | 138 (89/49) | NA | II and III | No | 7.31 yr | IHC | Cambridge Laboratories | 1:80 | Score ≥ 0.5 | RFS = 0.45 (0.083-2.441) | Multivariate |
| Zhao et al.2005 | 2005 | China | Colon and rectum | 93 (53/40) | 51 yr | A-C (Ducks) | NA | 60 mo (median) | IHC | NA | Score ≥ 2 | OS = 0.905 (0.317-0.884) | Multivariate |
| Lustosa et al.2005 | 2005 | Brazil | Colon and rectum | 116 (58/58) | 65.4 yr | I-IV | No | 28.5 mo (29-96 mo) | IHC | Dako | NA | > 10% | OS = 0.858 (0.433-1.698) | Multivariate |
| Krajewska et al.2005 | 2005 | Poland | Colon and rectum | 106 (NA) | NA | II | No | 66 mo (median) | TMA/IHC | NA | 1:2000 | NA | OS = 0.251 (0.111-0.567) | Multivariate |
| Study            | Year | Country | Tumor Type | Cases | Age | Grade | Staining | Stain | Cut Off | Survival | Hazard Ratio | p Value | Method | Survival Measure | DFS | p Value |
|------------------|------|---------|------------|-------|-----|-------|----------|-------|---------|-----------|--------------|---------|--------|------------------|------|----------|
| Rosati et al.    | 2004 | Italy   | Colon and rectum | 103 (41/62) | 66 yr | B and C | Yes | 5 yr | IHC | Dako | NA | > 10% | OS = 0.71 (0.37-1.35) | Univariate | 7 |
| Garrity et al.   | 2004 | Canada  | Colon and rectum | 366 (97/269) | NA | B2 and C | Yes | 8.7 yr | IHC | Dako | NA | > 10% | OS = 0.99 (0.69-1.429) | Multivariate | 5 |
| Kouraklis et al. | 2003 | Greece  | Colon | 113 (55/58) | 70.9 yr | B and C | No | NA | IHC | Dako | NA | > 10% | OS = 0.99 (0.69-1.429) | Multivariate | 5 |
| Scopa et al.     | 2003 | Greece  | Colon and rectum | 117 (76/41) | 66 yr | A-D | No | 97 mo | IHC | Dako | NA | > 10% | OS = 0.99 (0.69-1.429) | Multivariate | 5 |
| Sun et al.       | 2003 | Sweden  | Colon and rectum | 138 (82/56) | 71 yr | A-D | No | NA | IHC | Nova Castra Laboratories Ltd | 1:50 | Cytoplasmic staining | OS = 0.99 (0.69-1.429) | Multivariate | 5 |
| Bendardaf et al. | 2003 | Finland | Colon and rectum | 58 (45/13) | 60.3 yr | T2-X,N0- | Yes | NA | IHC | Dako | 1:50 | Sum the intensity score and expression score ≥ 1.10 | OS = 1.02 (0.71-1.15) | Univariate | 6 |
| Elkaawaly et al. | 2001 | United Kingdom | Colon and rectum | 52 (38/14) | 68.8 yr | pT2-A, N0- | No | NA | IHC | Dako | 4 µg/mL | Multiply the intensity score and expression score ≥ 6 | OS = 0.552 (0.253-1.319) | Multivariate | 6 |
| Meterissian et al. | 2001 | Canada | Colon | 76 (62/14) | 71.2 yr | B | No | 59 mo | IHC | Dako | 1:50 | ≥ 10% | OS = 0.35 (0.13-0.94) | Univariate | 7 |
| Paradiso et al.  | 2001 | Italy   | Colon and rectum | 80 (29/51) | 60.3 yr | T2-X,N0- | Yes | NA | IHC | Dako | 1:40 | ≥ 30% or stain intensity scale ≥ 1 | OS = 0.35 (0.13-0.94) | Univariate | 7 |
| Schwandner et al. | 2000 | Germany | Rectum | 160 (47/113) | 66.7 yr | 1-III | No | 38 mo | IHC | Dako | 1:20 | > 10% | OS = 1.287 (0.76-2.183) | Univariate | 6 |
| Bugioni et al.   | 1999 | Italy   | Colon and rectum | 171 (57/114) | 64 yr | A-D | No | 50 mo | IHC | Dako | NA | A strong homogeneous cytoplasmic immunoreaction | OS = 0.192 (0.0439-0.84) | Multivariate | 6 |
| Leahy et al.     | 1999 | Ireland | Colon and rectum | 102 (22/80) | 69 yr | A-C | No | 9.9 yr | IHC | Dako | 1:50 | > 5% | OS = 0.5 (0.2-1) | Multivariate | 7 |
| Ishijima et al.  | 1999 | Japan   | Colon and rectum | 33 (10/23) | 61.6 yr | A-D | No | NA | IHC | Santa Cruz Biotechnology | 1:50 | > 10% | OS = 0.46 (0.21-1.10) | Multivariate | 7 |
| Sinicrope et al. | 1999 | United States | Colon | 137 (71/66) | 65.2 yr | T2-3, | No | 105.5 mo | IHC | Dako | 1:20 | > 20% | OS = 0.43 (0.21-0.96) | Multivariate | 7 |
| Hirvokoski et al. | 1999 | Finland | Rectum | 92 (62/30) | 72 yr | A-D | Yes | 32 mo | IHC | Dako | 1:20 | > 20% | OS = 0.55 (0.55-1.79) | Univariate | 6 |
| Biden et al.     | 1999 | Australia | Colon and rectum | 66 (49/17) | 66 yr | A-D | No | NA | IHC | Dako | 1:40 | > 5% | OS = 0.132 (0.057-0.306) | Univariate | 5 |
a favorable OS when the patients adopted no therapy before surgery (HR = 0.696, 95%CI: 0.502-0.964, P = 0.029) (Figure 3C). Our results also indicated that the NOS quality score had no significant effect on the prognostic value of Bcl-2 expression (Figure 3D). Meanwhile, a sensitive analysis was conducted to assess the role of each study on the overall environment. To achieve this, studies were excluded one at a time while the rest were analyzed. HR of Bcl-2 high expression on OS ranged from 0.664 (95%CI: 0.532-0.830) to 0.730 (95%CI: 0.585-0.909) (Figure 4A), and pooled HR of Bcl-2 high expression on DFS/RFS ranged from 0.597 (95%CI: 0.461-0.775) to 0.687 (95%CI: 0.528-0.894) (Figure 4B).

**Impact of Bcl-2 high expression on clinicopathological parameters**

Twelve studies were selected to assess the association between Bcl-2 high expression and tumor differentiation grade. The pooled OR was 2.475 (95%CI: 1.307-4.685, P = 0.005) with statistical heterogeneity (I² = 68.4%, P = 0.000), which indicated that low expression of Bcl-2 was correlated with differentiation of CRC. Correlation between Bcl-2 overexpression and Ducks’ stages were also evaluated in twelve studies. The pooled OR was 1.630 (95%CI: 1.009-2.632, P = 0.046) with significant heterogeneity (I² = 78.1%, P = 0.000), suggesting that downregulated Bcl-2 expression was associated with the progression of CRC. However, we did not find significant association between Bcl-2 expression and gender or the tumor location, the pooled OR being shown in Table 3.

**Publication bias**

Begg’s test was used to assess the potential publication bias. The funnel plots for the OS (Figure 5A) and DFS/RFS (Figure 5B) indicated that there was no evidence of significant publication bias in our present meta-analysis.

**DISCUSSION**

It is well documented that defects in the mitochondrial apoptotic pathway are closely related with carcinogenesis. Bcl-2 is a key inhibitor of apoptosis, playing a major role in the maintenance of normal balance between apoptosis and cellular survival. Currently, effective treatment of CRC remains a big challenge. The majority of patients will experience relapse or distant metastases within 5 years following surgical resection. Abnormal Bcl-2 activation has been implicated during the evolution of CRC. Up to this date, however, the exact role of Bcl-2 in CRC has not been established. The explanation of this inconsistency is not known, perhaps because of the variations with ethnicity and location in the patient population. By the same token, no consistent conclusion about the prognostic value of Bcl-2 expression in CRC patients has been made. So we speculate that the prognostic significance of
Bcl-2 expression in CRC may be restricted to specific subgroups. To the best of our knowledge, this is the first meta-analysis pertinently investigating the prognostic value of Bcl-2 expression in CRC.

Our meta-analysis incorporated 40 eligible studies with the survival data of OS, DFS and RFS. From our analyses results we found that Bcl-2 high expression is of significant association with increased OS and DFS/RFS in patients with CRC. When the subgroup analyses were conducted, the pooled results demonstrated that high expression Bcl-2 was a favorable prognostic factor in subgroup with number of patients more than 100 and subgroup with origin country of Europe and America. Additionally, Bcl-2 overexpression showed an

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**Table 2** Subgroup analysis of pooled hazard ratios for colorectal cancer patients with overexpressed Bcl-2

| Stratified analysis | No. of studies | No. of patients | Pooled HR (95%CI) | P value | Heterogeneity |
|--------------------|----------------|----------------|------------------|---------|---------------|
| No. of patients    |                |                |                  |         |               |
| ≥ 100              | 22             | 6274           | 0.684 (0.54-0.866) | 0.002   | 75.9          | 0.000         |
| < 100              | 12             | 712            | 0.693 (0.389-1.235) | 0.214   | 85.8          | 0.000         |
| Study location     |                |                |                  |         |               |
| Asia               | 7              | 777            | 1.021 (0.488-2.136) | 0.955   | 88.2          | 0.000         |
| Europe and America | 26             | 6143           | 0.691 (0.533-0.864) | 0.001   | 73.9          | 0.000         |
| Treatment before surgery |       |                |                  |         |               |
| Yes                | 7              | 2056           | 0.772 (0.55-0.947) | 0.394   | 73.8          | 0.001         |
| No                 | 18             | 2615           | 0.696 (0.502-0.964) | 0.029   | 79.9          | 0.000         |
| Quality score      |                |                |                  |         |               |
| ≥ 7                | 18             | 2471           | 0.678 (0.499-0.92) | 0.013   | 71.8          | 0.000         |
| < 7                | 16             | 4315           | 0.708 (0.503-0.996) | 0.047   | 84.9          | 0.000         |

**Table 3** Bcl-2 expression and clinicopathological features of colorectal cancer

| Clinicopathological features | No. of studies | No. of patients | Pooled OR (95%CI) | P value | Heterogeneity |
|------------------------------|----------------|----------------|------------------|---------|---------------|
| Gender (male vs female)      | 11             | 1671           | 1.125 (0.865-1.463) | 0.381   | 30.2%         | 0.158         |
| Tumor location (colon vs rectum) | 8           | 1361           | 1.168 (0.922-1.480) | 0.199   | 0%            | 0.628         |
| Tumor grade (1 + 2 vs 3)     | 12             | 1454           | 2.475 (1.307-4.685) | 0.005   | 68.4%         | 0.000         |
| Ducks' stage (A + B vs C + D) | 12            | 1572           | 1.630 (1.009-2.632) | 0.046   | 78.1%         | 0.000         |
increased OS when the patients adopted no therapy before surgery. As to clinicopathological parameters analysis, Bcl-2 was found to express more frequently in tumors with high differentiation grade and A/B Ducks’ stage. It should be noted that no publication bias was found in this meta-analysis.

Our study leads to several valuable conclusions. First, expression of Bcl-2 is a favorable factor for...
## Table A

| Study ID          | Bcl-2 positive vs Bcl-2 negative | HR (95%CI)       | Weight |
|-------------------|----------------------------------|------------------|--------|
| ≥ 100             |                                  |                  |        |
| Cai (2016)        |                                  | 0.70 (0.34, 1.45)| 2.97   |
| Huang (2015)      |                                  | 2.00 (1.21, 3.30)| 3.52   |
| Blazi (2015)      |                                  | 0.87 (0.51, 1.48)| 3.44   |
| Xu (2009)         |                                  | 3.06 (1.22, 7.72)| 2.50   |
| Zlobec (2008)     |                                  | 1.15 (0.94, 1.39)| 4.11   |
| Torsello (2008)   |                                  | 0.22 (0.10, 0.46)| 2.92   |
| Meleth (2007)     |                                  | 0.67 (0.49, 0.92)| 3.93   |
| Zavrides (2006)   |                                  | 0.27 (0.14, 0.53)| 3.10   |
| Georgiou (2006)   |                                  | 0.56 (0.33, 1.03)| 3.34   |
| Lustosa (2005)    |                                  | 0.86 (0.43, 1.70)| 3.07   |
| Krajevska (2005)  |                                  | 0.25 (0.11, 0.57)| 2.75   |
| Rosati (2004)     |                                  | 0.71 (0.37, 1.35)| 3.16   |
| Garity (2004)     |                                  | 0.99 (0.69, 1.43)| 3.83   |
| Kourakis (2003)   |                                  | 0.52 (0.30, 0.90)| 3.42   |
| Scopa (2003)      |                                  | 1.55 (0.70, 3.40)| 2.81   |
| Sun (2003)        |                                  | 0.50 (0.22, 1.15)| 2.73   |
| Buglioni (1999)   |                                  | 0.19 (0.04, 0.84)| 1.53   |
| Leahy (1999)      |                                  | 0.50 (0.20, 1.00)| 2.77   |
| Sinicrope (1999)  |                                  | 0.46 (0.21, 1.05)| 2.77   |
| Kaklamanis (1998) |                                  | 0.61 (0.38, 0.98)| 3.57   |
| Tollenaar (1998)  |                                  | 0.98 (0.66, 1.45)| 3.76   |
| Ofner (1995)      |                                  | 0.44 (0.25, 0.78)| 3.37   |
| Subtotal (I² = 75.9%, P = 0.000) |                  | 0.68 (0.54, 0.87)| 69.38  |

< 100

| Study ID          | Bcl-2 positive vs Bcl-2 negative | HR (95%CI)       | Weight |
|-------------------|----------------------------------|------------------|--------|
| Melincovici (2016)|                                  | 0.21 (0.03, 1.72)| 0.92   |
| Fucini (2012)     |                                  | 2.53 (1.15, 5.57)| 2.81   |
| Cahin (2008)      |                                  | 1.43 (1.00, 2.06)| 3.83   |
| Tsamandas (2007)  |                                  | 0.03 (0.01, 0.16)| 1.42   |
| Zhao (2005)       |                                  | 0.50 (0.32, 0.80)| 3.60   |
| Bendaraf (2003)   |                                  | 1.02 (0.70, 1.50)| 1.63   |
| Elkablawy (2001)  |                                  | 0.55 (0.23, 1.32)| 2.62   |
| Meterissian (2001)|                                  | 0.35 (0.13, 0.94)| 2.36   |
| Paradiso (2001)   |                                  | 1.29 (0.76, 2.18)| 3.46   |
| Hirvikkoski (1999)|                                  | 0.99 (0.55, 1.79)| 3.30   |
| Biden (1999)      |                                  | 0.13 (0.06, 0.31)| 2.69   |
| Bhatavdekar (1997)|                                  | 7.81 (2.38, 25.64)| 1.97   |
| Subtotal (I² = 85.8%, P = 0.000) |                  | 0.69 (0.39, 1.24)| 30.62  |

Overall (I² = 80.0%, P = 0.000)

| Study ID          | Bcl-2 positive vs Bcl-2 negative | HR (95%CI)       | Weight |
|-------------------|----------------------------------|------------------|--------|
| Overall           |                                  | 0.69 (0.55, 0.87)| 100.00 |

NOTE: Weight are from random effects analysis

### Figure

The figure illustrates the distribution of Bcl-2 positive vs Bcl-2 negative across various studies. The bars represent the HR (95%CI) with corresponding weights for each study. The overall I² value of 80.0% and P = 0.000 indicates significant heterogeneity among the studies.

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### B

| Study ID                | Nation                                                                 | Bcl-2 positive vs Bcl-2 negative | HR (95%CI)     | Weight |
|-------------------------|------------------------------------------------------------------------|----------------------------------|----------------|--------|
| Asia                    |                                                                        |                                  |                |        |
| Cai (2016)              |                                                                        | 0.70 (0.34, 1.45)                | 3.03           |        |
| Huang (2015)            |                                                                        | 2.00 (1.21, 3.30)                | 3.66           |        |
| Xu (2009)               |                                                                        | 3.06 (1.22, 7.72)                | 2.52           |        |
| Zhao (2005)             |                                                                        | 0.50 (0.32, 0.80)                | 3.76           |        |
| Krajewskia (2005)       |                                                                        | 0.25 (0.11, 0.57)                | 2.79           |        |
| Bhatavedkar (1997)      |                                                                        | 7.81 (2.38, 25.64)               | 1.95           |        |
| Ofner (1995)            |                                                                        | 0.44 (0.25, 0.78)                | 3.48           |        |
| Subtotal (I² = 88.2%, P = 0.000) |                                                   | 1.02 (0.49, 2.14)                | 21.19          |        |
| Europe and America      |                                                                        |                                  |                |        |
| Melincovici (2016)      |                                                                        | 0.21 (0.03, 1.72)                | 0.89           |        |
| Blazi (2015)            |                                                                        | 0.87 (0.51, 1.48)                | 3.57           |        |
| Fucini (2012)           |                                                                        | 2.53 (1.15 5.57)                 | 2.86           |        |
| Zlobec (2008)           |                                                                        | 1.15 (0.94, 1.39)                | 4.36           |        |
| Torsello (2008)         |                                                                        | 0.22 (0.10, 0.46)                | 2.98           |        |
| Cahlin (2008)           |                                                                        | 1.43 (1.00, 2.06)                | 4.03           |        |
| Tsamandas (2007)        |                                                                        | 0.03 (0.01, 0.16)                | 1.39           |        |
| Meleth (2007)           |                                                                        | 0.67 (0.49, 0.92)                | 4.14           |        |
| Zavrides (2006)         |                                                                        | 0.27 (0.14, 0.53)                | 3.18           |        |
| Georgiou (2006)         |                                                                        | 0.56 (0.33, 1.03)                | 3.45           |        |
| Lustosa (2005)          |                                                                        | 0.46 (0.43, 1.70)                | 3.15           |        |
| Rosati (2004)           |                                                                        | 0.71 (0.37, 1.35)                | 3.25           |        |
| Garrity (2004)          |                                                                        | 0.99 (0.69, 1.43)                | 4.02           |        |
| Kourakis (2003)         |                                                                        | 0.52 (0.30, 0.90)                | 3.54           |        |
| Scopa (2003)            |                                                                        | 1.55 (0.70, 3.40)                | 2.86           |        |
| Sun (2003)              |                                                                        | 0.50 (0.22, 1.15)                | 2.77           |        |
| Bendardaf (2003)        |                                                                        | 1.02 (0.70, 1.50)                | 1.60           |        |
| Elkablawy (2001)        |                                                                        | 0.55 (0.23, 1.32)                | 2.65           |        |
| Meterissian (2001)      |                                                                        | 0.35 (0.13, 0.94)                | 2.36           |        |
| Paradiso (2001)         |                                                                        | 1.29 (0.76, 2.18)                | 3.59           |        |
| Buglioni (1999)         |                                                                        | 0.19 (0.04, 0.84)                | 1.49           |        |
| Leahy (1999)            |                                                                        | 0.50 (0.20, 1.00)                | 2.82           |        |
| Sinicrope (1999)        |                                                                        | 0.46 (0.21, 1.05)                | 2.82           |        |
| Hirvokoski (1999)       |                                                                        | 0.99 (0.55, 1.79)                | 3.41           |        |
| Kaklamanis (1998)       |                                                                        | 0.61 (0.38, 0.98)                | 3.72           |        |
| Tollenaar (1998)        |                                                                        | 0.98 (0.66, 1.45)                | 3.94           |        |
| Subtotal (I² = 73.9%, P = 0.000) |                                                   | 0.69 (0.55, 0.86)                | 78.81          |        |
| Overall (I² = 78.2%, P = 0.000) |                                               | 0.73 (0.59, 0.91)                | 100.00         |        |

**NOTE:** Weight are from random effects analysis
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### C

| Study ID         | Bcl-2 positive vs Bcl-2 negative | HR (95%CI)       | Weight |
|------------------|----------------------------------|------------------|--------|
| Cai (2016)       |                                  | 0.70 (0.34, 1.45)| 4.13   |
| Huang (2015)     |                                  | 2.00 (1.21, 3.30)| 4.87   |
| Blazi (2015)     |                                  | 0.87 (0.51, 1.48)| 4.77   |
| Xu (2009)        |                                  | 3.06 (1.22, 7.72)| 3.49   |
| Cahnin (2008)    |                                  | 1.43 (1.00, 2.06)| 5.30   |
| Tsamandas (2007) |                                  | 0.03 (0.01, 0.16)| 2.00   |
| Meleth (2007)    |                                  | 0.67 (0.49, 0.92)| 5.43   |
| Zavrides (2006)  |                                  | 0.27 (0.14, 0.53)| 4.30   |
| Lustosa (2005)   |                                  | 0.86 (0.43, 1.70)| 4.27   |
| Krajevska (2005) |                                  | 0.25 (0.11, 0.57)| 3.83   |
| Kouraklis (2003) |                                  | 0.52 (0.30, 0.90)| 4.73   |
| Scopa (2003)     |                                  | 1.55 (0.70, 3.40)| 3.91   |
| Meterissian (2001)|                               | 0.35 (0.13, 0.94)| 3.29   |
| Paradiso (2001)  |                                  | 1.29 (0.76, 2.18)| 4.79   |
| Buglioni (1999)  |                                  | 0.19 (0.04, 0.84)| 2.14   |
| Leahy (1999)     |                                  | 0.50 (0.20, 1.00)| 3.86   |
| Sinicrope (1999) |                                  | 0.48 (0.21, 1.05)| 3.86   |
| Tollenaar (1998) |                                  | 0.98 (0.66, 1.45)| 5.20   |
| **Subtotal (I^2 = 79.9%, P = 0.000)** | | 0.70 (0.50, 0.98) | 74.17 |

| Yes              |                                  |                  |        |
| Melincovici (2016)|                               | 0.21 (0.03, 1.72)| 1.30   |
| Fucini (2012)    |                                  | 2.53 (1.15, 5.57)| 3.91   |
| Torselio (2008)  |                                  | 0.22 (0.10, 0.48)| 4.07   |
| Rosati (2004)    |                                  | 0.71 (0.37, 1.35)| 4.39   |
| Garrity (2004)   |                                  | 0.99 (0.69, 1.43)| 5.29   |
| Benderd (2003)   |                                  | 1.02 (0.70, 1.50)| 2.29   |
| Hirvikoski (1999)|                                  | 0.99 (0.55, 1.79)| 4.58   |
| **Subtotal (I^2 = 73.8%, P = 0.001)** | | 0.79 (0.45, 1.38) | 25.83 |

| Overall (I^2 = 77.7%, P = 0.000) | | 0.72 (0.55, 0.95) | 100.00 |

**NOTE:** Weight are from random effects analysis
CRC. The relationship between Bcl-2 expression and transformation from normal epithelium to invasive cancer is not entirely clear. However, there is evidence to suggest that during the evolution of CRC, the role of Bcl-2 oncoprotein is believed to be in the early stages of carcinogenesis[51,52]. Moreover, lack of Bcl-2 expression has been proved to be correlated with invasion, metastasis and recurrence of CRC. Our meta-analysis revealed that the upregulation of Bcl-2 was related to favorable prognosis in both OS and DFS/RFS. This is contradictory to the anti-apoptotic function of Bcl-2, which may be due to the interactions of various proteins involved in apoptotic pathways such as p53, Fas and so on. Second, our present results indicated that expression of Bcl-2 protein was associated with pathological grade and clinical stage, consistent with what Zavrides et al[12] reported. The survival of CRC patients largely depends on disease stage at the time of diagnosis and differs greatly between stages. It was reported earlier that Bcl-2 expression correlated with improved survival, a significantly higher MFS for the subgroup of patients with Dukes’ B[53]. It is logical to assume that the primary role of Bcl-2 during carcinogenesis and progression of CRC may depend

| Study ID                  | Bcl-2 positive vs Bcl-2 negative | HR (95%CI) | Weight |
|--------------------------|----------------------------------|------------|--------|
| ≥ 7                      |                                  |            |        |
| Cai (2016)               |                                  | 0.70 (0.34,1.45) | 2.97   |
| Melincovici (2016)       |                                  | 0.21 (0.03,1.72) | 0.92   |
| Huang (2015)             |                                  | 2.00 (1.21,3.30) | 3.52   |
| Blazi (2015)             |                                  | 0.87 (0.51,1.48) | 3.44   |
| Zavrides (2006)          |                                  | 0.27 (0.14,0.53) | 3.10   |
| Georgiou (2006)          |                                  | 0.56 (0.33,1.03) | 3.34   |
| Rosati (2004)            |                                  | 0.71 (0.37,1.35) | 3.16   |
| Kourakis (2003)          |                                  | 0.52 (0.30,0.90) | 3.42   |
| Scopa (2003)             |                                  | 1.55 (0.70,3.40) | 2.81   |
| Sun (2003)               |                                  | 0.50 (0.22,1.15) | 2.73   |
| Meterissian (2001)       |                                  | 0.35 (0.13,0.94) | 2.36   |
| Buglioni (1999)          |                                  | 0.19 (0.04,0.84) | 1.53   |
| Leahy (1999)             |                                  | 0.50 (0.20,1.00) | 2.77   |
| Sinicrope (1999)         |                                  | 0.46 (0.21,1.05) | 2.77   |
| Kaklaninis (1998)        |                                  | 0.61 (0.38,0.98) | 3.57   |
| Tollenaar (1998)         |                                  | 0.98 (0.66,1.45) | 3.76   |
| Bhatvdekar (1997)        |                                  | 7.81 (2.38,25.64) | 1.97   |
| Ofner (1995)             |                                  | 0.44 (0.25,0.78) | 3.37   |
| Subtotal (I² = 71.8%, P = 0.000) |                  | 0.68 (0.50,0.92) | 51.51  |
| < 7                      |                                  |            |        |
| Fucini (2012)            |                                  | 2.53 (1.15,5.57) | 2.81   |
| Xu (2009)                |                                  | 3.06 (1.22,7.72) | 2.50   |
| Zlobec (2008)            |                                  | 1.15 (0.94,1.39) | 4.11   |
| Torsello (2008)         |                                  | 0.22 (0.10,0.46) | 2.92   |
| Cahn (2008)              |                                  | 1.43 (1.00,2.06) | 3.83   |
| Tsamandas (2007)         |                                  | 0.03 (0.01,0.16) | 1.42   |
| Meleth (2007)            |                                  | 0.67 (0.49,0.92) | 3.93   |
| Zhao (2005)              |                                  | 0.50 (0.32,0.80) | 3.60   |
| Lustosa (2005)           |                                  | 0.86 (0.43,1.70) | 3.07   |
| Krajewska (2005)         |                                  | 0.25 (0.11,0.57) | 2.75   |
| Garnity (2004)           |                                  | 0.99 (0.69,1.43) | 3.83   |
| Bendardaf (2003)         |                                  | 1.02 (0.70,1.50) | 1.63   |
| Elkablawy (2001)         |                                  | 0.55 (0.23,1.32) | 3.62   |
| Paradiso (2001)          |                                  | 1.29 (0.76,2.18) | 3.46   |
| Hirvikoski (1999)        |                                  | 0.99 (0.55,1.79) | 3.30   |
| Biden (1999)             |                                  | 0.13 (0.06,0.31) | 2.69   |
| Subtotal (I² = 84.9%, P = 0.001) |                  | 0.71 (0.50,1.00) | 48.49  |
| Overall (I² = 80.0%, P = 0.000) |                  | 0.69 (0.55,0.87) | 100.00 |

NOTE: Weight are from random effects analysis

Figure 3 Hazard ratio of Bcl-2 expression associated with overall survival in the subgroup. A: Patients’ number; B: Patients’ country of origin; C: The condition of treatment before surgery; D: Quality score of study.
on disease stage. However, further study on large sample is needed to confirm this speculation. Third, the prognostic role of Bcl-2 expression on CRC patients is evident in Caucasian populations but not yet the case in Asians. Genomic polymorphisms among various ethnic groups may be the explanation. Thus, the clinical value of Bcl-2 should be studied separately based upon different population structures and aggregates in the future research. Additionally, the favorable effect of Bcl-2 expression on CRC patients’ overall survival is insignificant in subgroup receiving preoperative treatment. Some studies have suggested that preoperative chemoradiation can influence cancer cell’s apoptosis and treatment effect by changing Bcl-2 expression. Thus, it seems easy to explain such observation. However, Long-term prospective studies are needed to verify this.

Recently, targeting proteins involved in apoptotic pathways appeared as an attractive strategy to assist anticancer therapy. A particular concern has been
focused on the development of agents capable of inhibiting the activity of Bcl-2 family members that are overexpressed in various malignancies\textsuperscript{[54,55]}. In this regard, it seems that we need to reassess the of small-molecule drugs targeting Bcl-2. There is a serious need for more in vivo experiments to explicate the detailed mechanism. Finally, using Bcl-2 alone to evaluate prognostic information of CRC patients with different stages is probably limited. On the other hand, integration of multiple biomarkers may provide sufficient support for clinical application\textsuperscript{[56-59]}. We suggest focusing on the combination of key markers within the prominent pathways that occupy an important role in clinical prognosis, which better reflects the overall molecular environment in CRC. A systematic study on the prognostic value of multi-marker proteins in CRC patients can also be performed in the future.

There exists some limitations that should be noted in our meta-analysis. We only recruited articles published in English, thus a language bias might exist. Some HRs and their corresponding 95\%CIs were extracted from the survival curves. However, these data might be less reliable than those directly obtained from survival data. We use random effects model to deal with heterogeneity, however, the inter-study heterogeneity resulted from different populations, different antibody source and varying cutoff values was inevitable.

In summary, our meta-analysis suggests that expression of the Bcl-2 protein is associated with favorable prognosis in patients with CRC. Subgroup analysis showed that Bcl-2 overexpression may become a good prognosis factor in CRC where patients come from Europe and America but not Asian and patients not receive any adjuvant therapy before surgery. These significant associations were more remarkable in CRCs with high grade of differentiation and A/B Ducks’ stage. Our analysis also found those significant associations only be find in populations more than 100. This told us that further prospective studies with larger sample sizes are required to validate the prognostic value of Bcl-2 expression in CRC.

**COMMENTS**

**Background**

An increasing body of evidence from many studies indicates that Bcl-2 expression may be associated with prognosis in malignancies including colorectal cancer (CRC). However, neither the function nor the prognostic value of Bcl-2 expression in patients with CRC is clear to us.

**Research frontiers**

Currently, effective treatment of CRC remains a big challenge. Abnormal Bcl-2 activation has been implicated during the evolution of CRC and speculated playing a major role in the prognosis of CRC. Up to this date, however, the exact role of Bcl-2 in CRC has not been established.

**Innovations and breakthroughs**

In the present study, the authors explored the reason for present contradictory observations and determine the prognostic value of Bcl-2 in patients with CRC. This is the first meta-analysis pertinently investigating the prognostic value of Bcl-2 expression in CRC.

**Applications**

The present study allows understanding the prognostic-predictive capability of Bcl-2 in CRC.

**Peer-review**

This systematic review and meta-analysis of retrospective studies adds useful information for practice and research, and probably for policy.

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