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Association of SOX11 gene expression withclinical features and prognosis of mantle cell lymphoma

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Abstract. – OBJECTIVE: To study the expression of SOX11 in the patients with mantle cell lymphoma (MCL) and explore the clinical values of SOX11 in MCL.

PATIENTS AND METHODS: In the paraffin-embedded MCL tissues of 75 patients diagnosed in the Department of Hematology, Shanxi Tumor Hospital, were performed the immunohistochemical labeling of Ki67 and SOX11 by the EnVision method. Meanwhile, the expression of SOX11 mRNA was also detected by reverse transcriptase-polymerase chain reaction (RT-PCR), and the association of SOX11 with such prognostic indexes as pathological typing, staging, immunophenotyping, and MIPI was analyzed using the statistical method.

RESULTS: The immunohistochemistry showed that 97% of cases expressed SOX11 positive, and the RT-PCR results showed that the expression of SOX11 mRNA in the MCL patients was significantly higher than those with reactive hyperplasia lymphoid [3.097 (1.311, 6.216) and 1.058 (0.302, 2.623, respectively (p<0.05). Higher expression of SOX11 mRNA was positively correlated with some good prognostic factors such as ECOG<2, no bone marrow involvement and low-risk according to the International Prognostic Index (IPI). The comparison of the survival curves between group SOX11 mRNA <M and SOX11 mRNA≥M showed the median survival in the former was shorter than that in the latter, which was 27 months and 50 months, respectively. There was a significant difference between the two groups.

CONCLUSIONS: The expression of SOX11 in MCL patients is significantly higher than normal controls, which can be used as a diagnostic index. Upregulated SOX11 may be a good prognostic factor in MCL patients.

Key Words
Lymphoma, SOX11, Prognosis.

Introduction

Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin's lymphoma (NHL), accounting for 5-10% of all NHL cases, with the median age as 60-65 years and the ratio of male to female as 2: 1. It often presents advanced clinical stages and extensive disease such as widespread lymphadenopathy, splenomegaly, bone marrow and GI tract involvement when diagnosed[1]. Patients with MCL have a worse prognosis than many others B-cell lymphoma that only have 3-5 years median survival because of a high relapse rate, although most of them have a good response to initial treatment[2-4]. Treatment protocol containing high-dose cytarabine, rituximab, and consolidation with autologous stem cell transplantation (ASCT) have not yet reached survival plateau, although improved long-term remission[4-6]. Furthermore, about 10-15% of MCL patients have indolent clinical course, so they don't need immediate treatment once diagnosed[7]. It is necessary to explore more biological marker and prognostic factor to understand the pathogenesis of MCL and give patients stratified treatment.

The characteristic genetic abnormality of MCL is t (11; 14) (q13; q32), which translocates the CCND1 gene located on chromosome 11q13 to the IgH gene of 14q32, thus leading to the

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overexpression of the cyclin D1. So, cyclin D1 or t (11; 14)-positive is the important diagnostic criterion for MCL suggested by the WHO [3, 11]. However, studies[8] have shown that about 10% of MCL patients does not exist t (11; 14) or cyclin D1 expression-negative. Recent studies[9,10] appeared another gene that might have a crucial role in the pathogenesis of MCL is SOX11. 90%-95% of MCL patients express SOX11, which is unrelated to whether the cyclin D1 is expressed or not, confirming that SOX11 can be used as a diagnostic indicator of MCL[9,11-13]. Furthermore, studies indicated SOX11 had probable prognostic significance although there had not yet unified conclusion so far. In this study, we examined the mRNA and protein expressions of SOX11 in 75 MCL patients, aiming to explore the association of SOX11 with such prognostic indexes as pathological typing, staging, immunophenotyping, and MIPI, and to elucidate the clinical values of SOX11 in MCL.

Patients and Methods

Patients

The formalin-fixed, paraffin-embedded tissue blocks were collected from 75 newly diagnosed MCL patients in Shanxi Tumor Hospital from March 2005 to March 2014. All the patients were diagnosed and classified by two pathologists referring to the classification criteria of lymphoid hematopoietic neoplasms issued by the WHO in 2008[14]. Furthermore, 30 patients with reactive hyperplasia lymphoid (RHF) were selected as the control. The follow-up lasted until January 29, 2016, and the median follow-up time was 40 (2-98) months. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Shanxi Medical University. Written informed consent was obtained from all participants.

Preparation of Tissue Microarray

All the pathological specimens were fixed in 4% neutral formaldehyde buffer solution, followed by routine dehydration, hyalinization, and paraffin-embedding. Typical lesion zone was then observed by HE staining. One tissue array spotting instrument (Beecher Instrument, Sun Prairie, WI, USA) was then used to select the target sites in the corresponding paraffin blocks. Each specimen was sampled two 0.9-mm tissue columns using one tissue sampler (in case of losing information) and prepared two 6-point × 18-point tissue chips. The 4-μm paraffin slice was then placed onto one 3-amino alkyl silane-treated glass slide for future use.

Immunohistochemistry (IHC) and Result Determination

The protein expressions of cyclin D1, P53, Ki67, and SOX11 were detected by the two-step EnVision method. The SOX 11 antibody (Atlas Antibodies, Stockholm, Sweden) was purchased from Stockholm, Sweden, and the antibodies of P53, Ki67, and cyclin D1 were purchased from Fuzhou Maxim Bioengineering Co. Ltd (Fuzhou, China). One known positive tissue was set as the positive control, and the primary antibody-free sample was used as the negative control; all the samples were stained using diaminobenzidine (DBA) and hematoxylin for the contrast. Cyclin D1, P53, Ki67 locate in the nucleus. The positive reaction was defined as yellow or brown particles appearing in the cytoplasm or nucleus, and according to the percentage of the positive cells, P53 positive result was divided into three levels: -: <10%; +: 10%-50%; ++: >50%. The positive reaction of SOX11 was defined as yellow or brown particles appearing in the nucleus (-: <10%; +: 10%-30%; ++: >30%).

Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)

The total RNA was extracted from each paraffin tissue using the Recover A II Total Nucleic Acid Isolation Kit (Ambion, Austin, TX, USA) and then synthesized the cDNA. The reverse transcription system was 40 μL (the cDNA reverse transcription reagent was purchased from Invitrogen Corporation, Carlsbad, CA, USA), containing 2 μg of total RNA and 4 μl of random primer Oligo DT (50 pmol/L). One ABI7500 FQ-PCR (Waltham, MA, USA) was used for the Real-time quantitative PCR detection. The reaction system was 20 μL, containing 0.4 μL of the SOX11 primer (ABI4331182) and internal reference β-actin (ABI4333762f), respectively. The reaction cycle parameters were: 95°C for 30 s, 95°C for 5 s, 61°C for 30 s, 95°C for 15s, 60°C for 60 s, 95°C for 15 s, for a total of 40 cycles. The relative expression of SOX11 mRNA was calculated by the method of $2^{-\Delta\Delta CT}$, $^{\Delta\Delta}Ct$ = (Ct SOX11 – Ct actin) of the experimental group – (Ct SOX11 – Ct actin) of the control group.

Statistical Analysis

Statistical product and service solutions (SPSS22.0, IBM Corp., Armonk, NY, USA) software was used to analyze the data. The intergroup and intragroup comparison used Wilcoxon rank sum test, and Kruskal-Wallis H test. The survival analyzed by the Kaplan-Meier method, with $p<0.05$ considered as statistically significant.

Results

Clinical Features

The 75 MCL tissues were obtained from 58 males (77%) and 17 females (23%) patients, with the ratio of male to female as 3.4:1. The patients' ages ranged from 39 to 79 years, with the median age of 63 years. When diagnosed, 27 cases (36%) had the ECOG as 0-1 point, and 48 cases (64%) had the ECOG as 2-4 points. 56 patients (75%) were classified as Stage III-IV of Ann Arbor, and 13 (17%) patients exhibited the B symptom. The initial involvement tissue in 55 patients (73%) was in lymph nodes, and 11 patients (15%) in the gastrointestinal tract, followed by the Wechsler's ring, pleural effusion and spleen. There were 22 (29%) patients with bone marrow invasion. 11 (15%) patients exhibited the peripheral white blood cells (WBC) ≥10×109/L, 17 patients (23%) exhibit-ed LDH elevation, and 33 (44%) patients exhibited β2-MG elevation. According to the risk stratifica-tion criteria of the MCL International Prognostic Index (MIPI), 31 patients (41%) were classified as low-risk group, 23 patients (31%) were classified as intermediate-risk group, and 21 patients (28%) were classified as high-risk group (Table I).

Pathomorphological and Immunophenotypic Features

All cases exhibited diffuse growth pattern, 65 cases (87%) with classical pathomorphology and 10 cases (13%) occurred blast cell variant. The positive expression rates revealed by the immunohistochemical assay were cyclin D1 (100%, 75/75), bcl-2 (97%, 66/68), CD5 (82%, 60/73), CD23 (21%, 15/72), Bcl-6 (12%, 8/69 cases), and P53 (21%, 16/75) in turn. In addition, 29% of the patients (22/75) exhibited Ki67 ≥ 30%, and SOX11 was expressed as ++, +, and – in 92% of the patients (69/75), 5% of the patients (4/75), and 3% of the patients (2/75), respectively (Figure 1).

Expression of SOX11 mRNA

The expression level of SOX11 mRNA in 75 MCL patients was 3.097 (1.311, 6.216). The expression level of SOX11 mRNA in the control group was 1.058 (0.302, 2.623). The expression level of SOX11 mRNA in MCL patients was significantly higher than the control group ($p<0.05$), (Figure 2).

Correlation of SOX11 mRNA Expression with Clinicopathologic Features

The patients with ECOG < 2 points exhibited higher SOX11 mRNA expression level than that with ECOG ≥ 2 points ($p=0.0011$). The expression of SOX11 mRNA in the patients with normal bone marrow was significantly higher than that with bone marrow involvement ($p=0.0038$); namely, the expression of SOX11 mRNA was positively correlated with ECOG and bone marrow involvement, but not correlated with the age, pathological type, count of WBC, or related with the age, and B symptom. Based on Kruskal-Wallis test, SOX11 expression level had a significant difference between the 3 International Prognostic Index (IPI) groups (Table I). Furthermore, the results of multiple comparisons by Nemenyi test[15] revealed SOX11 expression level of the low-risk group was higher than that of the intermediate-risk group and high-risk group respectively, however, which had no significant difference between intermediate-risk group and high-risk group ($p<0.05$) (Table II).

Association of SOX11 Expression With Survival

The median survival time for this patient cohort was 33 (30-38) months (Figure 3A). The median survival of the patients with SOX11 mRNA lower than normal (SOX11 mRNA<M) was 27 months, much shorter than that of the patients with SOX11 mRNA higher than normal (SOX11 mRNA≥M), which was 50 months. There was a significant difference in the median survival between the two groups ($p<0.001$, Figure 3B)

Discussion

The SOX11 gene is located on chromosome 2q25.2. Studies have found that the expression of SOX11 gene is significantly higher in MCL patients than in other patients with B cell tumors, which is especially helpful to distinguish MCL with other small B cell lymphoma such as chronic lymphocytic leukemia (CLL) that were easily confused each other in morphology; furthermore, its expression is independent from cy-

Table I. Characteristics of 75 MCL patients and correlation of SOX11 mRNA. expression.

Variables	No. (%)	X±S	M (Q1, Q3)	*p*
Gender				
Male	58 (77)	3.949±2.8417	3.349 (1.302, 6.57)	0.531
Female	17 (23)	3.263±2.5072	1.767 (1.348, 5.282)	
Age (y)				
<60	29 (39)	2.989±2.3712	1.981 (1.358, 6.897)	0.0652
≥60	46 (61)	4.301±2.902	4.101 (1.19, 3.449)	
Morphology				
Common morphology	65 (87)	3.955±2.7948	3.366 (1.386, 6.57)	0.0857
Blastoid morphology	10 (13)	1.941±1.6441	1.353 (1.099, 1.48)	
Ki-67				
<30%	53 (71)	3.547±2.6012	2.811 (1.302, 4.81)	0.3086
≥30%	22 (29)	4.388±3.1183	4.269 (1.358, 7.469)	
ECOG				
<2 point	27 (36)	5.324±2.7515	4.55 (3.331, 7.367)	0.0011*
≥2 point	48 (64)	2.933±2.403	1.632 (1.263, 3.889)	
WBC				
<10×10^9/L	64 (85)	3.749±2.7471	3.024 (1.33, 5.643)	0.8398
≥10×10^9/L	11 (15)	4.054±3.0123	3.62 (1.122, 7.042)	
LDH				
<240 IU/L	58 (77)	3.582±2.7588	2.406 (1.302, 5.282)	0.2057
≥240 IU/L	17 (23)	4.516±2.7584	4.503 (1.598, 6.897)	
β2-MG				
<3 mg/L	42 (56)	4.191±3.0548	3.378 (1.302, 7.14)	0.3394
≥3 mg/L	33 (44)	3.288±2.3006	2.811 (1.358, 4.55)	
P53				
Positive	16 (21)	2.685±1.9894	1.573 (1.263, 3.717)	0.1018
Negative	59 (79)	4.095±2.8847	3.449 (1.386, 6.921)	
Ann Arbor stage				
I-II	19 (25)	3.879±3.0346	3.331 (1.236, 6.004)	0.9272
III-IV	56 (75)	3.765±2.7005	3.024 (1.33, 6.393)	
B symptoms				
No	62 (83)	3.889±2.7138	3.349 (1.386, 6.57)	0.3203
Yes	13 (17)	3.339±3.0893	1.415 (1.122, 4.503)	
Bone marrow				
Involvement	22 (29)	2.571±2.2278	1.353 (1.084, 3.62)	0.0038*
Normal	53 (71)	4.301±2.8294	3.497 (1.491, 6.921)	
MIPI				
Low-risk	31 (41)	2.9618±2.4421	1.491 (1.134, 4.503)	0.0031
Intermediate-risk	23 (31)	3.3859±2.5796	1.666 (1.236, 5.282)	
High-risk	21 (28)	5.469±2.8065	4.457 (3.331, 8.259)	

MCL indicates mantle cell lymphoma; WBC: white blood cell; LDH: lactate dehydrogenase; β2-MG: serum 2-microglobulin levels; Smipi: simplified MCL International Prognostic Index. 0 to 11 points were given to each patient. Patient with 0 to 3 points in summary were classified as low risk, patients with 4 to 5 points as intermediate risk, and patients with 6-11 points as high risk. B symptoms: fever, night sweet and loss of weight; Bone marrow involvement: lymphoma cell ≥5%.

clinD1 and t (11; 14)[16,17], suggesting that SOX11 may be a new diagnostic marker of MCL, especially for those cases with negative cyclin D1 expression. Due to the impact of such factors as pathological section production techniques, storage time, and pathophysiologist's observation level on the immunohistochemical results, some studies[18,19] detect the SOX11 mRNA level in tumor cells so as to more accurately reflect the expression of SOX11. This study showed that 97% of the MCL patients (73/75) had a positive SOX11 expression, and their SOX11 mRNA expression level was significantly higher than the patients with RHF, consistent with

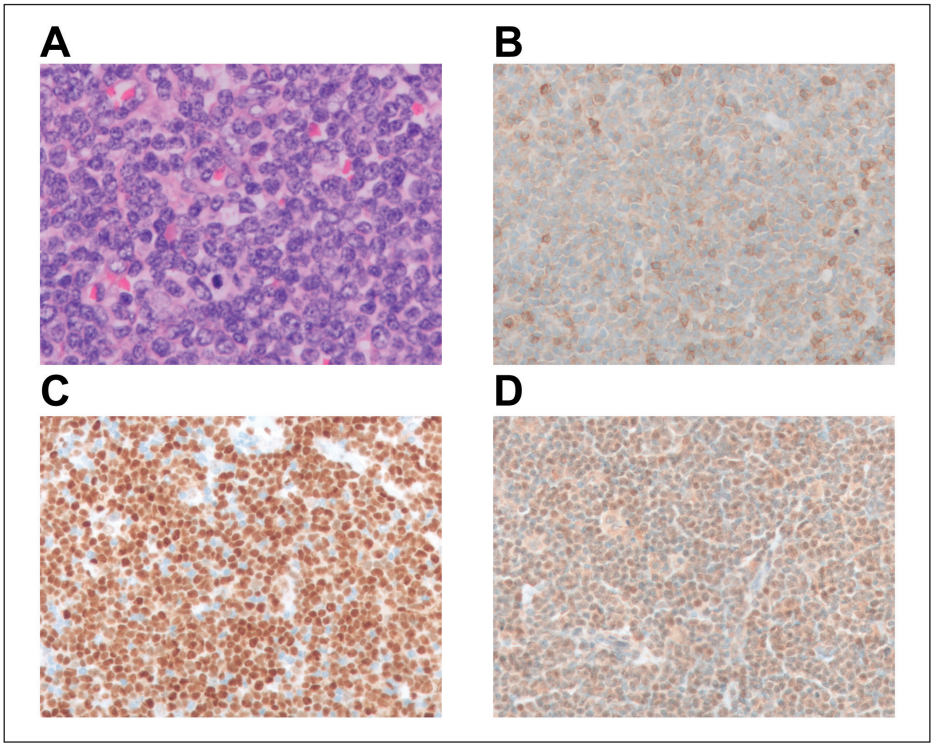

Figure 1. A, Blastoid morphology in MCL HE×400; **B**, IHC CD5+; **C**, IHC cyclin D1+; **D**, IHC SOX11++.

other foreign reports. In addition to its diagnostic value against MCL, limited studies have also suggested that SOX11 may be associated with clinical outcomes[13,19,20]. Wang et al[21] studied 53 MCL cases and found that the survival time of 5 cases with negative SOX11 expression in the nuclei is significantly shorter than those with positive nuclear SOX11 expression (median survival period of the two groups were 494 days and 1488 days, respectively). So, it can be speculated that the SOX11 expression in the nuclei is associated with the survival period of MCL patients. However, Fernandez et al[22] found that in the MCL patients with positive cyclin D1, the survival period of the patients with positive SOX11 nuclear expression was short, and the prognosis was poor, just opposite to the former conclusions. It suggests that there exist much more complex factors and mechanisms, so further studies are necessary. This study showed that the higher expression of SOX11 mRNA was positively correlated with some good prognostic factors, ECOG<2, no bone marrow involvement and low-risk IPI. The comparison of the survival curves between group SOX11 mRNA<M and SOX11 mRNA ≥ M, showed the median survival in the former was shorter than that in the latter, which was 27 months and 50 months, respectively. There was a significant difference between the two groups.

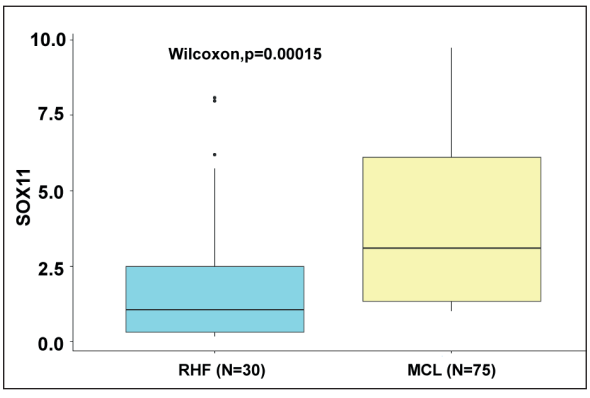

Figure 2. SOX11 mRNA level in patients with MCL were significantly higher than in patients with RHF.

Conclusions

We showed that the high expressions of SOX11 mRNA may be a good prognostic factor in MCL patients. The specific mechanisms of SOX11 in

Table II. Correlation of SOX11 mRNA expression with 3 IPI subgroups.

IPI subgroup	Difference between x	95% CI
Low risk-high risk	16.498	1.839-31.157***
Low risk- intermediate risk	20.363	6.637-34.09***
High risk- low risk	-16.498	-31.157-(-1.839)***
High risk- intermediate risk	3.865	-9.501-17.231
Intermediate risk- low risk	-20.363	-34.09-(-6.637)***
Intermediate risk- high risk	-3.865	-17.231-9.501

Comparisons significant at the 0.05 level are indicated by ***.

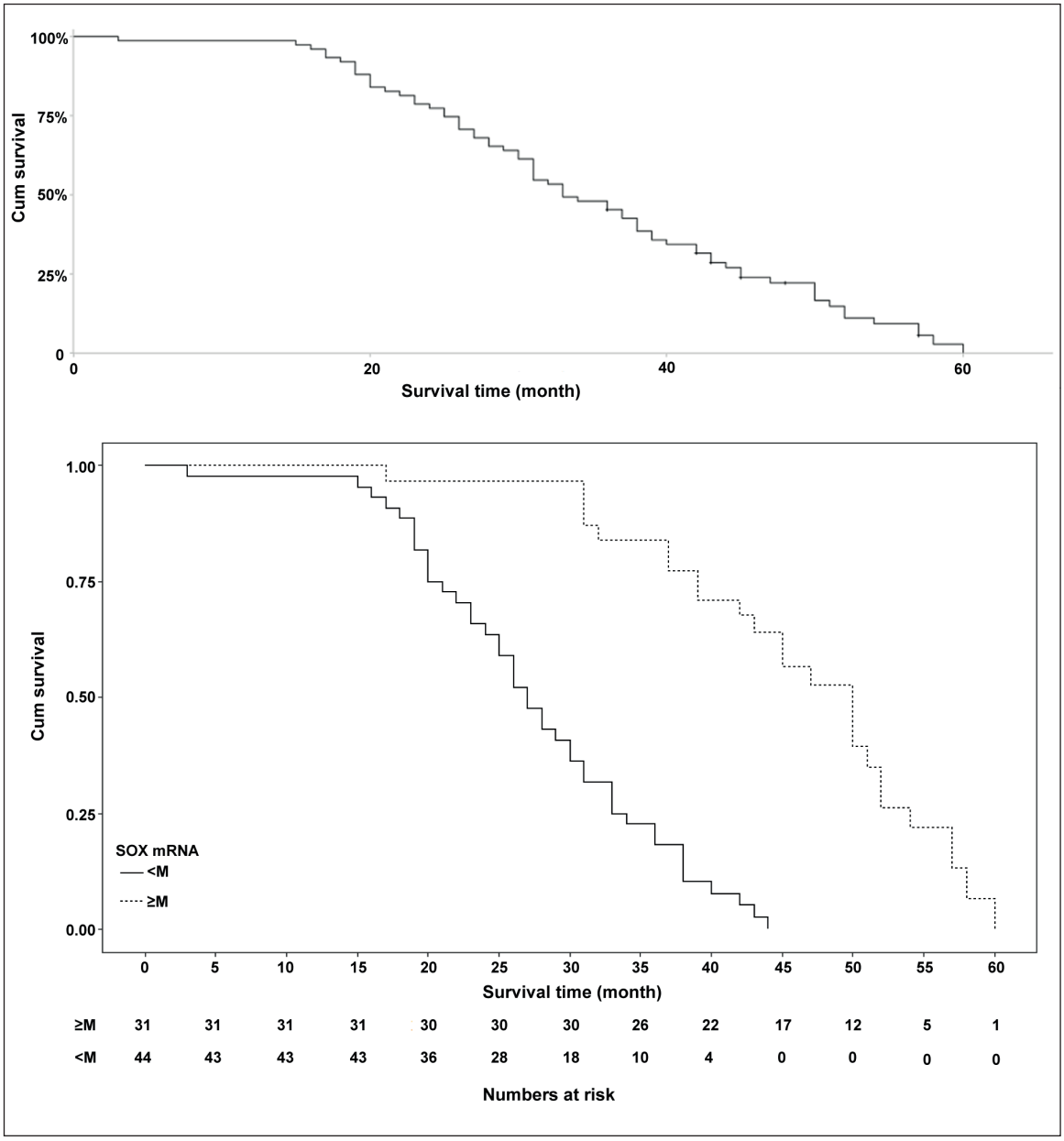

Figure 3. A, The overall survival of 75 MCL patients; **B**, SOX11 mRNA level and overall survival rate.

MCL are still unknown, but due to its high expression in MCL patients, SOX11 may become a therapeutic target for MCL in the future and thus add a new treatment against MCL.

Acknowledgments

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Conflicts of interest

The authors declare no conflict of interest.

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