Original Article
Prognostic value of survivin in patients with non-Hodgkin's lymphoma: a meta-analysis

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Abstract: Background and objectives: Numerous studies have focused on the role of survivin in non-Hodgkin's lymphomas (NHLs), but evidence regarding the prognostic value of survivin with respect to overall survival (OS) in NHL remains controversial. The aim of this study is to gain a better insight about the direct relationship between survivin expression and patients' survival statuses. Materials and methods: Relevant publications addressing the association between survivin expression and OS in NHL patients were selected from PubMed, Embase, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure Database (CNKI), China Science and Technology Journal Database (VIP), Wanfang Database and the Cochrane library. Studies were pooled and summary hazard ratios (HR) were calculated. Sensitivity analyses and publication bias were also conducted. Statistical analysis was performed by STATA 12.0 software. Results: 12 studies met the inclusion criteria. Combined HRs suggested that survivin overexpression had an unfavorable impact on NHL patients' survival (HR=1.55, 95% CI=1.12-2.13, *P*=0.008). Subgroup analyses according to the studies categorized by histological type, ethnicity, cutoff scores and follow-up period were also conducted, and all the above analyses supported the stability of the prognostic role of survivin. Conclusion: Our findings suggest that survivin high expression might be a poor prognostic factor for patients with NHL. However, further large scale studies are needed to confirm these findings.

Keywords: Non-Hodgkin's lymphoma, survivin, prognosis, meta-analysis

Introduction

Non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of lymphoproliferative malignant diseases with differing patterns of behavior and response to treatment [1]. According to different types of lymphoid cells, NHL is further classified into B-cell lymphomas which account for about 90% and T-cell lymphomas which is about 10% [2]. Although combined chemotherapy has improved the outcome, many patients do not achieve complete remission (CR) and they ultimately relapse. Therefore, the search for biomarkers predicting the evolution of NHL is particularly urgent, so that more appropriate therapies could be designed [3].

Molecular abnormalities of the cell death-cell viability balance have emerged as important prognostic indicators of NHL. A candidate molecule to influence the apoptotic balance in cancer recently identified was survivin, also called baculoviral inhibitor of apoptosis repeat containing 5 (BIRC5), which is a member of the inhibitor of apoptosis (IAP) family. As a 16.5 kDa intracellular protein and expressed in G2/M phase of cell cycle, it is involved in both inhibition of apoptosis and enhancement of proliferation and angiogenesis [4, 5]. It has been reported that large difference in survivin expression exists between normal and malignant tissue [6]. The expression of survivin has been demonstrated to be a promising prognostic indicator, associated with a worse overall survival (OS) in a number of cancers, including carcinomas of breast, lung, colon, bladder, endometrial and prostate [7-12]. In recent years, numerous studies have focused on the role of survivin in NHL [13-24]. However, evidence regarding the prognostic value of survivin with respect to OS in NHL remains controversial. As meta-analysis is an essential tool for accurately and reliably summarizing evidence, we conducted this meta-analysis to gain a better insight about the direct relationship between survivin expression and patients' survival statuses, which, to the

best of our knowledge, has not been previously performed.

Materials and methods

Literature search

Studies were identified via an electronic search of PubMed, Embase, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure Database (CNKI), China Science and Technology Journal Database (VIP), Wanfang Database and the Cochrane library (updated to December 31, 2014) using the following key words: lymphoma, non-Hodgkin's lymphoma, NHL, BIRC5, baculoviral inhibitor of apoptosis repeat-containing 5, survivin, prognostic, prognosis and survival. No language of published papers was restricted. Reference lists from retrieved documents were also searched.

Selection criteria

Studies had to meet the following criteria: (1) full text publication compared the OS between different expressions of survivin in NHL; (2) measured survivin expression in NHL with immunohistochemistry (IHC), reverse transcription-polymerase chain reaction (RTPCR) or fluorescence in situ hybridization (FISH); (3) hazard ratios (HRs) and their 95% confidence intervals (95% CIs) for OS according to survivin status either had to be reported or could be computed from the data presented; (4) to avoid duplicated publications, the most recent report or the most informative one was included. Reviews, conference abstracts or comments were excluded due to insufficient data. We also used a manual reference search for relevant articles, including original articles and reviews, to identify additional studies.

Data extraction

Data were extracted independently by two investigators (H. C and L. Z. G). Disagreements between the reviewers were resolved by consensus. The following data were collected from each article: first author, year of publication, country, number of patients, survivin high/low expression cases, detecting methodology, cutoff, follow-up period, histological type and HR with 95% CI. Some published researches didn't provide HR and 95% CI directly. In that case,

two reviewers (H. C and J. J) independently digitized and extracted the data through the Kaplan-Meier curves by using GetData Graph Digitizer 2.24 (http://getdata-graph-digitizer. com) and then reconstructed the HR and its variance (GraphPad Software, Inc, La Jolla, CA, USA).

Statistical analysis

The HR with its variance estimates (95% CI) was abstracted or calculated to quantitatively evaluate the association between survivin expression and NHL prognosis. High expression of survivin indicated poor prognosis in patients with NHL if HR>1 with the 95% CI did not overlap 1. To assess heterogeneity among the studies, Cochrane's Q test (Chi-squared test) and inconsistency (I^2) statistics were used. Where there is no heterogeneity (P>0.1; I^2<50%), the fixed effects model analysis was made, otherwise, the random effect model should be used. One-way sensitivity analysis was conducted to assess the stability of the results by deleting one study each time to reflect the influence of the individual data set to the pooled HR [25]. The publication bias was tested by Begg's funnel plots. Funnel plot symmetry was further assessed using Egger's linear regression method [26]. For all analyses, a two-sided *P* value less than 0.05 was considered as statistically significant. All analyses were performed by STATA version 12.0 software (Stata Corporation, College Station, TX).

Results

Selection and characteristics of studies

After the initial literature search, a total of 192 potentially relevant citations were retrieved. The title and abstract of relevant articles were read by two authors independently. 155 articles were excluded after the first screening based on abstracts or titles, since they were reviews, abstracts, letters to editor, animal/in vitro studies, duplications, or studies irrelevant to the current topic, leaving 37 studies for detailed evaluation. After carefully reading the full text articles, 25 were excluded for the meta-analysis (6 were duplicate publications; 15 studies were lacking sufficient survival data; 4 investigated efficacy of survivin suppressants not correlation with survivals). As a result, 12 eligible studies including 885 NHL cases were

Table 1. Characteristics and results of eligible prognostic studies evaluating surviving

First author, year	Country	N. of Patient	Method	Histological type	Duration of follow-up	N. of Positive	Cutoff value	Staining pattern	OS		
									HR Estimate	HR	95% CI
Bedewy AM, 2013	Egypt	80	IHC	B cell NHL	30	32	30%	Nuclear staining	Sur. Curve	0.79	0.15-4.06
Guo RZ, 2003	China	62	IHC	B cell NHL	48	19	5%	Cytoplasmic staining	Sur. Curve	1.41	0.91-2.18
Huang HQ, 2006	China	83	IHC	T cell NHL	76	73	25%	NA	Sur. Curve	0.62	0.17-2.21
Karabatsou K, 2006	UK	44	IHC	B/T cell NHL	90	28	Scores >2	Nuclear staining	HR 95% CI	0.57	0.29-1.13
Li B, 2008	China	83	IHC	B/T cell NHL	70	52	5%	Cytoplasmic staining	Sur. Curve	3.73	1.7-8.18
Li JF, 2006	China	60	IHC	T cell NHL	96	NA	30%	Nuclear staining	Sur. Curve	2.12	1.2-3.77
el Aziz LM, 2014	USA	46	IHC	B/T cell NHL	24	33	10%	Cytoplasmic staining	Sur. Curve	29.21	Not applicable
Paydas S (a), 2009	Turkey	77	IHC	DLBCL	160	40	NA	NA	Sur. Curve	1.76	0.75-4.13
Paydas S (b), 2008	Turkey	117	IHC	B/T cell NHL	160	74	NA	NA	Sur. Curve	2.22	0.67-7.36
Yang WJ, 2008	China	52	IHC	B/T cell NHL	120	30	NA	Nuclear or cytoplasmic staining	Sur. Curve	1.58	0.71-3.51
Zhang HY, 2010	China	128	IHC	DLBCL	88	84	5%	Cytoplasmic staining	Sur. Curve	1.85	1.15-2.97
Zhang ZJ, 2011	China	53	IHC	DLBCL	101	45	Scores >3	Nuclear or cytoplasmic staining	Sur. Curve	2.26	0.27-19.2

N, number; IHC; DLBCL, diffuse large B cell non-Hodgkin's lymphoma; NA, no available; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 2. Summarized HRs of subgroup analyses for survivin on NHL survival

	N. of studies	Effect model	HR (95% CI)	Heterogeneity test	
				I^2	P-value
Overall	11	Random	1.55 (1.12-2.13)	44.8%	0.053
Ethnicity					
Asian	7	Fixed	1.77 (1.39-2.26)	21.2%	0.268
Non-Asian	4	Random	1.11 (0.54-2.29)	50.7%	0.107
Histological type					
B cell NHL	5	Fixed	1.59 (1.19-2.13)	0.0%	0.821
T cell NHL	2	Random	1.32 (0.41-4.26)	66.0%	0.086
Cutoff value					
5%	3	Random	1.95 (1.21-3.11)	55.7%	0.104
10%	3	Fixed	1.61 (0.98-2.65)	46.4%	0.155
Staining pattern					
Nuclear	3	Random	1.04 (0.38-2.85)	76.9%	0.013
Cytoplasmic	3	Random	1.95 (1.21-3.11)	55.7%	0.104
Duration of follow-up					
<90 months	5	Random	1.64 (1.03-2.61)	49.1%	0.097
≥90 months	6	Random	1.47 (0.89-2.43)	49.1%	0.080

N, number; HR, hazard ratio; 95% CI, 95% confidence interval.

included in this meta-analysis [13-24]. The main characteristics of studies enrolled are summarized in **Table 1**. Briefly, sample sizes ranged from 44 to 128. Among the 12 studies, 5 were from Europe and 7 were from Asia. The mean follow-up period for the studies was 88.58 months, ranging from 24 to 160 months. 5 studies reported B cell NHL, 3 of which focused on DLBCL only. 2 studies were about T cell NHL and the rest 5 compared the OS between different expressions of survivin in both T and B cell NHL. All the studies investigated survivin by IHC. 4 of the 12 included studies identified survivin high expression as a significant poor prognostic factor, whereas the other 8 studies reported that survivin high expression had no significant association with NHL prognosis.

Meta-analysis results

The main results of this meta-analysis are summarized in **Table 2**. 11studies had sufficient data for estimating HR and 95% CI, including 839 patients. As shown in **Figure 1**, using fixed-effect model, survivin high expression was a prognostic factor for poor survival in NHL patients (HR=1.55, 95% CI=1.12-2.13, P=0.008). Our results indicated that survivin

was an independent prognostic factor in patients with NHL.

We also conducted subgroup analyses based on histological type, ethnicity, cutoff scores and follow-up period. When grouped according to the histological type, the combined HR was 1.59 (95% CI: 1.19-2.13) for B cell NHL and 1.32 (95% CI: 0.41-4.26) for T cell NHL. Stratified by ethnicity, the combined HR of the 7 studies in Asian population indicated that patients with survivin high expression had a risk of death 1.77 times greater than patients without survivin high expression (HR=1.77, 95% CI: 1.39-2.26). However, no such statistical significant death risk when pooling the 4 trials conducted in non-Asian populations (HR=1.11, 95% CI: 0.54-2.29). In the subgroup analysis according to the positive threshold for survivin expression, as defined by the studies' authors, the combined HRs of 5% and 10% cutoff value were 1.95 (95% CI: 1.21-3.11) and 1.61 (95% CI: 0.98-2.65), separately. Furthermore, we aggregated the studies separately according to survivin staining pattern, the summary HR of the studies defining nuclear staining as positive was 1.04 (95% CI: 0.38-2.85). The combined HRs were 1.95 (95% CI: 1.21-3.11) based on studies defining cytoplasmic staining as positive. Finally, in the subgroup analysis based on the follow-up period, the combined HR was 1.64 (95% CI: 1.03-2.61) for studies of shorter follow-up period (<90 months) and 1.03 (95% CI: 0.89-2.43) for those of longer follow-up period (≥90 months).

Sensitivity analyses and publication bias

Sensitivity analyses were performed by omitting one study per time to check if individual study affected the final results. All the results were not materially altered. The Egger's test and Begg's funnel plot were applied to detect publication bias in the meta-analysis. In all included studies, there was no funnel plot asymmetry observed, with P=0.78 in the
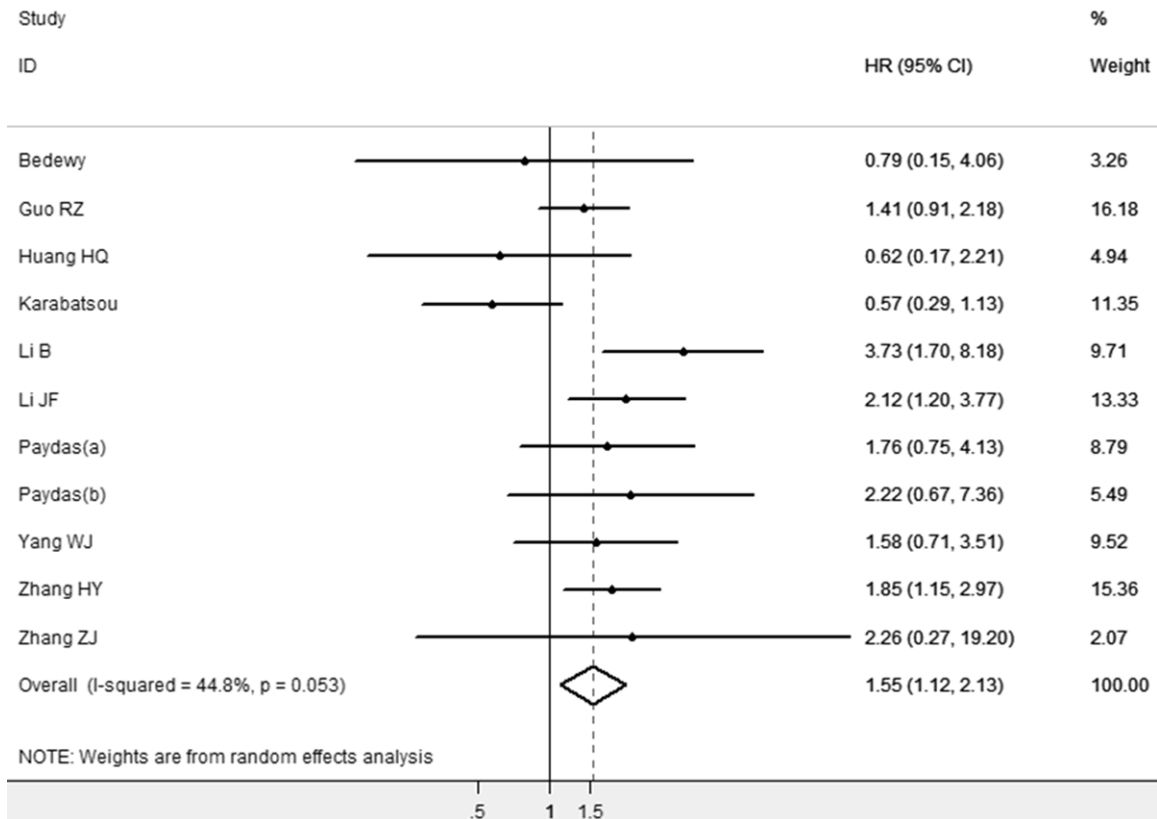
Figure 1. The association between survivin overexpression and overall survival of NHL stratified by HR estimation. The summary HR and 95% CIs were shown (according to the random effect estimations).

Egger's test (**Figure 2**), indicating no evidence of significant publication bias.

Discussion

Survivin, as a biomarker of prognosis in malignancies, has attracted much interest. Although the prognostic role of survivin in NHL has been investigated over the past decade, the results were still conflicting. Therefore, we performed the present meta-analysis to summarize all of the available researches on the impact of the survivin on the survival of NHL, which to the best of our knowledge, has not been previously performed.

By pooling all the studies which compared the survival outcomes of NHL patients according to expression status of survivin, our meta-analysis showed promising prognostic value of survivin detected in tumor samples for OS of NHL. Patients with elevated survivin expression had 1.55 times higher risk of poor prognosis, compared with those without high survivin expression. Moderately significant heterogeneity was

found in this meta-analysis (I^2=44.8%, P= 0.053) for OS. Most of the included studies were retrospective and differed in their study designs, adding the heterogeneity between studies. So we performed the analysis using random-effects model which considers the between-study heterogeneity. Moreover, a stratified subgroup analysis was performed to reduce the heterogeneity. As in the subgroup analyses for OS, the results suggested that survivin was a poor prognostic indicator in Asian population, but not in non-Asian population. When stratified analysis was conducted about different histological type of NHL, the associations were also found in B cell NHL, but not in T cell NHL. However, the small number of studies about T cell NHL might bring bias, which could partly explain the disparity. When cutoff scores was taken into account, a dismal impact on survival was observed by using 5% cutoff value, whereas studies using 10% cutoff value combined didn't get a similar conclusion, indicating that lower level of cutoff score, 5% for example, would be more helpful leading to a differential
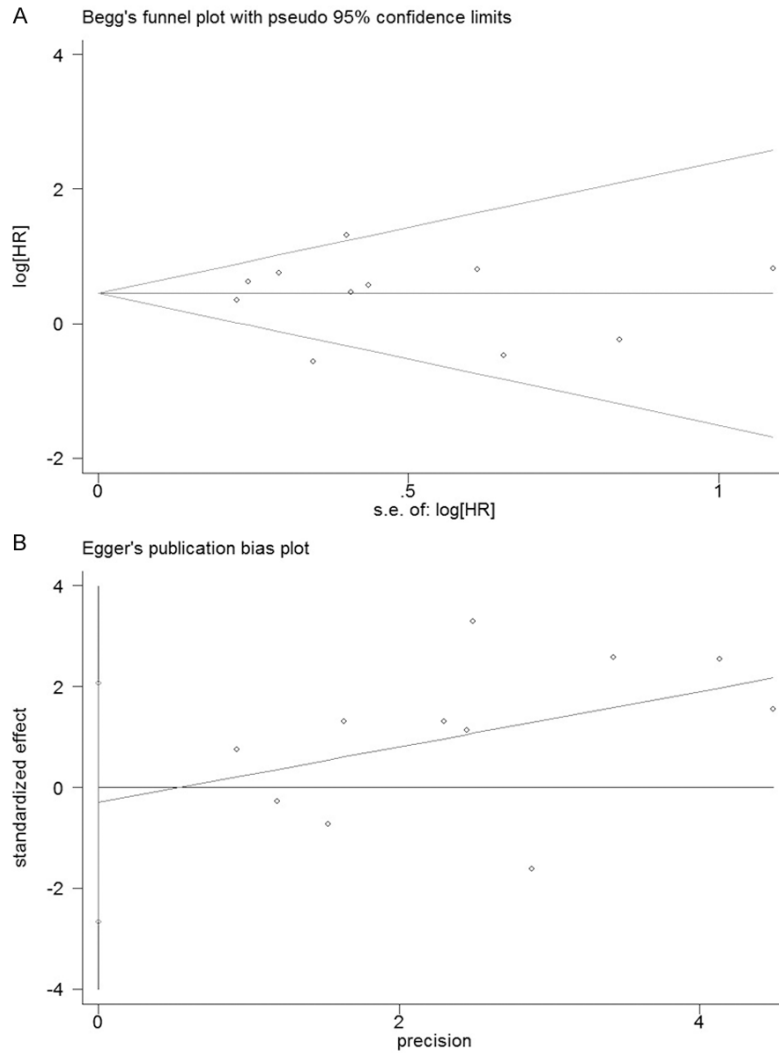
Figure 2. Funnel plots of Begg's (A) and Egger's (B) to detect publication bias on overall estimate.

conclusion. Immunolocalization of survivin also reflected different clinical significance. Cytoplasmic overexpression correlated with patients' poor survival, while nuclear expression was not an independent marker for patient survival, suggesting that survivin overexpression locating on cytoplasm but not on nuclear was probably a useful marker to predict clinical outcome of NHL patients. Moreover, we found that the association was significant for studies of shorter follow-up period (<90 months), while no significant association was observed for studies of follow-up period ≥90 months.

To interpret the results of the present meta-analysis, some limitations should be taken into account. First of all, although we tried to iden-

tify all relevant data, potential publication and reporting bias were unavoidable since unpublished papers, abstracts and letters to the editor were not taken into account, and positive results tend to be more acceptable by journals. Second, the small sample-sized studies might be vulnerable to selection bias and no RCTs had been found. Third, NHL patients had received different treatments and different therapies especially targeted therapies may influence the survival of NHL. Nevertheless, the majority of published studies lacked required data regarding patient treatment and all these sources of variability could produce additional inconsistencies and cause potential selection bias [27]. Therefore, our results need to be evaluated by further prospective randomized controlled trials. Fourth, most survival outcomes were calculated from Kaplan-Meier curves, which may have introduced some imprecision. In addition, el Aziz LM's study did not provide sufficient OS data for meta-analysis. The missing information showed "positive"association of survivin with NHL survival that might increase the significance of survivin expression as a predictor of OS in NHL. Finally, our study was based on published literatures, which limited us to correct the potential confounding factors [28]. Thus, appropriate multivariate analysis should be performed to examine whether survivin is a prognostic factor, independently of as known clinical factors, such as age, sex, differentiation, stages, and performance status.

Apart from its prognostic role, survivin might also be an attractive target for the development of anticancer therapies. In the past few

years, many investigations have been performed to develop survivin antagonists as the targeted therapy agents aiming at eliminating tumor cells and sparing normal tissues at the same time [29]. A recent clinical trial of YM155 (a small molecule survivin suppressant) showed that it was well tolerated and have a role in combination strategies with the potential to improve the outcome of patients with NHL [30]. Meanwhile, it is worth mentioning that several other members of the IAP family have been investigated for their role in different tumors. Xi et al demonstrated that high expression levels of both Survivin and Livin may influence the prognosis of human colorectal cancer [31]. The results of Chen's study showed that the expression of IAPs acted cooperatively to predict prognosis in human bladder cancer patients [32] and may be a potential multitarget of gene therapy [33-35]. Further analysis about the prognostic role of survivin with other members of IAPs for NHL patients is needed.

In conclusion, despite of the above limitations, the combined data of our meta-analysis demonstrated that survivin high expression might be a poor prognostic factor for patients with NHL. However, these findings had to be interpreted with caution when used in clinical practice, since the reported associations were diverse. Larger well-designed prospective cohort studies are still needed to further evaluate the association between survivin and the survival of patients with NHL.

Acknowledgements

Disclosure of conflict of interest

None.

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