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Research article

Yin Yang 1 expression predicts a favourable survival in diffuse large B-cell lymphoma

Tian Xue [a,b,#], Jia-Xin Lin [a,b,#], Ya-Qi He [a,b], Ji-Wei Li [a,b], Ze-Bing Liu [a,b], Yi-Jun Jia [a,b], Xiao-Yan Zhou [a,b], Xiao-Qiu Li [a,b], Bao-Hua Yu [a,b,*]

[a] Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China
[b] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

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ABSTRACT

Aims: Yin Yang 1 (YY1) is a multifunctional transcription factor that plays an important role in tumour development and progression, while its clinical significance in diffuse large B-cell lymphoma (DLBCL) remains largely unexplored. This study aimed to investigate the expression and clinical implications of YY1 in DLBCL.

Methods: YY1 expression in 198 cases of DLBCL was determined using immunohistochemistry. The correlation between YY1 expression and clinicopathological parameters as well as the overall survival (OS) and progression-free survival (PFS) of patients was analyzed.

Results: YY1 protein expression was observed in 121 out of 198 (61.1 %) DLBCL cases. YY1 expression was significantly more frequent in cases of the GCB subgroup than in the non-GCB subgroup ($P = 0.005$). YY1 was positively correlated with the expression of MUM1, BCL6, pAKT and MYC/BCL2 but was negatively associated with the expression of CXCR4. No significant relationships were identified between YY1 and clinical characteristics, including age, sex, stage, localization, and B symptoms. Univariate analysis showed that the OS ($P = 0.003$) and PFS ($P = 0.005$) of patients in the YY1-negative group were significantly worse than those in the YY1-positive group. Multivariate analysis indicated that negative YY1 was a risk factor for inferior OS ($P < 0.001$) and PFS ($P = 0.017$) independent of the international prognostic index (IPI) score, treatment and Ann Arbor stage. Furthermore, YY1 is more powerful for stratifying DLBCL patients into different risk groups when combined with MYC/BCL2 double-expression (DE) status.

Conclusions: YY1 was frequently expressed in DLBCL, especially in those of GCB phenotype and with MYC/BCL2-DE. As an independent prognostic factor, YY1 expression could predict a favourable outcome in DLBCL. In addition, a complex regulatory mechanism might be involved in the interactions between YY1 and MYC, pAKT as well as CXCR4 in DLBCL, which warrants further investigation.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), representing almost 40 % of

* Corresponding author. Department of Pathology, Fudan University Shanghai Cancer Center, 270 Dong'an Road, Shanghai, 200032, China.
E-mail address: yubh2014@163.com (B.-H. Yu).
# Tian Xue and Jia-Xin Lin contributed equally to the study and are co-first authors of this paper.

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NHL cases. Although the rituximab (R) plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen has been demonstrated to significantly improve the survival of DLBCL patients [1], approximately 30 %–40 % of patients fail to achieve complete response or suffer from early relapse [2]. More effective biomarkers with high repeatability and refined predictive power are needed to stratify patients for precise treatment.

Yin Yang 1 (YY1) is a multifunctional transcription factor that plays an important role in numerous biological functions. Considerable data have indicated the overexpression of YY1 in various malignancies, including osteosarcoma [3] and cancers of the prostate [4], colon [5], breast [6] and cervix [7]. However, the prognostic significance of YY1 varies among different cancers [8–10]. There is increasing evidence that YY1 can recruit either coactivators or corepressors, which may account for its biphasic transcriptional functions and contrary clinical prognostic relevance in different malignancies.

The expression and function of YY1 in haematopoietic malignancies are insufficiently elucidated, although a few studies have revealed that YY1 is highly expressed in Burkitt lymphoma [11], follicular lymphoma (FL) and DLBCL [12]. Sakhinia et al. once reported the high expression of YY1 in both DLBCL (n = 25) and FL (n = 63) compared with reactive lymph nodes, although the case series was relatively small [12]. Castellano et al. found that overexpression of YY1 was much more frequent in high-grade B-NHLs (including Burkitt lymphoma and DLBCL) than in low-grade B-NHLs and normal B cells, indicating that YY1 may be involved in the malignant transformation of B cells [13]. Additionally, Ramkumar et al. demonstrated that YY1 could promote the proliferation of DLBCL cells and that YY1 could be degraded by Smad ubiquitination regulatory factor-2 (Smurf2)-mediated ubiquitination, suggesting a therapeutic target in DLBCL [14]. Recently, Morales-Martinez and colleagues revealed that YY1 positively regulated the expression of Krüppel-Like Factor 4 (KLF4), a transcription factor regulating the cell cycle of B cells, and YY1 and KLF4 may induce the progression of B-cell lymphoma [15]. Furthermore, YY1 and KLF4 were negatively regulated by microRNA-7, and downregulation of microRNA-7 could further promote the migration and chemoresistance of NHL in vitro, indicating that YY1 could be a potential therapeutic target in NHL [16]. Nevertheless, to the best of our knowledge, the expression of YY1 in DLBCL has never been thoroughly investigated, and its clinical relevance as well as prognostic value is largely unknown.

Herein, we aimed to investigate the expression of YY1 in a large series of DLBCLs and to elucidate its relevance with important clinicopathological parameters and prognosis in DLBCL.

2. Materials and methods

2.1. Case selection and tissue microarray (TMA) construction

A total of 205 DLBCL cases newly diagnosed between January 2005 and August 2011 were collected from the archival files of the Pathology Department, Fudan University Shanghai Cancer Center. The pathological diagnosis was confirmed by two pathologists (TX and BHY) independently according to the World Health Organization classification criteria [17,18]. Based on five clinical factors (age>60 years, serum LDH > normal, performance status 2–4, stage III or IV and extranodal involvement>1 site), the international prognostic index (IPI) scores were calculated. Patients were then divided into a low IPI risk group (0–2) and a high IPI risk group (3–5) [19]. Clinical information, including sex, age, stage, location, B symptoms, and treatment was collected. The CHOP and CHOP-like treatment regimens are classified as anthracycline-based regimen. If rituximab is added to the above strategies, it is classified as R-anthracycline-based regimen. Follow-up data were obtained from medical records and telephone inquiries.

A TMA was constructed by taking two representative 0.6-mm tissue cores from each block using a tissue arrayer (Beecher Instruments, Silver Spring, MD, USA). Sections (4 μm thick) were then cut from TMA blocks, stained with H&E and submitted for immunohistochemical procedures.

2.2. Immunohistochemistry (IHC)

The IHC analysis was carried out using a Ventana Bench Mark ultra autostainer (Ventana Medical System Inc., Roche Tuson, AZ, USA) and the Ventana ultra view universal DAB detection kit. IHC staining of YY1 (EPR4652, 1:100 dilution, Abcam), CXCR4 (UMB2, 1:100 dilution, Epitomics) and phospho-AKT (Ser473) (D9E, 1:150 dilution, Cell Signaling Technology) was performed. Other primary antibodies, including CD10 (MX002, MXB), BCL6 (LN22, Lecia), MUM1 (MUM1P, Dako), BCL2 (SP66, Roche), and MYC (Y69, 1:100 dilution, Abcam), were also included in the present study. CD10, BCL6, MUM1 and BCL2 were ready-to-use antibodies. For each antibody, the cases with already known positive reaction were used as positive controls, and PBS was used instead of primary antibodies for negative control. YY1 expression was scored using the following standards: negative (0), <10 % of the tumour cells stained positive; weakly positive (+1), 10%–25 % of the tumour cells stained positive; moderately positive (+2), 25%–75 % of the tumour cells stained positive; and strongly positive (+3), >75 % of the tumour cells stained positive [20]. Based on previously described scoring methods with a slight modification, pAKT and CXCR4 expression was scored according to the staining intensity (0, negative; 1, weak; 2, moderate; 3, strong staining) and the percentage of positive tumour cells (0, less than 5 %; 1, 5%–25 %; 2, 26%–50 %; 3, 51%–75 %; 4, 76%–100 % positively stained tumour cells), and the final score was obtained by multiplying these two. A final score of ≥2 was defined as positive [21,22]. The thresholds considered in our study for CD10, BCL6, MUM1, BCL2 and MYC were consistent with the WHO-defined thresholds [17].

The IHC results of the entire TMA were evaluated by two authors (TX and BHY) independently. Discordant cases were re-examined under a multiheaded microscope and discussed to reach a final consensus. DLBCLs were divided into germinal centre B (GCB)-cell-like subtype and non-GCB subtype based on the expression of CD10, BCL6 and MUM1, according to Hans' algorithm [23]. Cases were designated as double-expression (DE) if MYC protein was positive in ≥40 % and BCL2 was positive in ≥50 % of neoplastic cells [17].

2.3. Statistical analysis

Overall survival (OS) was defined from the date of initial diagnosis to death from any cause or last follow-up. Progression-free survival (PFS) was calculated from the date of initial diagnosis to disease progression, relapse, death or last follow-up. The survival curves of OS and PFS were generated using the Kaplan–Meier method and the log-rank test. Multivariate analysis was carried out with Cox proportional hazard regression analysis. Correlations between groups of categorical variables were analyzed with the chi-square test, Pearson test, and Spearman test. In the analysis of the Gene Expression Omnibus (GEO) database, the optimal cut-off value of the YY1 mRNA level was established based on X-tile software (version 3.6.1; Yale University School of Medicine, New Haven, CT, USA). SPSS software (SPSS version 20.0; SPSS Inc., Chicago IL, USA) was used for statistical analysis. A two-tailed *P* value of less than 0.05 was considered statistically significant.

Table 1
Correlation analysis between YY1 protein expression and clinicopathological variables in DLBCL.

	Total cases (n = 198)	YY1 expression (%)	P-value
Age			
>60years	78	51 (65.4)	0.320
≤60years	120	70 (58.3)	
Sex			
Male	118	72 (61.0)	0.974
Female	80	49 (61.3)	
Location			
Nodal	135	85 (63.0)	0.437
Extranodal	63	36 (57.1)	
Stage			
I-II	112	71 (63.4)	0.619
III-IV	72	43 (59.7)	
NA	14		
B symptoms			
With B symptoms	95	52 (54.7)	0.090
Without B symptoms	99	66 (66.7)	
NA	4		
IPI score			
0-2	142	88 (62.0)	0.746
3-5	37	24 (64.9)	
NA	19		
Subgroup			
GCB	98	69 (70.4)	0.005
Non-GCB	95	48 (50.5)	
NA	5		
BCL2 expression			
Positive	125	83 (66.4)	0.032
Negative	69	35 (50.7)	
NA	4		
BCL6 expression			
Positive	120	93 (77.5)	<0.001
Negative	73	24 (32.9)	
NA	5		
MYC expression			
Positive	93	82 (88.2)	<0.001
Negative	99	37 (37.4)	
NA	6		
DE status			
DE	72	66 (91.7)	<0.001
non-DE	119	53 (44.5)	
NA	7		
MUM1 expression			
Positive	61	53 (86.9)	<0.001
Negative	137	68 (49.6)	
pAKT expression			
Positive	140	96 (68.6)	0.001
Negative	58	25 (43.1)	
CXCR4 expression			
Positive	113	58 (51.3)	0.001
Negative	85	63 (74.1)	

DLBCL, diffuse large B-cell lymphoma; NA, not available; GCB, germinal center B; DE, double-expression.

3. Results

3.1. Clinical and pathological findings

In our series, 7 cases were failed to be investigated because of the tissues' dropping off during the conduction of immunostaining, and therefore 198 DLBCL cases were recruited in the current study. The clinicopathological characteristics of these 198 cases are summarized in Table 1. There were 118 male and 80 female patients, with a male-to-female ratio of 1.5:1. The median age at diagnosis was 57 years (range, 16–86 years), with 39.4 % (78/198) of patients older than 60 years. Primary nodal disease accounted for 68.2 % (135/198) and stage I-II accounted for 60.9 % (112/184) of the total cases. Patients with B symptoms (95/194, 49.0 %) were nearly equivalent to those without B symptoms (99/194, 51.0 %). The majority of patients (142/179, 79.3 %) had low IPI scores (0–2). Phenotypically, the frequencies of the GCB subtype (98/193, 50.8 %) and the non-GCB subtype (95/193, 49.2 %) were similar. In addition, 37.7 % (72/191) of the total cases were classified as DE.

Treatment information was available for 168 patients. Among them, 96 patients received an anthracycline-based regimen, whereas 68 patients received an R-anthracycline-based regimen, and the remaining four patients were treated with other strategies, including the RESHAP (rituximab plus etoposide, cytarabine, cisplatinum and methylprednisolone) regimen and the MINE (mitoxantrone, mesna/ifosfamide and etoposide) regimen.

3.2. YY1 protein expression and its clinicopathological correlation analysis

YY1 expression was observed in 61.1 % (121/198) of DLBCL cases with nuclear staining (Fig. 1A–D). As shown in Table 1, YY1 expression was significantly more frequent in GCB cases (69/98, 70.4 %) than in non-GCB cases (48/95, 50.5 %) ($P = 0.005$). The

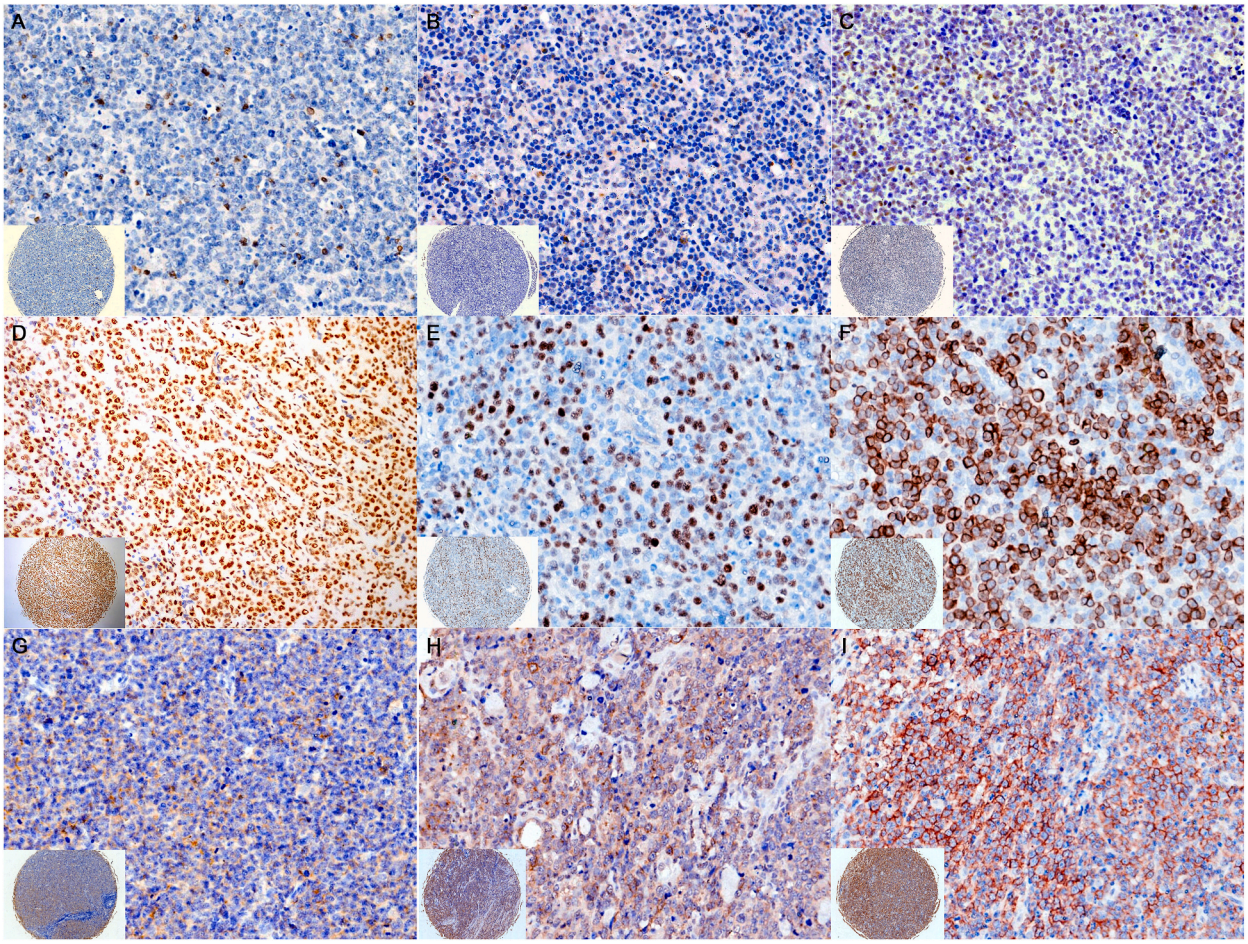

Fig. 1. Representative IHC stainings of different markers in DLBCL (magnification, × 200). (A–D) Represented negative, weakly positive, moderately positive and strongly positive staining of YY1, respectively. (E) MYC was positively stained in more than 40 % of tumor cells. (F) BCL2 staining demonstrated that >50 % of neoplastic cells were positive. (G–I) Represented weakly positive, moderately positive and strongly positive staining of CXCR4, respectively.

expression of YY1 protein showed statistically significant associations with the expression of BCL2 ($P = 0.032$), BCL6 ($P < 0.001$), MYC ($P < 0.001$) and MUM1 ($P < 0.001$) (Fig. 1E and F). Furthermore, the proportion of YY1-positive cases was strikingly higher in cases with DE status (66/72, 91.7 %) than in their counterparts (53/119, 44.5 %) ($P < 0.001$). YY1 expression was also positively correlated with pAKT ($P = 0.001$), whereas more frequently observed in CXCR4-negative cases (63/85, 74.1 %) than in CXCR4-positive cases (58/113, 51.3 %) ($P = 0.001$) (Fig. 1, G-I). There was no significant correlation between YY1 protein expression and the age, sex, stage, location, IPI score and B symptoms of patients in the current DLBCL series (all $P > 0.05$). (Table 1, Supplement Fig. 1).

3.3. Prognostic relevance analysis of YY1 expression

Follow-up information was available for 185 patients in our series, with a median follow-up time of 44 months (range, 0.5–128 months). The results of the OS and PFS analyses are summarized in Table 2. In the YY1-negative group, 50.0 % (35/70) of the patients died, compared with 27.8 % (30/115) of the patients in the YY1-positive group ($P = 0.003$) (Fig. 2A). The PFS rate of patients in the YY1-positive group (70/115, 60.9 %) was superior to that in the YY1-negative group (27/70, 38.6 %) ($P = 0.005$) (Fig. 2B). Univariate analysis revealed that negative YY1, advanced Ann Arbor stage, B symptoms and high IPI score were associated with lower OS rates; negative YY1, advanced Ann Arbor stage, high IPI score and BCL6-negative status were associated with lower PFS rates. Besides, there were significant differences in OS ($P = 0.016$) and PFS ($P < 0.001$) between patients receiving anthracycline-based regimen with or without R. The prognostic value of YY1 in different treatment groups was investigated thereafter. As shown in Table 3 and Fig. 3, among the patients receiving anthracycline-based regimen, the patients with positive-YY1 had significantly higher OS rate ($P = 0.009$) (Fig. 3A) and PFS rate ($P = 0.013$) (Fig. 3B) than those with negative-YY1. Among the patients receiving R-anthracycline-based regimen, YY1-positive group also had a trend for superior survival than YY1-negative group, although the differences in OS ($P = 0.181$) (Fig. 3C) and PFS ($P = 0.084$) (Fig. 3D) rates were not statistically significant.

Further multivariate analysis confirmed that negative YY1 was an independent risk factor for both inferior OS ($P < 0.001$) and PFS ($P = 0.017$). In addition, Ann Arbor stage III-IV and high IPI score were also independent predictors for both inferior OS and PFS (all $P < 0.05$). Treatment regimen was an independent prognostic factor for OS ($P = 0.022$), but not PFS ($P = 0.666$). (Table 2).

As a further validation, survival analysis was conducted using the series of DLBCL in the GEO database (GSE10846). A cut-off value

Table 2
Clinicopathological data and survival analysis in our DLBCL series.

		Overall survival		Progression free survival	
	Patients (%)	Univariate analysis P-value	Multivariate analysis P-value HR (95 % CI)	Univariate analysis P-value	Multivariate analysis P-value HR (95 % CI)
Male	109/185 (58.9)	0.311		0.216	
Age>60years	72/185 (38.9)	0.340		0.192	
Nodal site	127/185 (68.6)	0.738		0.853	
Ann Arbor stage III-IV	70/179 (39.1)	<0.001	0.038 2.057 (1.042–4.062)	<0.001	0.008 2.086 (1.215–3.581)
With B symptoms	87/184 (47.3)	0.001	0.052 1.754 (0.995–3.091)	0.087	
IPI >2 scores	37/179 (20.7)	<0.001	0.002 2.979 (1.503–5.903)	<0.001	0.046 1.816 (1.010–3.266)
Treatment		0.016	0.022 0.502 (0.279–0.906)	<0.001	0.666 0.903 (0.569–1.434)
anthracycline-based regimen	96/168 (57.1)				
R-anthracycline-based regimen	68/168 (40.5)				
others	4/168 (2.4)				
GCB subgroup	91/180 (50.6)	0.703	0.046 0.552 (0.308–0.989)	0.695	0.032 0.471 (0.237–0.936)
BCL2 positive	118/181 (65.2)	0.207		0.213	
BCL6 positive	113/180 (62.8)	0.069		0.006	0.056 0.485 (0.230–1.020)
MYC positive	87/179 (48.6)	0.262		0.075	
DE status	69/178 (38.8)	0.590		0.392	
MUM1 positive	56/185 (30.3)	0.342		0.865	
pAKT positive	132/185 (71.4)	0.723		0.794	
CXCR4 positive	104/185 (56.2)	0.203		0.246	
YY1 positive	115/185 (62.2)	0.003	<0.001 0.360 (0.204–0.635)	0.005	0.017 0.523 (0.308–0.889)

DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; CI, confidence interval; R, Rituximab; GCB, germinal center B; DE, double-expression.

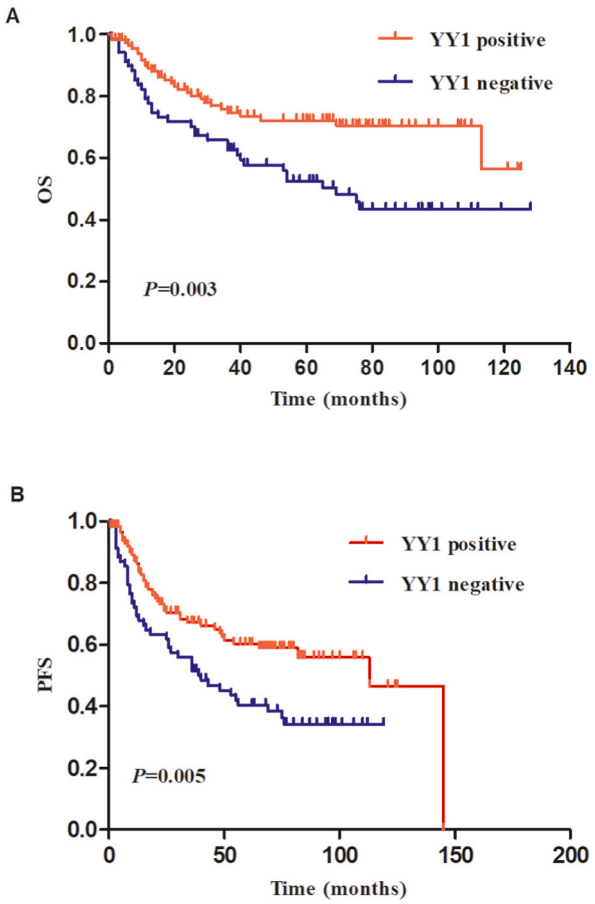

Fig. 2. Prognostic value of YY1 in DLBCL. (A) The YY1-positive group showed a superior overall survival compared with the YY1-negative group ($P = 0.003$); (B) The YY1-positive group showed a superior progression-free survival compared with the YY1-negative group ($P = 0.005$).

Table 3
Prognostic value of YY1 in DLBCL patients with different treatments.

Treatment	anthracycline-based regimen without rituximab		anthracycline-based regimen with rituximab	
YY1	YY1 positive	YY1 negative	YY1 positive	YY1 negative
Total	55	41	50	18
Dead	17	25	8	6
Relapsed	24	29	14	9
P-value (OS)	0.009		0.181	
P-value (PFS)	0.013		0.084	

DLBCL, diffuse large B-cell lymphoma; OS, overall survival; PFS, progression-free survival.

of 13.4 was determined by X-tile software. YY1 mRNA levels greater than 13.4 were defined as a high level, and those less than 13.4 were defined as a low level. The OS rate was significantly higher in patients with high YY1 mRNA levels (n = 207) than in those with low YY1 mRNA levels (n = 207) ($P = 0.003$) (Supplemental Fig. 2).

3.4. Prognostic relevance analysis of combined YY1 and DE status

Our results demonstrated that there was no significant difference in OS ($P = 0.590$) and PFS ($P = 0.392$) between patients with DE and non-DE status. YY1 positivity indicated a higher OS rate in both DLBCLs with DE status ($P = 0.005$) and their counterparts ($P = 0.013$), as well as a higher PFS rate in both groups ($P < 0.001$ and $P = 0.049$, respectively) (Fig. 4). Interestingly, when combined with YY1, patients with positive-YY1 and non-DE status showed the highest OS rate ($P < 0.001$) and PFS rate ($P < 0.001$), whereas those with negative-YY1 and DE status showed the worst.

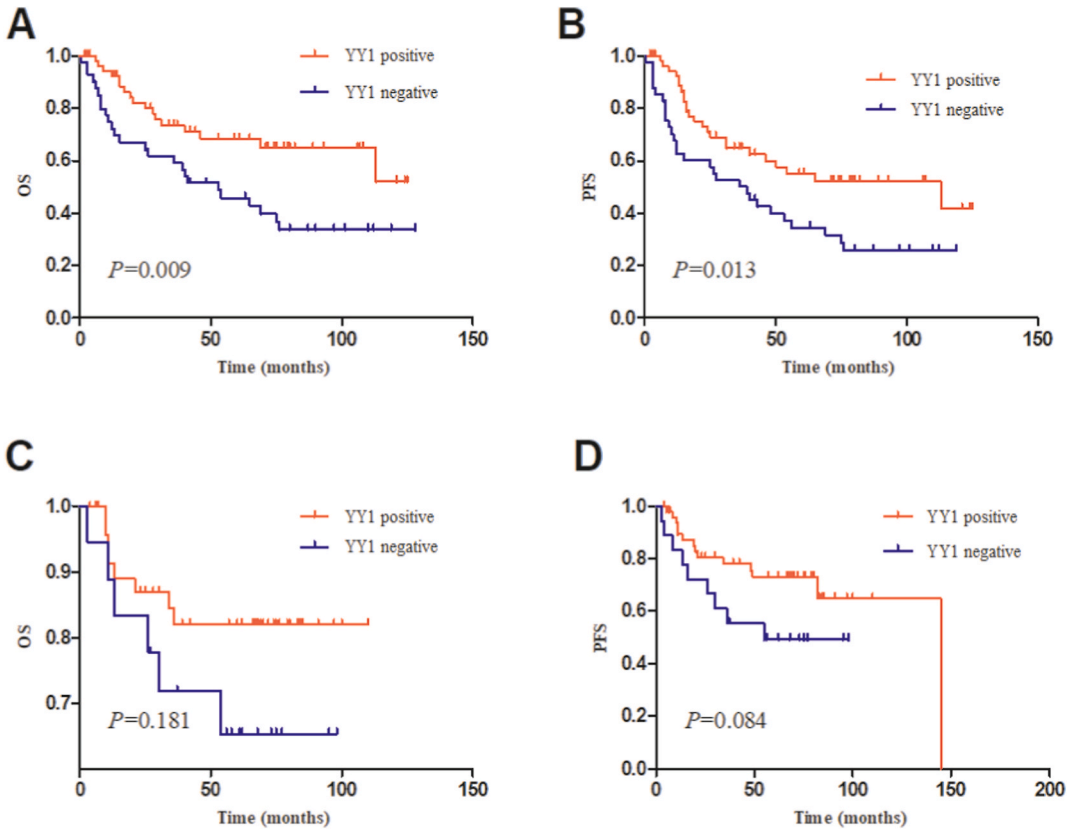

Fig. 3. Survival analysis in DLBCL patients according to YY1 and treatments. (A, B) OS and PFS of patients receiving anthracycline-based regimen without rituximab; (C, D) OS and PFS of patients receiving R-anthracycline-based regimen.

4. Discussion

YY1 is a multifunctional zinc-finger transcription factor that plays regulatory roles in various tumour-related signalling pathways in diverse malignancies, resulting in either activation or repression of these targets [24]. In the current study, for the first time, we thoroughly investigated the expression of YY1 in a large series of DLBCL and its clinicopathological relevance. As a critical regulator of the GCB-specific transcriptional program [25], YY1 showed a significantly higher expression rate in GCB cases. Consistent with previous findings that YY1 could activate the expression of MYC [26,27], YY1 was positively associated with MYC expression in DLBCL in our series. Furthermore, our results demonstrated that YY1 positively associated with both BCL2 expression and MYC/BCL2-DE, which had never been documented in the literature to the best of our knowledge. In addition, a positive correlation between the expression of YY1 and BCL6 was also observed, consistent with the result reported by Castellano et al. [13].

The relationship between YY1 and clinical prognosis is controversial. Overexpression of YY1 related to poor clinical outcomes in some malignancies, such as breast cancer [28] and osteosarcoma [29]. In contrast, a high level of YY1 protein predicts favourable outcomes in other situations, including prostate cancer [30], ovarian cancer [8] and colon cancer [31]. However, the literature on the prognostic value of YY1 expression in lymphomas is limited. In this study, univariate analysis showed that increased YY1 protein levels were correlated with superior survival in DLBCL patients. To exclude the impact of treatment, we conducted a stratified survival analysis to determine the prognostic value of YY1 among different treatment groups. Our results indicated that YY1 positivity was still significantly associated with better outcome in the anthracycline-based regimen group and showed a trend for superior survival in the R-anthracycline-based regimen group. The relatively small sample size of patients in the latter group (n = 68) might contribute to the insignificant *P*-value. Multivariate analysis further confirmed that YY1 expression was an effective prognostic predictor for DLBCL patients independent of Ann Arbor stage, IPI score and treatment regimen. Moreover, our results were validated by the data in the GEO database, which demonstrated a better OS in patients with high YY1 mRNA levels than in those with low mRNA levels. Consistently, it was reported that knockout of the *YY1* gene could lead to decreased survival of DLBCL cells [32]. However, Byers et al. indicated that high YY1 mRNA level was related to a shorter survival time in DLBCL, although the case series in their study was relatively small (n = 25) [12]. Interestingly, Byers et al. also demonstrated that high YY1 protein expression was associated with longer survival in FL, despite the negative correlation between YY1 mRNA levels and survival [12,33,34]. The contrary results between protein and mRNA level indicated that YY1 protein might be more stable and suitable as clinical biomarkers than transcript levels in some circumstances [35,36]. Although further studies are warranted, these findings demonstrated that YY1 protein expression might represent as a useful

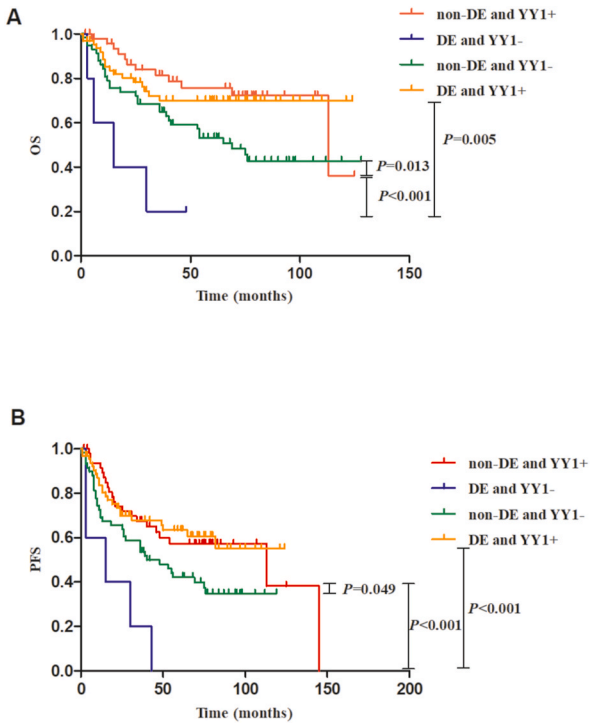

Fig. 4. Survival analysis in DLBCL according to YY1 and double expression status. (A) Overall survival analysis according to YY1 and double expression status; (B) Progression-free survival according to YY1 and double-expression status.

predictor of better prognosis in DLBCL patients.

Our results demonstrated that YY1 was positively correlated with DE, which was an intriguing finding because YY1 predicted a good prognosis in the current DLBCL series whereas DE appeared to be a poor prognostic factor according to a considerable number of previous studies [37]. Actually, some studies have shown that DE status has no prognostic value, especially among patients with stage I/II DLBCL or in young patients in the R-MegaCHOEP trial [38–41]. Xu-Monette et al. found that phenotypic DE showed significant prognostic impact in two LymphGen genetic subsets of DLBCL, EZB and 'Other', but not MCD/ST2 [40]. Therefore, DLBCLs with DE are of great heterogeneity, which might at least partially contribute to the discrepant results of its prediction of prognosis. Various combinations of prognostic markers have been explored, including the panel of CD10, FOXP1 and BCL6 protein expression [42] as well as the integration of *MYC* rearrangement status with protein levels of MYC, BCL2, and BCL6 [43]. In the current study, we also failed to find any prognostic relevance of DE status in DLBCL patients. We further combined the two factors, YY1 and DE, for stratified survival analysis. Notably, cases with YY1+/non-DE status revealed the best outcome, whereas those with YY1-/DE status showed the worst outcome, indicating that the combination of YY1 with DE status demonstrated better power to determine prognosis. Actually, the interactions between YY1 and MYC have been investigated in some studies. For example, the HDAC2/YY1/MYC signalling axis regulated lung cancer cell migration and proliferation [44]. The Smurf2/YY1/MYC regulatory axis might suppress B-cell proliferation and lymphomagenesis [14]. Therefore, we speculate that complicated molecular mechanisms might be involved in the interactions between YY1 and DE in DLBCL, ultimately affecting the clinical biological behavior, which warrant to be illustrated further.

Double-hit (DH) is defined as a dual rearrangement of *MYC* and *BCL2* with/without *BCL6*, accounting for 5 %–7 % of all DLBCLs [18,45], and DH is usually associated with advanced stages and poor outcome [46]. While, Johnson et al. showed that DH-DLBCL were heterogeneous in morphology, clinical presentation, and outcome [47], and those DH-DLBCL lacking the molecular high-grade signature showed no significant difference in prognosis compared with other GCB cases [48]. Given the low incidence of DH [45], we failed to illustrate the correlation between DH and YY1, which is warranted to be further studied by accumulating more cases. *TP53* is another unfavorable prognostic factor in DLBCL and *TP53* alterations, including single-base missense mutations, deletion, frameshift mutations, splice mutations and insertion, confer a very poor prognosis in patients treated with either R–CHOP or DA-EPOCH-R [49–51]. Besides, Hong et al. found that *TP53* mutations in exon 7 resulted in inferior OS, while *TP53* mutations in exons 5 and 6 were associated with worse PFS, indicating different prognostic values of mutations in different exons of *TP53* gene [50]. Notably, YY1 might regulate the function of *TP53* according to the literature [52]. Zhou et al. indicated that YY1 overexpression could significantly reduce the protein levels of TP53, promoting the proliferation of melanoma cells [52]. Owing to the complexity of *TP53* mutations and the potential reduction in DNA quality of the paraffin-embedded tissues in this series caused by the prolonged storage, *TP53* mutation was not tested in the current study. Further explorations are warranted to elucidate the relationship between YY1 and *TP53* as well as their interactions at molecular levels in DLBCL.

As a transcription factor, YY1 interacts with many genes involved in cell cycle signalling pathways and apoptotic signalling

pathways in various tumours [53], while studies on the mechanisms of YY1 in DLBCL are scarce [54]. Several previous studies showed that YY1 was associated with chemoresistance in B-NHL cell lines [16,55], and inhibition of YY1 could induce cell apoptosis [56]. However, both our findings and the data from the GEO database suggested that YY1 may act as a tumour suppressor according to the survival analysis. Worthy to be noticed, the present study revealed a negative association between YY1 and CXCR4 in DLBCL, which had never been documented in the literature. As the first cytokine discovered to inhibit the expression of CXCR4, YY1 could inhibit the activity of CXCR4 by binding upstream of the CXCR4 promoter region [57]. Other researches showed that YY1 repressed CXCR4 transcription in human herpesvirus 6-infected cells [58] and in rhabdomyosarcomas [59]. In addition, a CXCR4 antagonist could inhibit the survival and proliferation of acute myeloid leukaemia cells [60]. These findings are consistent with those of the present study. Moreover, the current study revealed that YY1 expression was positively related with pAKT. Although YY1 may play a negative regulatory role in the PI3K/AKT pathway in pancreatic cancer [61], some studies have demonstrated a positive association and regulation between YY1 and pAKT in breast cancer [62], renal cell carcinoma [63], endometrial cancer [64], and lung adenocarcinoma [65]. The above results suggested that YY1 may exert its biological functions through the CXCR4 and AKT pathways. However, it was reported that CXCR4 could activate the AKT pathway and prevent the apoptosis of glioma cells [66]. There may be additional signalling pathways involving YY1, CXCR4 and AKT in DLBCL which need to be investigated further in the future.

There are several limitations of our study. One weakness is that it is an observational study and lacks in vitro experiments on the mechanisms. In addition, considering the low incidence of DH and the complexity of *TP53* mutation in DLBCL, as well as the potential reduction in the quality of the samples with prolonged storage, we did not investigate these two important prognostic factors and illustrate their association with YY1 in the current series, which are warranted to be further explored.

In conclusion, YY1 was frequently expressed in DLBCL, especially in DLBCLs of GCB phenotype and with DE status. YY1 expression predicted favourable survival in DLBCL, supporting the idea that YY1 might be considered as a powerful prognostic indicator, especially when combined with DE status. A significant correlation between YY1 and MYC, CXCR4 and pAKT indicated a complex regulatory mechanism involved in their interactions and the pathogenesis of DLBCL, which warrants to be elucidated by further multidimensional investigations.

Ethics statement

This study was approved by the Institutional Review Board of Fudan University Shanghai Cancer Center (Shanghai Cancer Center Ethical Committee, APPROVAL NUMBER: 050432-4-1911D).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Tian Xue: Writing – original draft, Investigation, Data curation. **Jia-Xin Lin:** Investigation, Formal analysis, Data curation. **Ya-Qi He:** Methodology, Data curation. **Ji-Wei Li:** Validation, Data curation. **Ze-Bing Liu:** Data curation. **Yi-Jun Jia:** Data curation. **Xiao-Yan Zhou:** Supervision, Methodology, Conceptualization. **Xiao-Qiu Li:** Methodology, Conceptualization. **Bao-Hua Yu:** Writing – review & editing, Supervision, Project administration, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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Definition of Abbreviations

YY1: Yin Yang 1
DLBCL: diffuse large B-cell lymphoma
NHL: non-Hodgkin lymphoma
R: Rituximab
CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone regimen
RESHAP: rituximab plus etoposide, cytarabine, cisplatinum and methylprednisolone regimen
MINE: mitoxantrone, mesna/ifosfamide and etoposide regimen
FL: follicular lymphoma
Smurf2: Smad ubiquitination regulatory factor-2
KLF4: Krüppel-Like Factor 4
TMA: tissue microarray
IPI: international prognostic index
IHC: immunohistochemistry
GCB: germinal centre B
DE: double-expression
DH: Double-hit
OS: Overall survival
PFS: Progression-free survival
GEO: Gene Expression Omnibus database