OncoTargets and Therapy

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ORIGINAL RESEARCH

Prognostic value of Bcl-2 expression in patients with non-small-cell lung cancer: a meta-analysis and systemic review

This article was published in the following Dove Press journal:
OncoTargets and Therapy
18 November 2015
Number of times this article has been viewed

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Objective: B-cell-lymphoma-2 (Bcl-2) is a proto-oncogene that plays an important role in the regulation of apoptosis and cell survival. However, there are much conflicting data in the literature concerning the association between Bcl-2 and prognosis in non-small-cell lung cancer (NSCLC). There is little in the way of meta-analysis focused on Bcl-2 and its effect on NSCLC prognosis. This study was performed to provide an assessment of whether expression levels of Bcl-2 are associated with prognosis in patients with NSCLC.

Materials and methods: We searched PubMed, the Cochrane Library, and China National Knowledge Infrastructure for all eligible studies. The combined hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) in terms of overall survival were evaluated.

Results: Fifty published studies including 6,863 patients with lung cancer were included in this meta-analysis. Overall, Bcl-2 was expressed in 33% of the NSCLC tumors studied. Our analysis indicates that NSCLC patients with Bcl-2-positive expression have a better prognosis than those with Bcl-2-negative expression in both Asian and non-Asian study populations (HR 0.79, 95% CI 0.72–0.87, $P<0.00001$). However, Bcl-2-positive expression seems to have no significant impact on survival of stage I NSCLC patients.

Conclusion: Our results indicated that Bcl-2 might be a useful prognostic marker for NSCLC generally. Larger clinical trials are needed to confirm the prognostic value of Bcl-2 in stage I NSCLC.

Keywords: Bcl-2, non-small-cell lung cancer, meta-analysis, prognosis

Introduction

Lung cancer is the most common cause of cancer-related death worldwide. Non-small-cell lung cancer (NSCLC) accounts for >85% of primary lung cancers, and approximately two-thirds of NSCLC patients are diagnosed at an advanced stage.[1] Pathological features, such as pathological stage, histological type, and lymph node metastasis, have been independent prognostic markers predicting the development of metastasis.[2] However, they are imperfect, represent only crude measures of the biological behavior of a tumor, and cannot predict the optimal therapeutic course for the individual patient. Thus, it is important to identify biological markers which can predict survival.

The ability of cancer cells to avoid apoptosis and continue to proliferate is one of the fundamental hallmarks of cancer. B-cell-lymphoma-2 (Bcl-2) is a key regulator of the mitochondrial apoptotic pathway promoting survival by inhibition of adapters necessary for the activation and cleavage of caspases.[3] The *Bcl-2* gene was discovered in a follicular B-cell lymphoma, and its tumorigenic potential has been shown in animal

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models.[4] Bcl-2 is overexpressed in a variety of human tumors including lung cancer.[3,5]

In lung cancer, the prognostic value of Bcl-2 expression has been analyzed by several groups, but results have been conflicting and controversial. One group investigated Bcl-2 expression in a meta-analysis of nine studies with a total of 673 small-cell lung cancer patients and concluded that Bcl-2 expression was associated with a better prognosis, but this did not reach significance.[6] Also, although there are a large number of studies investigating the prognostic value of Bcl-2 expression in NSCLC survival, no consensus has been reached. These conflicting results have been reported from different laboratories. We, therefore, carried out a meta-analysis of data from published studies to quantitatively review the effect of Bcl-2 overexpression in tumor tissue on overall survival (OS) in patients with NSCLC.

Materials and methods

Search strategy and study selection

The search was performed by consulting the electronic database PubMed, the Cochrane Library, and China National Knowledge Infrastructure. Searches included the terms "non-small cell lung cancer" and "Bcl-2". The keywords hit 553 citations. Manual selection of relevant studies was carried out based on the summary analysis. The citation lists of all retrieved articles were scanned to identify other potentially relevant reports.

The following criteria for eligibility among studies were set before collecting articles: 1) Bcl-2 expression was evaluated in primary NSCLC tissue. 2) Survival information at specific times was reported in the article. 3) Follow-up time exceeded 5 years. 4) Articles were published in English and in Chinese. 4) When several articles were published by the same authors or group, the newest or most informative single article was selected. Exclusion criteria were the following: 1) No information on survival was provided, or the hazard ratio (HR) of OS could not be calculated based on the given information. 2) Letters to editor, reviews, and articles published in a book or papers published in non-English. 3) Studies with radiotherapy or concurrent chemoradiotherapy treatment investigating response rates only.

Two authors (SW and JZ) did the search and identification independently, and selection of an article was reached by consensus. The following information was extracted from each report by the two authors independently: year of publication, patient size, time period of patient enrollment, patient source, histology, disease stage, test method, cutoff value, and survival data. If data from any of the above categories were not reported in the primary study, items were treated as "not applicable".

Quality assessment

Quality assessment of each study was performed using the Newcastle–Ottawa Quality Assessment Scale for cohort studies. This scale is an 8-item instrument that allows for assessment of patient population and selection, study comparability, follow-up, and outcome of interest. The scale was recommended by the Cochrane Non-Randomized Studies Methods Working Group. Two investigators (JZ and SW) performed quality assessment independently. Disagreement was resolved by consensus.

Statistical analysis

Analysis of variance was used to compare the means of quality scores between different groups. For quantitative aggregation of survival results, HR and their 95% confidence intervals (CIs) were combined to give the effective value. The HR was calculated from the reported data directly by number of events. If data were presented in the form of Kaplan–Meier survival curve, we extracted them from the survival rates at specified times in order to reconstruct the HR estimate and its variance using methods reported by Parmar et al.[7] Data were entered into the Cochrane Collaboration software, RevMan Version 5.0 for Windows (the Cochrane Collaboration, Oxford, UK). The Cochran's test was used to assess the heterogeneity of included studies. For heterogeneity tests, P-value <0.05 was considered to indicate significance. If the test of heterogeneity was significant ($P<0.05$; $I^2>50\%$), the random-effect model was used. Otherwise, the fixed-effect model was used. By convention, an observed HR of <1 implied a better survival for the group with positive Bcl-2 expression. This impact of Bcl-2 on survival was considered as statistically significant if the 95% CI for the overall HR did not overlap.

Results

Studies selection and characteristics

Five hundred and fifty-three potentially relevant citations were reviewed (Figure 1). Among them, six studies were based on the same patient cohorts. Thus, the less informative ones were excluded (studies excluded were the following: Fontanini et al (1996), Laudanski et al (1995), and O'Byrne et al (2001); studies included were the following: Fontanini et al,[53] Laudanski et al,[35] and Cox et al[37]). Forty papers were review articles, 354 were not clinical studies including signal transduction, cell lines, animals, or

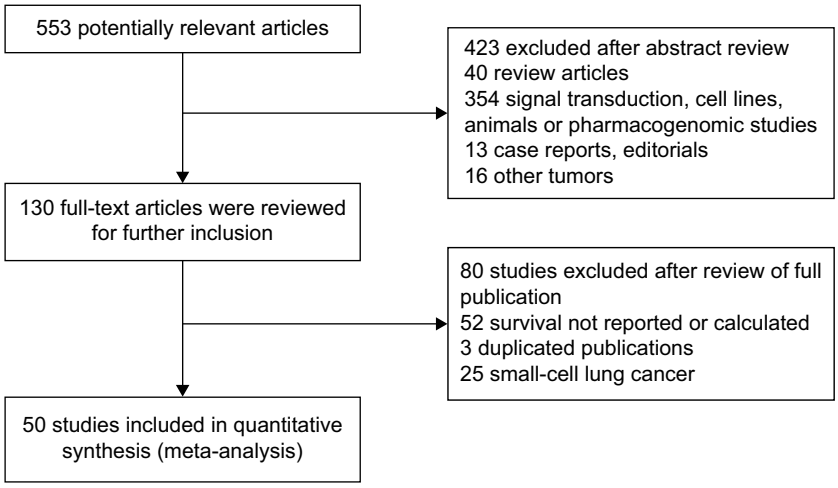


Figure 1 Flow chart of article selection in meta-analysis.
Note: Fifty studies involving 6,863 patients were analyzed.

pharmacogenomic studies, 13 were case reports, and the other 16 papers were designed without lung cancer. Ultimately, 50 studies[3,8–56] that reported the prognostic value of Bcl-2 status for OS were analyzed. The total number of patients included was 6,863, ranging from 24 to 534 patients per study (median, 137). The major characteristics are shown in Table 1. These 50 studies included all lung cancer subtypes (n=46), adenocarcinomas only (n=2), or squamous cell carcinomas (SCCs) only (n=2). Twenty-nine studies had information for stages I–III, eight for advanced-stage (III–IV) disease, and 13 for all stages, I–IV. Forty-eight studies used immunohistochemistry to evaluate Bcl-2 expression, one used reverse transcription polymerase chain reaction, and one used Western blot.

Table 1 Baseline characteristics of the 50 trials used in the meta-analysis

Studies	Year	Patients source	Number of patients	Method	Stage	Study quality points
Cakir et al[8]	2011	Turkey	166	IHC	I–IV	6 out of 9
Anagnostou et al[3]	2010	USA/Greece	534	IHC	I–IV	6 out of 9
Grimminger et al[9]	2010	Germany	91	RT-PCR	I–IIIA	6 out of 9
Jeong et al[10]	2010	Republic of Korea	39	IHC	IIIA–IIIB	5 out of 9
Porebska et al[11]	2009	Poland	30	IHC	I–IV	6 out of 9
Lee et al[12]	2009	Republic of Korea	50	IHC	IIIB–IV	7 out of 9
Renouf et al[13]	2009	Canada	451	IHC	I–II	7 out of 9
Zhao et al[14]	2008	People's Republic of China	62	IHC	I–IIIA	6 out of 9
Yoo et al[15]	2007	Republic of Korea	219	IHC	I–III	6 out of 9
Hu et al[16]	2006	People's Republic of China	88	IHC	I–III	6 out of 9
Wang et al[17]	2006	People's Republic of China	111	IHC	I–III	6 out of 9
Yaren et al[18]	2006	Turkey	69	IHC	I–IV	6 out of 9
Yilmaz et al[19]	2005	Turkey	46	IHC	I–IV	6 out of 9
Groeger et al[20]	2004	USA	76	IHC	I–IV	5 out of 9
Shibata et al[21]	2004	Japan	120	IHC	I–III	7 out of 9
Kren et al[22]	2004	USA	102	IHC	I–IIIA	6 out of 9
Ludovini et al[23]	2004	Italy	85	IHC	IIIA–IV	7 out of 9
Grossi et al[24]	2003	Italy	213	IHC	I–IIIA	5 out of 9
Huang et al[25]	2003	USA	91	WB	I–IV	6 out of 9
Gregorc et al[26]	2003	Italy	102	IHC	IIIA–IV	7 out of 9
Han et al[27]	2003	Republic of Korea	34	IHC	IIIB–IV	6 out of 9
Krug et al[28]	2003	USA	31	IHC	IIIB–IV	8 out of 9
Poleri et al[29]	2003	Argentina	53	IHC	I	8 out of 9
Tomita et al[30]	2003	Japan	60	IHC	IIIA–IV	7 out of 9
Lai et al[31]	2002	Taiwan	114	IHC	I–IIIA	6 out of 9

(*Continued*)

Table 1 (*Continued*)

Studies	Year	Patients source	Number of patients	Method	Stage	Study quality points
Hanaoka et al[32]	2002	Japan	70	IHC	I–III	6 out of 9
Han et al[33]	2002	USA	85	IHC	I	7 out of 9
Hwang et al[34]	2001	Republic of Korea	53	IHC	I–IIIB	6 out of 9
Laudanski et al[35]	2001	Poland	102	IHC	I–IIIA	6 out of 9
Tanaka et al[36]	2001	Japan	162	IHC	I	8 out of 9
Cox et al[37]	2000	USA	178	IHC	I–IIIA	6 out of 9
Moldvay et al[38]	2000	France	226	IHC	I–IV	7 out of 9
van de Vaart et al[39]	2000	the Netherlands	24	IHC	IIIA–IIIB	6 out of 9
Chen et al[40]	1999	Japan	40	IHC	I	7 out of 9
D'Amico et al[41]	1999	USA	408	IHC	I	8 out of 9
Huang et al[42]	1999	Japan	203	IHC	I–IIIB	8 out of 9
Mehdi et al[43]	1999	USA	241	IHC	I–II	6 out of 9
Silvestrini et al[44]	1998	Italy	101	IHC	I–III	7 out of 9
Anton et al[45]	1997	USA	427	IHC	I–IV	8 out of 9
Apolinario et al[46]	1997	the Netherlands	116	IHC	I–IIIA	6 out of 9
Higashiyama et al[47]	1997	Japan	174	IHC	I–IIIB	6 out of 9
Ishida et al[48]	1997	Japan	114	IHC	I–IIIA	6 out of 9
Koukourakis et al[49]	1997	USA	107	IHC	I–IIIA	6 out of 9
Pastorino et al[50]	1997	UK	485	IHC	I	7 out of 9
O'Neill et al[51]	1996	Ireland	54	IHC	I–IV	5 out of 9
Ohsaki et al[52]	1996	Japan	99	IHC	I–IV	6 out of 9
Fontanini et al[53]	1995	Italy	89	IHC	I–IIIA	5 out of 9
Ritter et al[54]	1995	USA	126	IHC	I	7 out of 9
Walker et al[55]	1995	UK	27	IHC	I–IV	6 out of 9
Pezzella et al[56]	1993	UK	115	IHC	I–III	7 out of 9

Abbreviations: IHC, immunohistochemistry; RT-PCR, reverse transcription polymerase chain reaction; WB, Western blot.

In 50 studies evaluating Bcl-2 expression, the proportion of patients exhibiting Bcl-2 overexpression in individual studies ranged from 5% to 71%. Twenty-six out of the 50 studies identified Bcl-2 overexpression as an indicator of positive prognosis; Bcl-2 expression in six studies was significantly associated with poor prognosis. Eighteen studies showed no statistically significant impact of Bcl-2 overexpression on survival.

Quality assessment

We used the Newcastle–Ottawa Scale to perform quality assessment of all 50 studies. Studies that fulfill five or more of the eight criteria were higher quality studies. Overall, the total quality score of the included studies ranged from 5 to 8 (Table 1).

Impact of Bcl-2-positive expression on OS of NSCLC

The effect of Bcl-2 expression on OS was evaluated in 50 studies with a total of 6,863 patients. Overall, Bcl-2 was expressed in 33% of the NSCLCs studied. HRs were calculated from the reported data directly by number of events (25 out of 50), or data reading from Kaplan–Meier survival curve from the survival curves reading (25 out of 50). The combined HR was calculated using a random-effect model, and a value was obtained that was statistically significant (HR 0.79, 95% CI 0.72–0.87, $P<0.00001$), indicating that Bcl-2-positive expression was an indicator of better prognosis.

The data extracted were adequate to aggregate the studies of stage I NSCLC. When we aggregated the eight studies which reported data from 1,432 patients, no heterogeneity was found. The combined HR was not statistically significant (HR 0.93, 95% CI 0.80–1.07, $P=0.50$). Thus, no relationship between Bcl-2 and survival was observed for stage I NSCLC (Figure 2A).

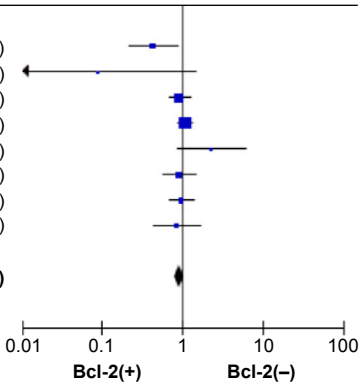
When 29 studies containing 4,390 patients who had received radical surgery (I–III) were considered, highly significant heterogeneity was detected ($\chi^2=92.48$, $P<0.00001$; $I^2=70\%$). The random-effect model was used to perform meta-analysis, and the result was significant in favor of patients with positive Bcl-2 expression (HR 0.77, 95% CI 0.69–0.89, $P<0.0001$) (Figure 2B).

The advanced-stage subgroup included eight studies comprising 425 patients. Because no heterogeneity was found in this subgroup ($\chi^2=7.77$, $P=0.35$; $I^2=10\%$), the fixed-effect model was used to perform meta-analysis. The aggregated survival data also showed a good survival prognosis where

A

Study or subgroup	Bcl-2(+) Events	Total	Bcl-2(–) Events	Total	Weight	Risk ratio M–H, fixed, 95% CI
Apolinario et al[46]	8	37	18	36	8.3%	0.43 (0.22, 0.87)
Chen et al[40]	0	17	7	23	2.9%	0.09 (0.01, 1.46)
D'Amico et al[41]	34	95	122	313	25.8%	0.92 (0.68, 1.24)
Pastorino et al[50]	46	83	206	402	32.0%	1.08 (0.87, 1.34)
Poleri et al[29]	6	16	6	37	1.6%	2.31 (0.88, 6.09)
Ritter et al[54]	17	47	32	79	10.8%	0.89 (0.56, 1.42)
Han et al[33]	23	39	28	46	11.7%	0.97 (0.68, 1.37)
Tanaka et al[36]	8	33	37	129	6.8%	0.85 (0.44, 1.64)
Total (95% CI)		**367**		**1,065**	**100%**	**0.93 (0.80, 1.07)**
Total events	142		456			

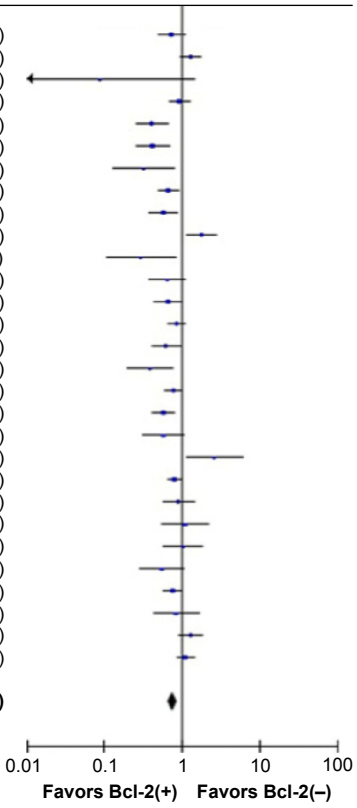
Heterogeneity: χ^2=12.88, *df*=7 (*P*=0.07); I^2=46%
Test for overall effect: *Z*=1.04 (*P*=0.30)



B

Study or subgroup	Bcl-2(+) Events	Total	Bcl-2(–) Events	Total	Weight	Risk ratio M–H, random, 95% CI
Apolinario et al[46]	22	57	31	59	3.9%	0.73 (0.49, 1.10)
Grossi et al[24]	35	69	56	144	4.5%	1.30 (0.96, 1.78)
Chen et al[40]	0	17	7	23	0.2%	0.09 (0.01, 1.46)
D'Amico et al[41]	34	95	122	313	4.5%	0.92 (0.68, 1.24)
Fontanini et al[53]	17	59	21	30	3.5%	0.41 (0.26, 0.65)
Grimminger et al[9]	12	40	36	51	3.3%	0.42 (0.26, 0.70)
Koukourakis et al[49]	4	20	54	87	1.7%	0.32 (0.13, 0.79)
Shibata et al[21]	20	35	73	85	4.6%	0.67 (0.49, 0.90)
Hu et al[16]	18	48	26	40	3.7%	0.58 (0.38, 0.89)
Hwang et al[34]	18	22	14	31	3.7%	1.81 (1.17, 2.80)
Ishida et al[48]	4	43	22	71	1.5%	0.30 (0.11, 0.81)
Yoo et al[15]	9	25	107	194	3.1%	0.65 (0.38, 1.12)
Kren et al[22]	11	21	64	81	3.8%	0.66 (0.43, 1.01)
Lai et al[31]	19	26	75	88	4.9%	0.86 (0.67, 1.10)
Laudanski et al[35]	18	49	31	53	3.7%	0.63 (0.41, 0.97)
Higashiyama et al[47]	7	36	69	138	2.4%	0.39 (0.20, 0.77)
Cox et al[37]	34	62	81	116	4.8%	0.79 (0.61, 1.01)
Pastorino et al[50]	27	83	225	402	4.4%	0.58 (0.42, 0.80)
Pezzella et al[56]	8	25	50	90	2.8%	0.58 (0.32, 1.05)
Poleri et al[29]	8	16	7	37	1.9%	2.64 (1.16, 6.05)
Renouf et al[13]	62	124	203	327	5.2%	0.81 (0.66, 0.98)
Ritter et al[54]	17	47	32	79	3.5%	0.89 (0.56, 1.42)
Hanaoka et al[32]	14	41	9	29	2.4%	1.10 (0.55, 2.19)
Han et al[33]	14	39	16	46	2.9%	1.03 (0.58, 1.84)
Silvestrini et al[44]	8	32	31	69	2.6%	0.56 (0.29, 1.07)
Mehdi et al[43]	37	83	93	158	4.7%	0.76 (0.58, 1.00)
Tanaka et al[36]	8	33	37	129	2.5%	0.85 (0.44, 1.64)
Wang et al[17]	37	59	25	52	4.3%	1.30 (0.92, 1.84)
Zhao et al[14]	28	33	22	29	4.9%	1.12 (0.87, 1.44)
Total (95% CI)		**1,339**		**3,051**	**100%**	**0.77 (0.67, 0.89)**
Total events	550		1,639			

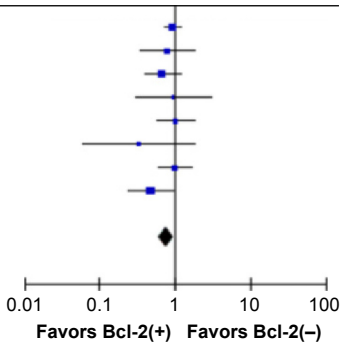
Heterogeneity: τ^2=0.09; χ^2=92.48, *df*=28 (*P*<0.00001); I^2=70%
Test for overall effect: *Z*=3.63 (*P*=0.0003)



C

Study or subgroup	Bcl-2(+) Events	Total	Bcl-2(–) Events	Total	Weight	Risk ratio M–H, fixed, 95% CI
Gregorc et al[26]	7	8	89	94	18.0%	0.92 (0.71, 1.21)
Han et al[27]	5	14	9	20	9.6%	0.79 (0.34, 1.86)
Jeong et al[10]	9	19	14	20	17.6%	0.68 (0.39, 1.18)
Krug et al[28]	2	5	11	26	4.6%	0.95 (0.30, 3.03)
Lee et al[12]	5	8	26	42	10.7%	1.01 (0.56, 1.82)
Ludovini et al[23]	1	4	61	81	7.4%	0.33 (0.06, 1.82)
van de Vaart et al[39]	6	8	12	16	10.3%	1.00 (0.61, 1.63)
Tomita et al[30]	5	12	42	48	21.7%	0.48 (0.24, 0.94)
Total (95% CI)		**78**		**347**	**100%**	**0.74 (0.59, 0.94)**
Total events	40		264			

Heterogeneity: χ^2=7.77, *df*=7 (*P*=0.35); I^2=10%
Test for overall effect: *Z*=2.53 (*P*=0.01)



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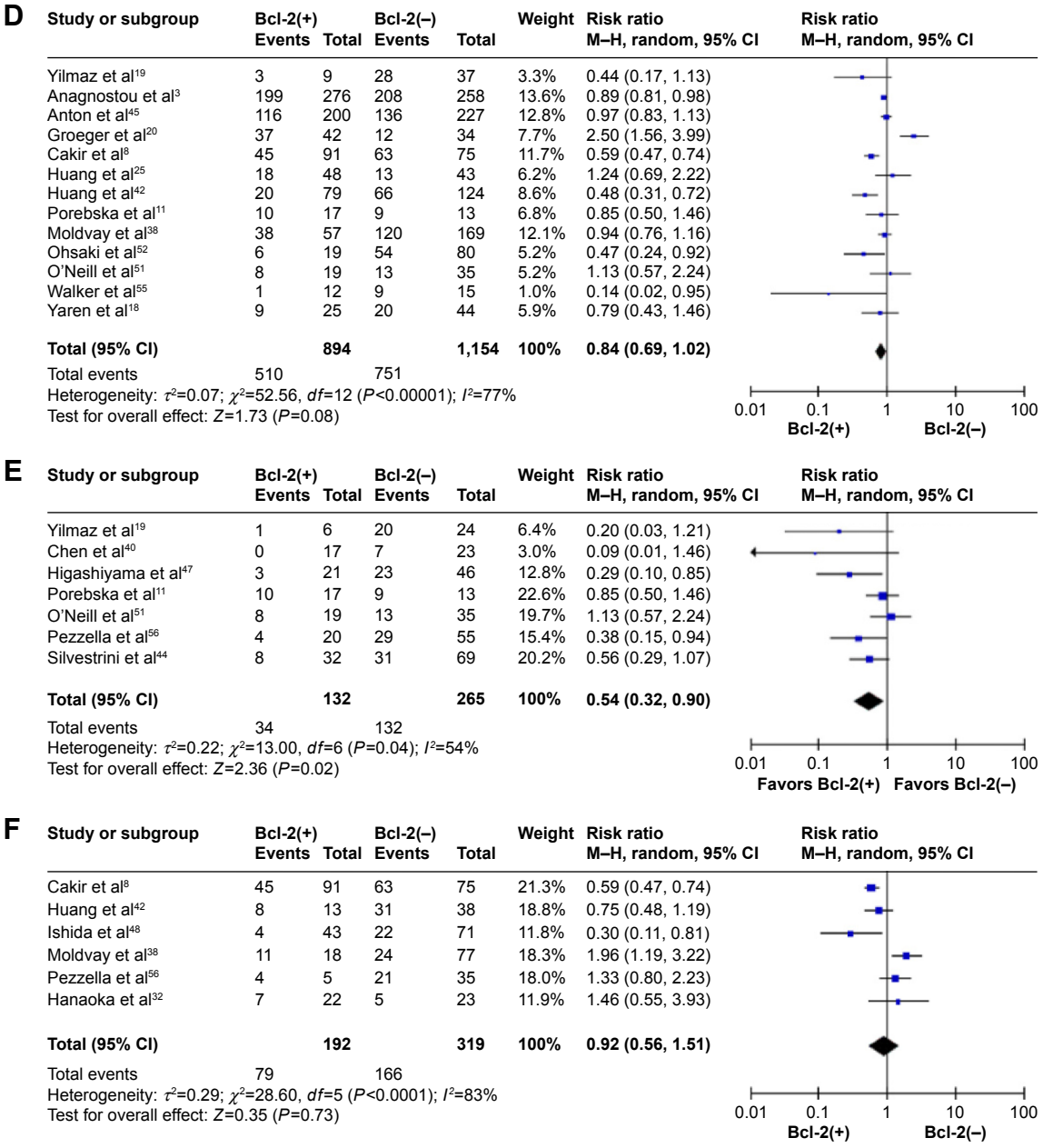

Figure 2 Meta-analysis (Forest plot) of 50 studies assessing Bcl-2 in NSCLC.

Notes: (**A**) Forest plot of stage I group analysis; pooled data from eight studies did not show significant impact on survival with Bcl-2-positive expression compared with those with Bcl-2-negative expression (HR 0.93, 95% CI 0.80–1.07, *P*=0.50). (**B**) Forest plot of stage I–III group analysis; pooled data from 29 studies showed that NSCLC patients with Bcl-2-positive expression have better prognosis than those with Bcl-2-negative expression (HR 0.77, 95% CI 0.69–0.89, *P*<0.0001). (**C**) Forest plot of stage III–IV group analysis; pooled data from eight studies showed that patients with Bcl-2-positive expression have better prognosis than those with Bcl-2-negative expression (HR 0.74, 95% CI 0.59–0.94, *P*=0.01). (**D**) Forest plot of all stage group analysis; pooled data from 13 studies did not show significant impact on survival in patients with Bcl-2-positive expression compared with those with Bcl-2-negative expression (HR 0.84, 95% CI 0.69–1.02, *P*=0.08). (**E**) Forest plot of SCC group analysis; pooled data from seven studies showed that patients with Bcl-2-positive expression have better prognosis than those with Bcl-2-negative expression (HR 0.54, 95% CI 0.32–0.90, *P*=0.02). (**F**) Forest plot of adenocarcinoma group analysis; pooled data from six studies did not show significant impact on survival in patients with Bcl-2-positive expression compared with those with Bcl-2-negative expression (HR 0.92, 95% CI 0.56–1.51, *P*=0.73).

Abbreviations: Bcl-2, B-cell-lymphoma-2; NSCLC, non-small-cell lung cancer; HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma.

there was Bcl-2-positive expression (HR 0.74, 95% CI 0.59–0.94, *P*=0.01) (Figure 2C).

Thirteen studies comprising 2,048 patients were included in the all-stage subgroup. The result of the test for heterogeneity was significant (χ^2=52.56, *P*<0.0001; I^2=77%), and then, the combined HR was calculated using a random-effect model. Bcl-2 expression was not significantly associated with OS (HR 0.84, 95% CI 0.69–1.02, *P*=0.08) (Figure 2D). There were not adequate data to aggregate studies of stage II or III disease.

The data extracted were also adequate to aggregate the studies of SCC and adenocarcinoma for subgroup analyses. When we aggregated seven studies that reported results for SCC, the combined HR was statistically significant (HR 0.54, 95% CI 0.32–0.90, P=0.02) (Figure 2E). We observed no statistically significant effect of Bcl-2 expression on survival in patients with adenocarcinoma, however (HR 0.92, 95% CI 0.56–1.51, P=0.73) (Figure 2F).

There were 32 studies from Europe and USA and 18 from East Asia. The combined HRs of East Asian studies and non-East Asian studies were 0.78 (95% CI 0.63–0.96, $P<0.0001$) and 0.82 (95% CI 0.72–0.92, $P<0.0001$), respectively. In both East Asian and European/USA populations, Bcl-2 expression was an indicator of better prognosis.

Discussion

Identification of prognostic factors allows the definition of high-risk groups of patients for whom further specific therapy might be necessary and stratification should thus be performed in randomized trials.

A previous meta-analysis showed an association between Bcl-2 positivity and better survival of patients with lung cancer.[57] This analysis included 18 NSCLC, three neuroendocrine, and four small-cell lung cancer trials reported from 1993 to 1999. However, data were insufficient to evaluate the prognostic value of Bcl-2 in surgical cases. The effect of Bcl-2-positive expression on specific stage, such as stage I, advanced stages, and adenocarcinomas, was not assessed. We have improved upon that previous meta-analysis by including more recent studies and by generally using a more comprehensive search strategy.

In this meta-analysis, 50 published studies including 6,863 patients with lung cancer were included. Our analysis indicates that NSCLC patients with Bcl-2-positive expression have a better prognosis than those with Bcl-2-negative expression in both East Asian and non-East Asian study populations (HR 0.79, 95% CI 0.72–0.87, $P<0.00001$). However, Bcl-2 expression seems to have no significant impact on survival of stage I NSCLC patients.

The mechanisms through which Bcl-2 might exert its protective effect in NSCLC are unclear. One group demonstrated that Bcl-2 expression showed an association with biologic features, such as the absence of c-erb-B2 and mutant p53 expression, which define a better prognosis.[58] Therefore, although *bcl-2* is a proto-oncogene involved in oncogenesis, because of its ability to prolong cell survival through the inhibition of apoptosis, its expression may be associated with other features that define a more favorable prognosis. Bcl-2 may also suppress the proliferative activity of tumor cells. It has been reported that the proliferative activity of Bcl-2-positive tumors tended to be lower than that in negative tumors.[51] Furthermore, the process of apoptosis involves many proteins such as antiapoptotic proteins (Bcl-2, Bcl-X) and proapoptotic proteins (Bax, Bak, Bad). Thus, it remains to be clarified if other proteins or bcl homologs potentiate the tumor suppressor role of Bcl-2 in NSCLC. Recently, Bcl-2 was found to inhibit DNA replication and DNA repair.[59,60] Due to its dual function, NSCLC patients with Bcl-2-positive expression had a better prognosis than those with Bcl-2-negative expression in both Asian and non-Asian study populations in this analysis.

Some potentially important methodologic biases need to be discussed. When the analysis was limited to eight advanced-stage studies, or eight studies assessing Bcl-2 in stage I subgroup, heterogeneity was not detected. However, heterogeneity was detected when analyses were limited to the 18 East Asian studies or the seven studies including only SCC. Therefore, patient type and histologic type were not a major source of heterogeneity. The heterogeneity in this study could be explained by the stage or by differences in the method used to detect Bcl-2 status. Small sample size was also a source of bias. When the analysis was limited to >100 patients in studies in surgical group, no significant heterogeneity was detected (χ^2=35.29, P=0.01; I^2=46%).

Additional biases could be introduced by the methodology used. We performed a methodological assessment of the studies to avoid selection biases where possible. The comparison of the scores of the three groups (positive, nonsignificant, negative studies) showed no statistically significant difference, allowing a meaningful data aggregation.

In conclusion, Bcl-2-positive expression was associated with a better prognosis in patients with NSCLC, so Bcl-2 might be a useful prognostic marker.[61] However, Bcl-2-positive expression seems to have no significant impact on survival of stage I patients as determined in our meta-analysis. These results should be confirmed by an adequately designed prospective study. Because there was only limited number of patients to test for Bcl-2 expression in platinum-based chemotherapy, these results need to be confirmed by well-designed prospective studies.

Acknowledgments

The authors acknowledge support from the National Natural Science Foundation of China (grant numbers 81101761 and 81172218), Shanghai science and technology commission foundation key project, Longhua Medicial Project (D25), Ministry of Education Returned Scientific Research

Foundation, key project from the Shanghai Municipal Science and Technology Commission Foundation (14JC1401400), Trans-Century Training Programme Foundation for the Talents by the State Education Commission (to JZ), and key technology support project of the field of medicine and agriculture science from Shanghai Municipal Science and Technology Commission (15411951602).

Author contributions

JZ, LW, RW, and HC were involved in concept and design of the study. LW and JZ drafted the manuscript. All authors participated in acquisition, analysis, and interpretation of data, revised the manuscript, and read and approved the final version.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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