Identification of miRNA-34a and miRNA-155 as prognostic markers for mantle cell lymphoma

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Abstract

Objective: MicroRNAs (miRNAs) with functional relevance have not been previously identified in mantle cell lymphoma (MCL). Here, we aimed to evaluate the relationships between miR-34a and miR-155-5p and MCL clinicopathology and prognosis.

Methods: Seventy-five paraffin-embedded tissue samples from patients with MCL who completed at least four cycles of chemotherapy from January 2006 to October 2016, and 27 samples from control patients with reactive lymphoid hyperplasia (RLH), were collected. MiRNA expression levels were measured by qRT-PCR.

Results: The miR-155-5p levels were significantly higher in patients with MCL than in the controls. The Eastern Cooperative Oncology Group (ECOG) $\geq$ 2 and Sex-Determining Region Y-Box transcription factor 11 (SOX11) < median value (M) groups presented lower miR-34a expression than the ECOG < 2 and SOX11 $\geq$ M groups, respectively. MiR-155-5p expression differed between low, intermediate, and high MCL International Prognostic Index risk groups. The AUCs of miR-34a and miR-155-5p were 0.5819 and 0.7784, respectively. The median survival times of the miR-34a $\leq$ 0.2150 and miR-155-5p > 2.11 groups were shorter than those of the miR-34a > 0.2150 and miR-155-5p $\leq$ 2.11 groups, respectively.

Conclusions: Low miR-34a and elevated miR-155-5p levels may be correlated with poor prognosis in MCL.

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Introduction

Mantle cell lymphoma (MCL) is a subtype of mature B-cell lymphoma that accounts for 5% to 10% of non-Hodgkin's lymphoma cases and has a median patient age of 60 to 65 years. It originates from B cells in the mantle zone of the lymph node, and extranodal invasion is common. The median survival time of patients with MCL is significantly lower than that of patients with other subtypes of B-cell lymphoma.[1,2] There has been no substantial improvement in patient survival with the common treatment protocols for MCL, including the use of high-dose Ara-c and rituximab, a CD20 antibody, although autologous peripheral blood stem cell transplantation (APBSCT) improves the long-term remission rate.[3]

The characteristic cytogenetics of MCL include a translocation between chromosomes 11 and 14, that is, t (11;14), which leads to the overexpression of cyclin D1.[1,4] In addition to this major genetic alteration, most MCL cases have several recurrent secondary mutations with important roles in disease pathogenesis.[5] These mutations occur in coding genes involved in various cell functions, including cell cycle regulation, post-DNA damage responses, and signaling pathways. Recent studies indicate that genes in these pathways may be downregulated by microRNAs (miRNAs), and these changes in gene expression may be associated with clinicopathological features.[6,7] Interestingly, studies have suggested an association between miRNAs and MCL prognosis.[7,8]

MiRNAs are small non-coding single-stranded RNA molecules and are typically 19 to 25 nucleotides in length. They play a direct role in the post-transcriptional regulation of many genes, some of which are involved in cell differentiation, proliferation, and apoptosis.[9,10] Abnormal expression of multiple miRNAs has been detected in several solid tumors and hematologic neoplasms, including lymphoma.[11–13] In 2002, Calin et al. demonstrated that a deletion at 13q14.3 leads to a decrease in miR-15/miR-16 expression, thereby affecting the development of chronic lymphocytic leukemia (CLL).[14] Subsequent studies have identified various miRNAs that play important roles in lymphoma development and prognosis by regulating the expression of target genes.[12,15] For example, abnormalities in the expression of miR-17–92, miR-34a, miR-150, and miR-155-5p are common events in B-cell tumorigenesis.[6] MiR-34a is involved in the regulation of the tumor suppressor gene *TP53* via forkhead box protein P1 (FOXP1) and B-cell lymphoma 2 (BCL2), thus affecting the differentiation and apoptosis of B cells. The decreased expression levels of miR-34a in lymphomas, such as diffuse large B-cell lymphoma (DLBCL), are associated with prognosis.[6,16] The causal role of miR-155-5p in lymphoma has been established in two mouse model studies. Functional studies of miR-155-5p in anaplastic large cell lymphoma have demonstrated its association with lymphocyte differentiation and immunity.[17] Furthermore, elevated expression of miR-155-5p is associated with the transformation of monoclonal B lymphocytosis (MBL) to CLL, a poor therapeutic response, and short survival in patients with CLL.[18]

Only a few studies have evaluated the role of miRNAs in MCL. Some studies have reported *SOX11* as a critical gene with diagnostic value,[19,20] but it may also have prognostic value.[21] Furthermore, the biological information databases TargetScan and miRdb predict that miR-155-5p may participate in the regulation of Sex-Determining Region Y-Box transcription factor 11 (SOX11), as indicated by a systematic search of miRNAs targeting SOX11, a definitive diagnostic indicator of MCL.[22] In the present study, we identified miR-34a and miR-155 as candidate markers, evaluated their expression, and assessed their prognostic value in MCL.

Patients and methods

Patients

We obtained paraffin-embedded MCL tissue samples (excluding biopsy specimens) from the Department of Pathology, Shanxi Tumor Hospital, and Shanxi Provincial People's Hospital from January 2006 to October 2016. Patients with detailed clinical data who had completed at least four cycles of chemotherapy including the CHOP/R-CHOP or HyperCAVD/R-HyperCAVD regimen[3] were selected and subjected to follow-up. Subsequently, 75 samples from patients with MCL and 27 samples from patients with reactive lymphoid hyperplasia (RLH) (controls) were obtained. The baseline characteristics of the cases were the same as those previously reported by He et al.[23] The study was approved by the Ethics Committee of Shanxi Tumor Hospital (Taiyuan, China; Date of approval: 29 July 2019; Approval number: 201935) and written informed consent was obtained from all participants. It was performed in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The reporting of this study conforms to the STROBE statement.[24]

Exemption

The study was exempted from ethical committee review owing to its retrospective nature.

Quantitative real-time-polymerase chain reaction (qRT-PCR)

The Recover All Total Acid Isolation Kit (ABI AM1975; Thermo Fisher Scientific, Waltham, MA, USA) was used to extract total RNA from paraffin-embedded tissues according to the manufacturer's instructions. The RNA concentrations were measured by spectrophotometry. The TaqMan microRNA RT Kit (ABI 4366597; Thermo Fisher Scientific) was used to generate cDNA. The final reaction mixture comprised $5\,\mu L$ of total RNA and $3\,\mu L$ of RT primer. Quantitative real time-polymerase chain reaction (qRT-PCR) was conducted to measure miRNA expression using a fluorescence quantitative PCR amplifier (AB71700 ABI; Thermo Fisher Scientific). The total volume of the reaction mixture was $20\,\mu L$, and it contained $1.33\,\mu L$ of cDNA, $1\,\mu L$ of primer and probe mixture ($20\times$, miR-34a-specific primer, ABI 4427975; miR-155-5p-specific primer, ABI 4427975; U6 nuclear RNA, ABI 4427975), $10\,\mu L$ of TaqMan general mixture ($2\times$, ABI), and $7.67\,\mu L$ of nuclease-free water. The amplification conditions were as follows: $95°C$ for 10 minutes, followed by 40 cycles of $95°C$ for 15 s and $60°C$ for 60 s. MiRNA expression levels were calculated using the $2^{-\Delta Ct}$ method, where ΔCt (cycle threshold) $= (Ct\ miRNA - Ct\ U6)$ for the experimental group $- (Ct\ miRNA - Ct\ U6)$ for the control group.

Statistical analyses

SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. The median and quartile values were used for descriptive statistics. Wilcoxon rank-sum test and Kruskal–Wallis H test was used for intergroup and intragroup comparisons, respectively, and the Nemenyi method was used for multiple comparisons. The Kaplan–Meier method was used to analyze patient prognosis and survival. The log-rank test was used for univariate analyses and the Cox proportional hazards model was used for multivariate analyses. Additionally, the prognostic values of miR-34a and miR-155-5p for patients with MCL were analyzed by receiver operating characteristic (ROC) curve. Results with $P < 0.05$ were considered statistically significant.

Results

Expression of miR-34a and miR-155-5p in patients with MCL

The expression of miR-34a was 0.478 (0.202–0.821) and 0.572 (0.265–1.072) in patients with MCL and RLH, respectively, with no significant difference between the groups ($P = 0.2107$) (Figure 1a). The expression of miR-155-5p was 3.482 (2.136–5.048) and 0.774 (0.083–1.834) in patients with MCL and RLH, respectively, with significantly higher expression in patients with MCL than in patients with RLH ($P < 0.001$) (Figure 1b).

Correlations between miR-34a or miR-155-5p levels and clinicopathological features

As indicated in Table 1, miR-34a expression was significantly lower in patients with ECOG ≥ 2 than in those with ECOG < 2 (0.385 vs. 0.768, $P < 0.05$). Similarly, a significantly lower expression was detected in patients with SOX11 $< M$ (median value) than in patients with SOX11 $\geq M$ (0.162 vs. 0.503, $P < 0.05$) by Kruskal–Wallis rank test (Table 1).

The expression of miR-155-5p was 3.031 (1.27–3.643) in the MCL International Prognostic Index (MIPI) low-risk subgroup, 4.438 (2.704–5.134) in the medium-risk subgroup, and 4.438 (2.99–5.296) in the high-risk subgroup. A Kruskal–Wallis rank-sum test demonstrated statistical differences among the subgroups ($P = 0.0432$)
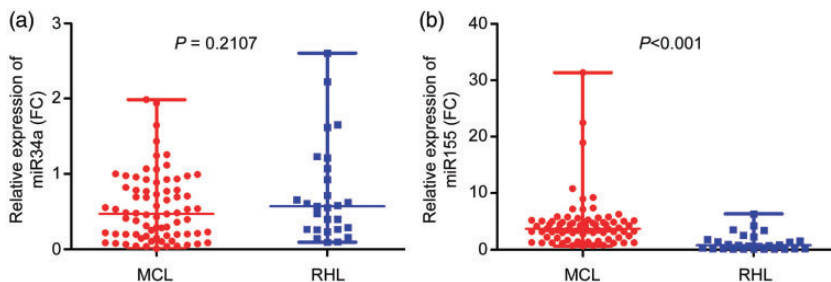

Figure 1. Expression levels of miR-34a and miR155-5p in the mantle cell lymphoma (MCL) and reactive lymphoid hyperplasia (RLH) groups. (a) No significant difference in expression between patients with MCL and RLH ($P = 0.2107$). The three horizontal lines represent the maximum, median, and minimum values of miR-34a in MCL (0.821, 0.478, and 0.202) and RLH (1.072, 0.572, and 0.265), respectively. (b) Expression of miR-155-5p in patients with MCL was significantly higher than that in patients with RLH ($P < 0.001$). The three horizontal lines represent the maximum, median, and minimum values of miR-155-5p in MCL (5.048, 3.482, and 2.136) and RLH (1.834, 0.774, and 0.083), respectively.

Table 1. Correlation between miR-34a and miR-155-5p levels and clinicopathological features in mantle cell lymphoma (MCL).

Variable	n	miR-34a M (Q1, Q3)	P-value	miR-155-5p M (Q1, Q3)	P-value
Sex					
Male	58	0.494 (0.203, 0.927)	0.4144	3.393 (2.085, 4.74)	0.1226
Female	17	0.47 (0.198, 0.576)		4.84 (3.031, 5.618)	
Age (y)					
≥60	46	0.54 (0.203, 0.933)	0.125	3.423 (1.828, 4.874)	0.4761
<60	29	0.362 (0.202, 0.553)		3.643 (3.031, 5.223)	
Morphology					
Classic morphology	69	0.485 (0.204, 0.821)	0.3337	3.458 (2.085, 4.874)	0.4065
Blastoid morphology	6	0.337 (0.066, 0.707)		4.512 (2.704, 5.408)	
Ki67					
≥30%	22	0.718 (0.195, 1)	0.1827	4.164 (2.274, 5.098)	0.9258
<30%	53	0.429 (0.203, 0.693)		3.458 (2.136, 5.011)	
ECOG					
≥2	48	0.385 (0.184, 0.69)	0.0214*	4.37 (2.489, 5.352)	0.0738
<2	27	0.768 (0.228, 0.976)		3.193 (1.51, 4.469)	
WBC					
≥10 × 10⁹/L	11	0.693 (0.107, 1.061)	0.3649	4.469 (2.136, 5.046)	0.4722
<10 × 10⁹/L	64	0.45 (90.203, 0.786)		3.422 (2.144, 5.054)	
LDH					
≥240 IU/L	17	0.771 (0.36, 1.061)	0.0611	3.891 (2.274, 4.74)	0.9093
<240 IU/L	58	0.42 (0.202, 0.73)		3.464 (2.085, 5.134)	
β2-MG					
≥3 mg/L	30	0.36 (0.173, 0.771)	0.4021	3.891 (2.274, 5.046)	0.8268
<3 mg/L	45	0.494 (0.283, 0.821)		3.452 (2.136, 5.011)	
p53					
Positive	16	0.466 (0.196, 0.906)	0.7269	4.025 (2.733, 5.513)	0.2889
Negative	59	0.478 (0.202, 0.787)		3.458 (1.51, 5.011)	
Ann Arbor stage					
I–II	19	0.429 (0.204, 0.821)	0.9272	3.643 (1.404, 5.098)	0.817
III–IV	56	0.491 (0.2, 0.835)		3.47 (2.359, 5.028)	
B symptoms					
No	62	0.444 (0.203, 0.886)	0.7742	3.393 (2.136, 5.134)	0.5242
Yes	13	0.576 (0.195, 0.73)		4.469 (3.482, 4.84)	
Bone marrow					
Involvement	22	0.531 (0.107, 0.771)	0.8706	4.454 (3.204, 5.223)	0.0513
Normal	53	0.459 (0.204, 0.821)		3.283 (1.51, 4.84)	
MIPI					
Low-risk	21	0.54 (0.228, 0.959)	0.1559	3.031 (1.27, 3.643)	0.0432*
Intermediate-risk	31	0.693 (0.195, 0.933)		4.438 (2.704, 5.134)	
High-risk	23	0.379 (0.173, 0.553)		4.438 (2.99, 5.296)	
SOX11 mRNA					
≥M	31	0.503 (0.219, 0.886)	0.0309*	3.458 (2.085, 4.84)	0.1352
<M	44	0.162 (0.107, 0.362)		5.117 (3.182, 5.598)	
Chemotherapy regimen					
CHOP/R-CHOP	36	0.481 (0.118, 0.964)	0.687	3.423 (1.587, 5.125)	0.574
yperCAVD/R-HyperCAVD	39	0.429 (0.204, 0.771)		3.891 (3.031, 5.046)	

Bone marrow involvement = lymphoma cells ≥ 5%; B symptoms = fever, night sweat, and weight loss.
*P < 0.05 indicates statistical significance.
LDH, lactate dehydrogenase; WBC, white blood cell; β 2-MG, β 2-microglobulin; MIPI, MCL International Prognostic Index; ECOG, Eastern Cooperative Oncology Group; SOX11, Sex-Determining Region Y-Box transcription factor 11; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-hyper-CVAD, rituximab, fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone.

(Table 1). The Nemenyi method was used for multiple comparisons[25] (Table 2). The expression of miR-155-5p in the low-risk subgroup was lower than that in the medium-risk and high-risk subgroups, with no statistical difference in the miR-155-5p expression between the high- and medium-risk subgroups.

Evaluation of the prognostic value of miR-34a and miR-155-5p in MCL

The ROC curve analysis showed that the area under the curve (AUC) of miR-34a and miR-155-5p expression was 0.5819 (95%CI = 0.4111–0.7527, $P = 0.477$) and 0.7784 (95%CI = 0.5912–0.9655, $P = 0.015$), and the cut-off values were 0.2150 and 2.110, respectively (Figure 2a and 2b).

Survival analysis using miR-34a and miR-155-5p expression levels in MCL

To determine the prognostic values of miR-34a and miR-155-5p in MCL, we divided the patients into two subgroups according to miRNA expression levels. Using the cut-off value of the ROC curve as the threshold for dividing patients, patient survival was evaluated using a Kaplan–Meier curve. The median survival time of patients with miR-34a expression ≤ 0.2150 was 25 months, whereas that of patients with miR-34a expression >0.2150 was 37 months. The median survival time of patients with miR-34a expression ≤ 0.2150

was significantly lower than that of patients with miR-34a expression >0.2150 ($P < 0.0001$) using the log-rank test (Figure 3a). The median survival time of patients in the miR-155-5p expression >2.11 subgroup was significantly shorter than that of patients in the miR-155-5p expression ≤ 2.11 subgroup (32 vs. 48 months), as indicated by analysis using the log-rank test ($P = 0.0046$) (Figure 3b).

Multivariate analysis of the main predictors in MCL

We performed a multivariate analysis of the main predictors, including International Prognostic Index (IPI), P53, miR-155-5p, and miR-34a. The results suggested that only IPI and miR-34a were associated with MCL prognosis. MiR-34a was a negative independent factor for OS. Survival time of patients with low miR-34a expression was 0.343 times that of patients with high miR-34a expression ($P < 0.001$). MiR-155-5p was also an independent factor for OS. Survival time of patients with high miR-155-5p expression was 1.734 times that of patients with low miR-155-5p expression ($P < 0.001$) (Table 3).

Discussion

MCL is a B-cell non-Hodgkin's lymphoma subtype with a poor prognosis. Although the recent treatment regimen containing a high cytarabine dose, combined with rituximab, and followed by APBSCT has

Table 2. Multiple comparisons of miR-155-5p levels among the three Mantle Cell Lymphoma International Prognostic Index (MIPI) subgroups.

MIPI subgroup	Difference	95%CI
High-risk vs. low-risk	14.552	0.208 to 28.896***
Intermediate-risk vs. low-risk	13.627	0.196 to 27.059***
High-risk vs. intermediate-risk	4.529	−8.963 to 19.527

*** indicates $P < 0.05$.
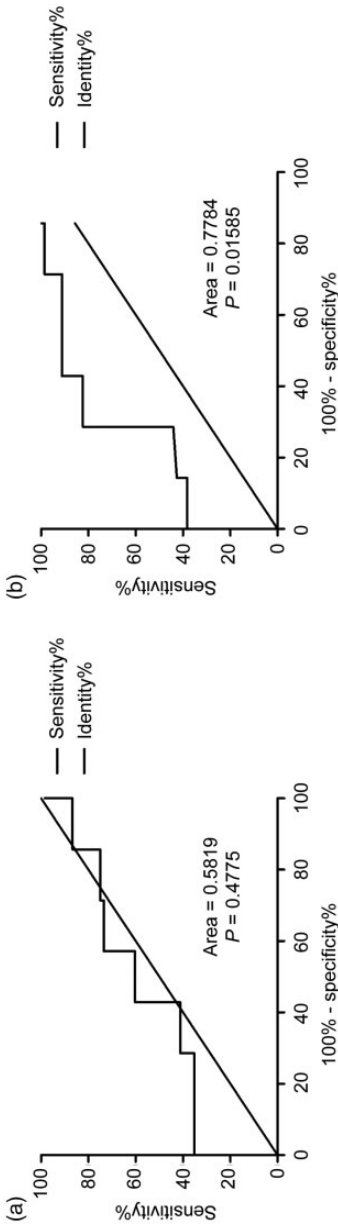MIPI, MCL International Prognostic Index; CI, confidence interval.

Figure 2. Evaluation of the prognostic value of miRNA-34a and miRNA-155-5p in mantle cell lymphoma (MCL). The receiver operating characteristic (ROC) curves of miR-34a and miR-155-5p are shown. (a) The area under the curve (AUC) of miR-34a was 0.5819 (95%CI = 0.4111–0.7527, $P = 0.4775$) and the cut-off value was 2.110. (b) The AUC of miR-155-5p was 0.7784 (95%CI = 0.5912–0.9655, $P = 0.01585$) and the cut-off value was 2.110.

significantly improved the remission rate and survival time of patients with MCL, there is no complete cure for this disease.[26] Therefore, it is important to identify new prognostic factors for targeted treatment to improve the remission rate and survival time of patients, especially in relapsed and refractory cases. Recent gene expression analyses have suggested the importance of miRNAs in the pathogenesis of hematological tumors.[7,14,27]

miR-155-5p is located on non-coding B cell integration cluster (BIC) transcripts on chromosome 21 and has a regulatory relationship with BIC transcript levels. It was the first miRNA identified to be involved in tumorigenesis and cancer development.[28] Previous studies indicate that miR-155-5p is highly expressed in most hematological tumors, including DLBCL, CLL, natural killer (NK)/T-cell lymphoma, and MCL.[28,29] Interestingly, studies on CLL indicate the association of high miR-155-5p expression with poor prognosis.[29–31]

In the present study, we found that miR-155-5p expression in patients with MCL was significantly higher than that in the control group, indicating that miR-155-5p may play a role in the development of the disease. A subgroup analysis revealed that miR-155-5p expression in the low-risk subgroup was significantly lower than that in the medium- and high-risk subgroups. Additionally, survival analysis confirmed that lower miR-155-5p expression is associated with an increased survival time in patients with MCL. These results suggest the possibility that miR-155-5p expression is related to the prognosis of MCL, and a high level of miR-155-5p expression is possibly indicative of poor prognosis. Limited by the small cohort of our study, future studies with a higher number of patients are needed to confirm the findings.

MiR-34a is a member of the miRNA-34 family along with miR-34b and miR-34c, with the expression of miR-34a higher
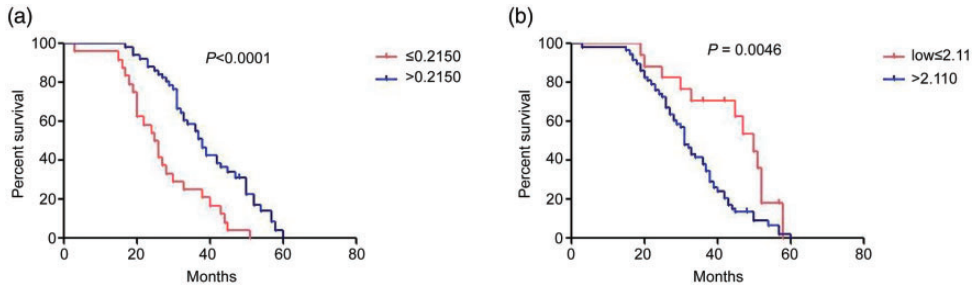
Figure 3. Survival analysis of miR-34a and miR-155-5p expression in patients with mantle cell lymphoma (MCL). (a) The median survival time of patients with miR-34a expression $\leq$ 0.2150 was significantly shorter than that of patients with miR-34a expression $>$ 0.2150 (25 vs. 37 months; $P < 0.0001$). (b) The median survival time of patients in the miR-155-5p expression $>$ 2.11 subgroup was significantly shorter than that of patients in the miR-155-5p expression $\leq$ 2.11 subgroup (32 vs. 48 months; $P = 0.0046$).

Table 3. Multivariate analysis of the main predictors in mantle cell lymphoma (MCL).

Variable	B	SE	Wald	df	Sig.	Exp(B)	95%CI for Exp(B)	
							Lower	Upper
miR-34a	−1.069	0.269	15.827	1	0.000	0.343	0.203	0.581
IPI	0.550	0.166	11.046	1	0.001	1.734	1.253	2.398

IPI, International Prognostic Index; CI, confidence interval; SE, standard error; B, partial regression coefficient; Wald, Wald test; Sig., significance; df, degree of freedom.

than that of other miRNAs in most tissues.[32,33] Recent studies have shown that 1p36, which includes the miR-34a site, is deleted in several tumors, resulting in low expression of miR-34a and high expression of its target gene *TP53*. This thereby affects cell differentiation, apoptosis, and senescence.[32,34,35] He et al.[16] demonstrated that significantly decreased expression of miR-34a, combined with high levels of Bcl-2 and p53, is observed in patients with gastric mucosa-associated lymphoma and DLBCL, with miR-34a serving as an independent poor prognostic factor.

In this study, the expression levels of miR-34a in patients with newly diagnosed MCL demonstrated no significant difference compared with those of the control group. This could be explained by the relatively small number of cases in our study or confounding factors. However, the subgroup analysis demonstrated that the expression of miR-34a in patients with ECOG $\geq$ 2 was lower than that in patients with ECOG $<$ 2. In addition, the survival analysis indicated that low miR-34a expression is related to a shorter survival time than high miR-34a expression, suggesting that low miR-34a expression may be a factor for poor prognosis. In this study, an association between miR-34a and its target gene *TP53* was not found. This could be explained by the complex interacting mechanisms and involvement of more than one biological pathway. Although this study showed a correlation between prognosis and both miR-155-5p and miR-34a, the multivariate analysis suggested that miR-34a, rather than miR-155-5p, is an independent prognostic factor. This finding is not consistent with the previous prediction and may be related to the small sample

size, retrospective nature of the study, or sample bias.

In conclusion, the expression levels of miR-34a and miR-155-5p may be correlated with prognosis in patients with MCL, and this could possibly help differentiate patients with poor prognosis. However, further studies with a higher number of patients are warranted.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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