

Blood MALT1 expression levels reflect the lymph node stage and disease-free survival in patients with non-small cell lung cancer

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Abstract. Mucosa-associated lymphoid tissue lymphoma translocation protein-1 (MALT1) promotes cancer development via both cancer cell-intrinsic and -extrinsic mechanisms, and can regulate cancer immunity and immune escape. Therefore, the present study aimed to assess the expression levels of MALT1 in blood samples and the association with clinical features, treatment options and survival outcomes in patients with non-small cell lung cancer (NSCLC). Peripheral blood mononuclear cells (PBMCs) from a total of 125 patients with resectable NSCLC prior to treatment (neoadjuvant therapy or surgery) were collected. The mRNA expression levels of MALT1 were detected by reverse transcription-quantitative PCR. Furthermore, the PBMC samples from 20 healthy individuals served as the control group. The results showed that MALT1 was upregulated in the blood samples of patients with NSCLC compared with the control group (~3.4:1 fold; $P<0.001$). Subsequently, for correlation analysis, blood MALT1 expression levels in patients with NSCLC were categorized into four grades according to the quartiles (Q1, Q2, Q3 and Q4). It was indicated that the MALT1 quartile was positively correlated with the tumor-node-metastasis ($P=0.036$) and N stage ($P=0.026$), and it had a tendency to be correlated with poor differentiation ($P=0.091$) and T stage ($P=0.058$), but this did not reach statistical significance. However, the MALT1 quartile was not associated with neoadjuvant therapy, surgical type or adjuvant therapy. Kaplan-Meier curves demonstrated that the MALT1 quartile was notably associated with shorter disease-free survival (DFS; $P=0.009$); however, the MALT1 quartile only showed a tendency to be associated with poor overall survival, but this did not reach statistical significance ($P=0.118$). Subsequent multivariate Cox analysis showed that the MALT1 quartile could independently

predict shorter DFS ($P=0.016$). In conclusion, the present study suggested that blood MALT1 expression levels could potentially predict the stage of lymph node metastasis and DFS in patients with NSCLC.

Introduction

Lung cancer, a common fatal malignancy, contributes to 2.21 million new cancer cases and 1.80 million new cancer-related deaths annually worldwide (1). In China, 0.83 million new lung cancer cases and 0.66 million new lung cancer-related deaths are recorded every year (2), thus causing heavy burdens to the patients and society (3,4). Non-small cell lung cancer (NSCLC) accounts for ~85% of lung cancer cases in China, thus giving an opportunity for research and development (5). Along with the advances in molecular detection technology and big-data gathering and analysis, biomarker-based precision therapy is considered an effective approach to improve prognosis and reduce disease burden in patients with NSCLC (6-8). However, the detection of a large proportion of predictive biomarkers requires the isolation of tissue lesions, which is not always feasible, particularly in patients who cannot undergo surgery.

Mucosa-associated lymphoid tissue lymphoma translocation protein-1 (MALT1), acting as a scaffolding gene/protein that triggers the activation of NF- κ B transcription factors and as a protease to modify immune activation-related signaling via diversified substrate cleavage, was recently discovered to facilitate cancer development via both cancer cell-intrinsic and -extrinsic mechanisms (9,10). MALT1 has been reported to promote cancer cell viability, migration, invasion and drug resistance, and particularly resistance to immune checkpoint inhibitors, in several malignancies, such as breast cancer, prostate cancer, hepatocellular carcinoma and lymphomas (11-15). Previous studies have also demonstrated that MALT1 was upregulated and associated with poor prognosis in patients with colorectal cancer, malignant melanoma and lymphomas (16-18). In terms of lung cancer, MALT1 could promote cancer progression via interacting with caspase recruitment domain-coiled-coil complexes and NF- κ B activation (19,20). Apart from the aforementioned direct regulation of cancer by MALT1, other studies indicated that MALT1 could regulate cancer immunity to promote cancer progression (15,21). These findings supported the potential of MALT1 expression levels as a prognostic biomarker in patients with NSCLC.

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Therefore, the present study aimed to investigate the utility of the expression levels of MALT1 in blood samples from patients with NSCLC and their association with the clinical features, treatment options and survival outcomes for these patients.

Patients and methods

Subjects. In the present study, a total of 125 patients with NSCLC who underwent tumor resection surgery between April 2019 and January 2022 at North Sichuan Medical University affiliated Nanchong Central Hospital (Nanchong, China) were enrolled. The inclusion criteria were as follows: i) Patients diagnosed with NSCLC by pathological examination; ii) aged ≥ 18 years; iii) received tumor resection surgery; and iv) followed the normal follow-up requirements. In addition, the exclusion criteria were as follows: i) Patients whose NSCLC was accompanied by other primary types of cancer; ii) suffering from hematological malignancies; iii) with needle or blood phobia; and iv) pregnant women or lactating mothers. Additionally, a total of 20 healthy individuals undergoing physical examination between February and March 2024 were enrolled as the control group. The recruitment criteria for individuals into the control group were as follows: i) Subjects without any abnormalities in recent physical examinations; ii) aged >18 years; and iii) those who were willing to cooperate with blood collection. The exclusion criteria of patients with NSCLC were also applied to individuals in the healthy control group. The present study was approved by the Ethics Committee of North Sichuan Medical University affiliated Nanchong Central Hospital (approval no. 2024018; Nanchong, China), and most patients with NSCLC and the controls had provided written informed consent, while a waiver was obtained for certain patients with NSCLC who had not provided informed consent.

Data collection and sample detection. The clinical characteristics of patients with NSCLC, including demographic, and disease- and therapy-related data, were collected. The tumor-node-metastasis (TNM) stage was defined according to the guidelines provided by the International Association for the Study of Lung Cancer (22). Prior to treatment initiation, neoadjuvant therapy or tumor resection surgery, 2 ml peripheral blood (PB) was collected from all patients with NSCLC. In addition, PB from healthy controls was collected immediately after enrollment. For MALT1 detection, PB mononuclear cells (PBMCs) were separated from PB, and MALT1 levels were detected by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) assay. For qPCR, the thermocycling was as follows: 95°C for 60 sec, 1 cycle; 95°C for 15 sec and 61°C for 60 sec, 40 cycles. GAPDH was used as the internal reference and MALT1 levels were quantified using the $2^{-\Delta\Delta C_q}$ method (23). The primer sequences were as follows: MALT1 forward (F), 5'-TCT TGGCTGGACAGTTTGTGA-3' and reverse (R), 5'-GCT CTCTGGGATGTCGCAA-3'; GAPDH F, 5'-TGACCACAG TCCATGCCATCAC-3' and R, 5'-GCCTGCTTCACCACC TTCTTGA-3'. The corresponding kits used for RT-qPCR are listed in Table SI and the kits were used according to the manufacturer's instructions.

Grading of MALT1 levels. MALT1 expression levels in patients with NSCLC were divided into four different grades. The quartile (Q) values for each grade were as follows: i) Q1, MALT1 ranged from the minimum value, 0.690, to the 1st quartile value, 2.190 (Q1, 0.690-2.190); ii) Q2, MALT1 ranged from the 1st quartile value to the 2nd quartile value, 3.600 (2.190-3.600); iii) Q3, MALT1 ranged from the 2nd quartile value to the 3rd quartile value, 5.945 (Q3, 3.600-5.945); and iv) Q4, MALT1 ranged from the 3rd quartile value to the maximum value, 12.770 (Q4, 5.945-12.770).

Follow-up and evaluation. Routine follow-up was conducted, with a median follow-up time of 18.1 months (range, 2.8-39.1 months). In the first year after surgery, follow-up was conducted once every 3 months and once every 3-6 months thereafter. If the patients experienced disease recurrence, a follow-up was performed once every 2 months. During the follow-up, the disease progression status, death and the corresponding periods were recorded. The accumulating disease-free survival (DFS) and overall survival (OS) rates were calculated.

Bioinformatics. The association of MALT1 gene expression levels with TNM stage, DFS and OS in patients with NSCLC using publicly data was performed as well, which was based on the Gene Expression Profiling Interactive Analysis (GEPIA) database (<http://gepia.cancer-pku.cn/>). Correlation analysis of MALT1 gene expression with immune infiltrates in various types of cancer and NSCLC specifically using publicly available data was performed using the TIMER database (<http://timer.comp-genomics.org/>).

Statistical analyses. Data analyses were performed using SPSS (version 26.0; IBM Corp.). Categorical data were expressed as number (percentage), normally distributed continuous data were expressed as the mean $\pm$ standard deviation and skewedly distributed continuous data were expressed as the median [interquartile range (IQR)]. To compare the clinical characteristics between different grades of MALT1, the Mann-Whitney U-test, χ^2 test or Fisher's exact test was carried out. In addition, to compare accumulating DFS/OS rates between patients with NSCLC with different grades of MALT1, a log-rank test was performed. The results were displayed by Kaplan-Meier curves. Enter-method Cox regression models were used to identify the factors that were independently associated with DFS or OS. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of patients with NSCLC. A total of 125 patients with NSCLC were included in the present study. The mean age of the patients with NSCLC was 57.1 ± 12.3 years. Among them, 27.2 and 72.8% were ≥ 65 and < 65 years old, respectively. A total of 54.4% of patients were males and 45.6% were females (Table I), while 61.6, 28.8 and 9.6% of the patients were categorized as lung adenocarcinoma, lung squamous cell carcinoma and others, respectively. In addition, 36.0% of the cases had poor differentiation, and 8.0, 8.8, 20.0, 39.2, 21.6 and 2.4% of patients were of TNM stage of IA, IB, IIA,

Table I. Clinical characteristics of patients with NSCLC.

Characteristics	Total (n=125)	Q1-MALT1 (n=31)	Q2-MALT1 (n=32)	Q3-MALT1 (n=31)	Q4-MALT1 (n=31)	P-value
Age, years						0.245
<65	91 (72.8)	24 (26.4)	21 (23.1)	26 (28.6)	20 (22.0)	
≥65	34 (27.2)	7 (20.6)	11 (32.4)	5 (14.7)	11 (32.4)	
Sex						0.793
Female	57 (45.6)	15 (26.3)	13 (22.8)	16 (28.1)	13 (22.8)	
Male	68 (54.4)	16 (23.5)	19 (27.9)	15 (22.1)	18 (26.5)	
Smoking status						0.463
Never smoked	84 (67.2)	24 (28.6)	22 (26.2)	19 (22.6)	19 (22.6)	
Former smoker	15 (12.0)	3 (20.0)	5 (33.3)	5 (33.3)	2 (13.3)	
Current smoker	26 (20.8)	4 (15.4)	5 (19.2)	7 (26.9)	10 (38.5)	
Histological type						0.263
Lung adenocarcinoma	77 (61.6)	16 (20.8)	17 (22.1)	21 (27.3)	23 (29.9)	
Lung squamous cell carcinoma	36 (28.8)	9 (25.0)	13 (36.1)	8 (22.2)	6 (16.7)	
Other	12 (9.6)	6 (50.0)	2 (16.7)	2 (16.7)	2 (16.7)	
Poor differentiation	45 (36.0)	9 (20.0)	9 (20.0)	10 (22.2)	17 (37.8)	0.091
T stage						0.058
1	14 (11.2)	6 (42.9)	4 (28.6)	1 (7.1)	3 (21.4)	
2	68 (54.4)	19 (27.9)	19 (27.9)	20 (29.4)	10 (14.7)	
3	34 (27.2)	5 (14.7)	6 (17.6)	8 (23.5)	15 (44.1)	
4	9 (7.2)	1 (11.1)	3 (33.3)	2 (22.2)	3 (33.3)	
N stage						0.026
0	66 (52.8)	21 (31.8)	14 (21.2)	14 (21.2)	17 (25.8)	
1	54 (43.2)	9 (16.7)	18 (33.3)	17 (31.5)	10 (18.5)	
2	5 (4.0)	1 (20.0)	0 (0.0)	0 (0.0)	4 (80.0)	
M stage						(-)
0	125 (100.0)	31 (24.8)	32 (25.6)	31 (24.8)	31 (24.8)	
TNM detailed stage						0.036
IA	10 (8.0)	4 (40.0)	3 (30.0)	1 (10.0)	2 (20.0)	
IB	11 (8.8)	2 (18.2)	3 (27.3)	3 (27.3)	3 (27.3)	
IIA	25 (20.0)	13 (52.0)	5 (20.0)	4 (16.0)	3 (12.0)	
IIB	49 (39.2)	7 (14.3)	14 (28.6)	18 (36.7)	10 (20.40)	
IIIA	27(21.6)	5 (18.5)	7 (25.9)	5 (18.5)	10 (37.0)	
IIIB	3 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)	
Neoadjuvant chemotherapy						0.188
No	102 (81.6)	27 (26.5)	25 (24.5)	28 (27.5)	22 (21.6)	
Yes	23 (18.4)	4 (17.4)	7 (30.4)	3 (13.0)	9 (39.1)	
Neoadjuvant TKI						0.754
No	121 (96.8)	31 (25.6)	31 (25.6)	30 (24.8)	29 (24.0)	
Yes	4 (3.2)	0 (0.0)	1 (25.0)	1 (25.0)	2 (50.0)	
Neoadjuvant ICI						0.571
No	120 (96.0)	31 (25.8)	31 (25.8)	29 (24.2)	29 (24.2)	
Yes	5 (4.0)	0 (0.0)	1 (20.0)	2 (40.0)	2 (40.0)	
Surgical type						0.817
Thoracoscopic surgery	19 (15.2)	5 (26.3)	6 (31.6)	5 (26.3)	3 (15.8)	
Thoracotomy	106 (84.8)	26 (24.5)	26 (24.5)	26 (24.5)	28 (26.4)	
Adjuvant chemotherapy						0.157
No	42 (33.6)	15 (35.7)	9 (21.4)	11 (26.2)	7 (16.7)	
Yes	83 (66.4)	16 (19.3)	23 (27.7)	20 (24.1)	24 (28.9)	

Table I. Continued.

Characteristics	Total (n=125)	Q1-MALT1 (n=31)	Q2-MALT1 (n=32)	Q3-MALT1 (n=31)	Q4-MALT1 (n=31)	P-value
Adjuvant TKI						0.406
No	102 (81.6)	25 (24.5)	29 (28.4)	23 (22.5)	25 (24.5)	
Yes	23 (18.4)	6 (26.1)	3 (13.0)	8 (34.8)	6 (26.1)	
Adjuvant ICI						0.737
No	110 (88.0)	29 (26.4)	28 (25.5)	26 (23.6)	27 (24.5)	
Yes	15 (12.0)	2 (13.3)	4 (26.7)	5 (33.3)	4 (26.7)	

The P-value reflects the association between different grades of MALT1 and the characteristics of patients with NSCLC. NSCLC, non-small cell lung cancer; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile; TNM, tumor-node-metastasis; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor. (-): Since all patients were at M0 stage, therefore the analysis cannot be performed, so (-) was presented.

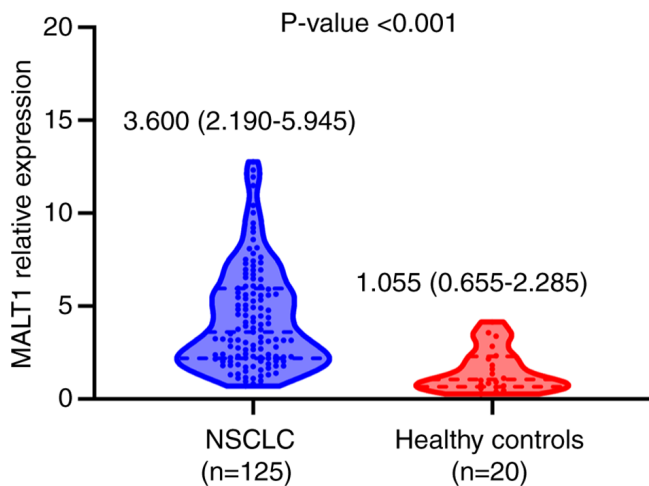


Figure 1. Comparison of blood MALT1 mRNA expression levels between patients with NSCLC and health controls. The values printed in the figure are expressed as the median (interquartile range). NSCLC, non-small cell lung cancer; MALT, mucosa-associated lymphoid tissue lymphoma translocation protein-1.

IIB, IIIA and IIIB, respectively. The mean age of the healthy control subjects was 55.5 ± 5.2 years, consisting of 50% females and 50% males. Age ($P=0.384$) and sex ($P=0.714$) were not significantly different between the healthy controls and patients with NSCLC (Table SII).

MALT1 is aberrantly expressed in the blood and is associated with the clinical characteristics of patients with NSCLC. The blood MALT1 mRNA expression levels were quantified in the 20 healthy subjects and patients with NSCLC. The relative expression levels of MALT1 mRNA were increased in the blood samples of patients with NSCLC (median, 3.60; IQR, 2.19-5.95) compared with the healthy controls (median, 1.06; IQR, 0.66-2.29; $P<0.001$; Fig. 1), suggesting MALT1 was aberrantly expressed in the blood of patients with NSCLC. Subsequently, to analyze the association between blood MALT1 levels and clinical features, treatment options and prognosis in patients with NSCLC, the mRNA expression

levels of MALT1 were divided into four groups, according to the quartiles (Q1, Q2, Q3 and Q4). The results demonstrated that the blood MALT1 quartile was markedly positively associated with the N ($P=0.026$) and TNM ($P=0.036$) stages in patients with NSCLC. Additionally, MALT1 expression levels displayed a tendency to be positively associated with poor differentiation ($P=0.091$) and T stage ($P=0.058$; Table I), but this did not reach statistical significance. By contrast, the blood MALT1 quartile was not associated with other clinical characteristics or with neoadjuvant therapy, surgical type or adjuvant therapy.

Prognostic value of blood MALT1 levels in patients with NSCLC. The blood MALT1 quartile was associated with shorter DFS ($P=0.009$), with 3-year accumulating DFS rates of 92.9, 68.8, 41.4 and 28.2% in patients with MALT1 levels at Q1, Q2, Q3 and Q4, respectively (Fig. 2A). However, the blood MALT1 quartile only showed a tendency to be associated with poor OS in these patients ($P=0.118$), but it did not reach statistical significance; 3-year accumulating OS rates of 100.0, 84.4, 65.7 and 44.5% were recorded in patients with MALT1 levels at Q1, Q2, Q3 and Q4, respectively (Fig. 2B). The aforementioned data suggested that blood MALT1 expression levels may potentially predict DFS; however, they lacked efficiency in OS estimations of patients with NSCLC. Furthermore, multivariate Cox analysis was performed to identify the factors that could affect DFS and OS in patients with NSCLC. Increased MALT1 quartile [$P=0.016$; hazard ratio (HR), 1.712], age ($P=0.026$; HR, 1.043) and TNM stage ($P=0.001$; HR, 10.734) had a negative impact on DFS independently, while adjuvant tyrosine kinase inhibitor therapy ($P=0.038$; HR, 0.244) was independently associated with satisfied DFS (Fig. 3). In terms of OS, a higher MALT1 quartile ($P=0.293$; HR, 1.477) was not significantly associated with OS. However, a higher TNM stage ($P=0.009$; HR, 21.113) was significantly associated with lower OS rates (Fig. 4).

Bioinformatic analyses based on public database. GEPIA is a developed interactive web server for analyzing the RNA sequencing expression data from the The Cancer Genome Atlas and the Genotype-Tissue Expression projects, using a

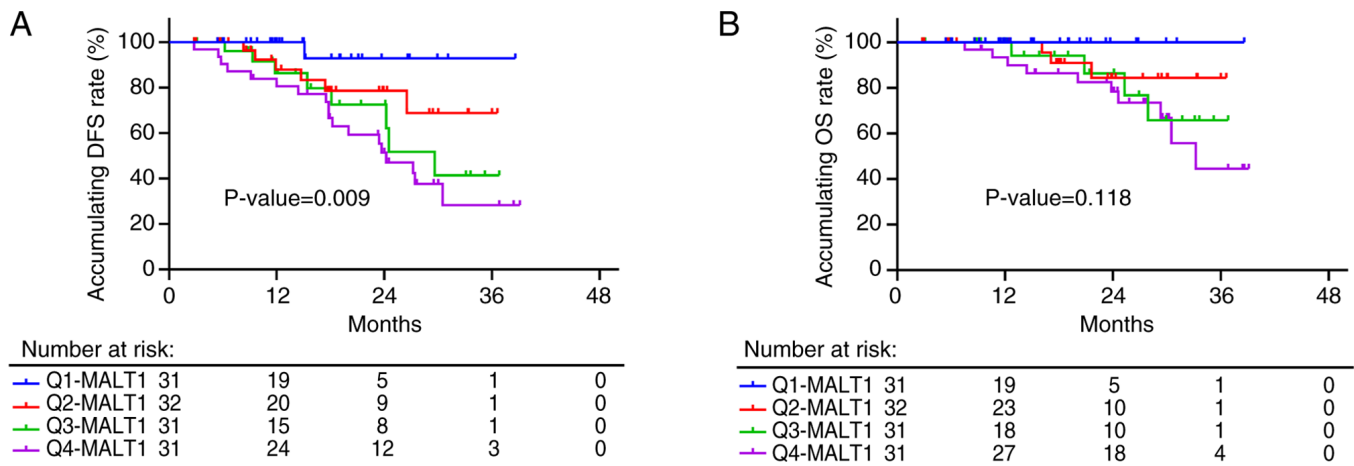


Figure 2. Correlation of MALT1 quartiles with prognosis of patients with NSCLC. Correlation of MALT1 quartiles with (A) DFS and (B) OS reflected by Kaplan-Meier curves in patients with NSCLC. NSCLC, non-small cell lung cancer; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein-1; DFS, disease-free survival; OS, overall survival.

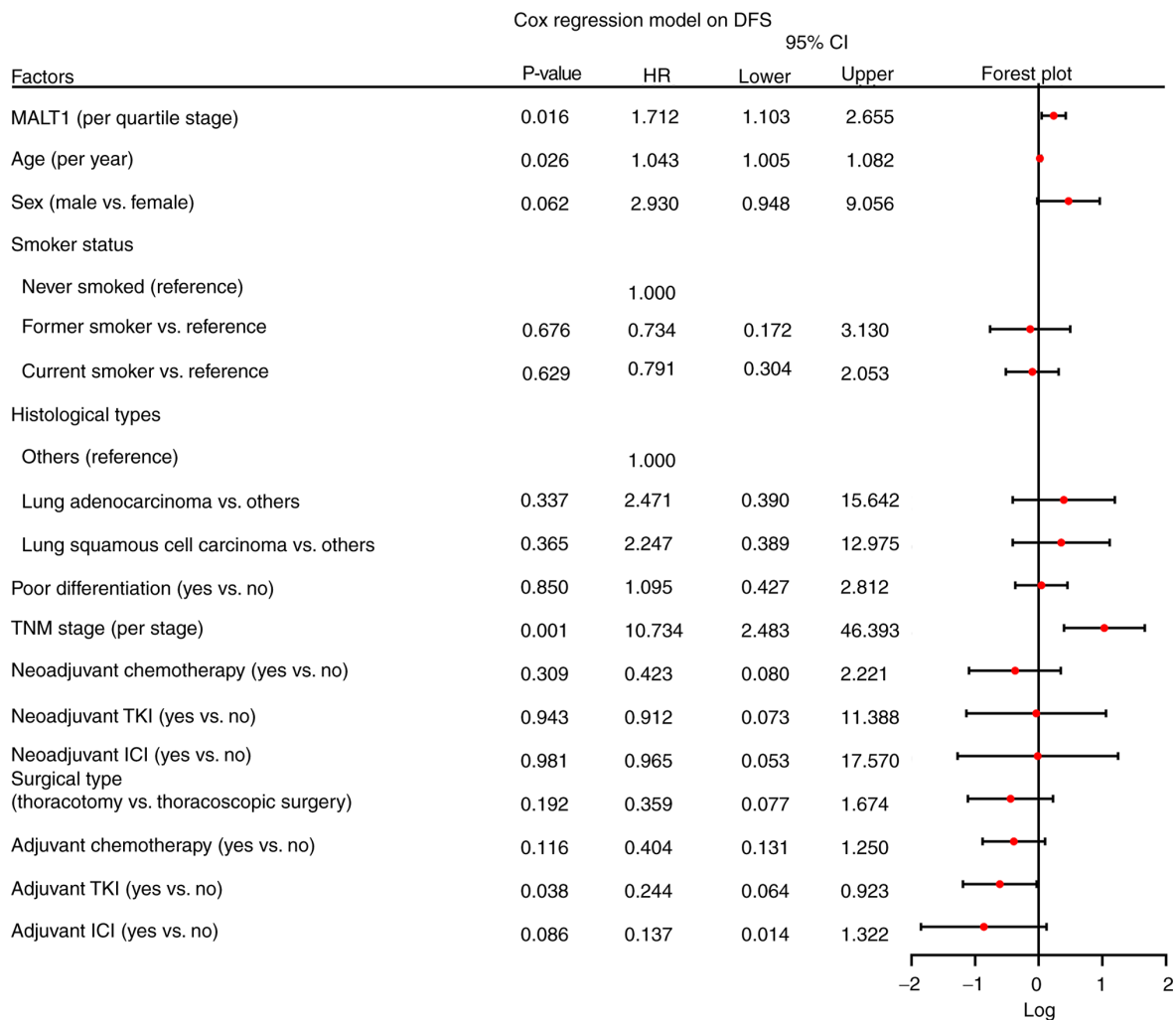


Figure 3. Multivariate Cox analysis for DFS. MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein-1; DFS, disease-free survival; HR, hazard ratio; TNM, tumor-node-metastasis; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor.

standard processing pipeline (24). With the use of GEPIA, it was observed that MALT1 was not related to TNM stage, DFS or OS in patients with lung adenocarcinoma (Fig. S1A),

nor in patients with lung squamous cell carcinoma (Fig. S1B). MALT1 showed a notable association with DFS in lung squamous cell carcinoma but this was not of statistical significance.

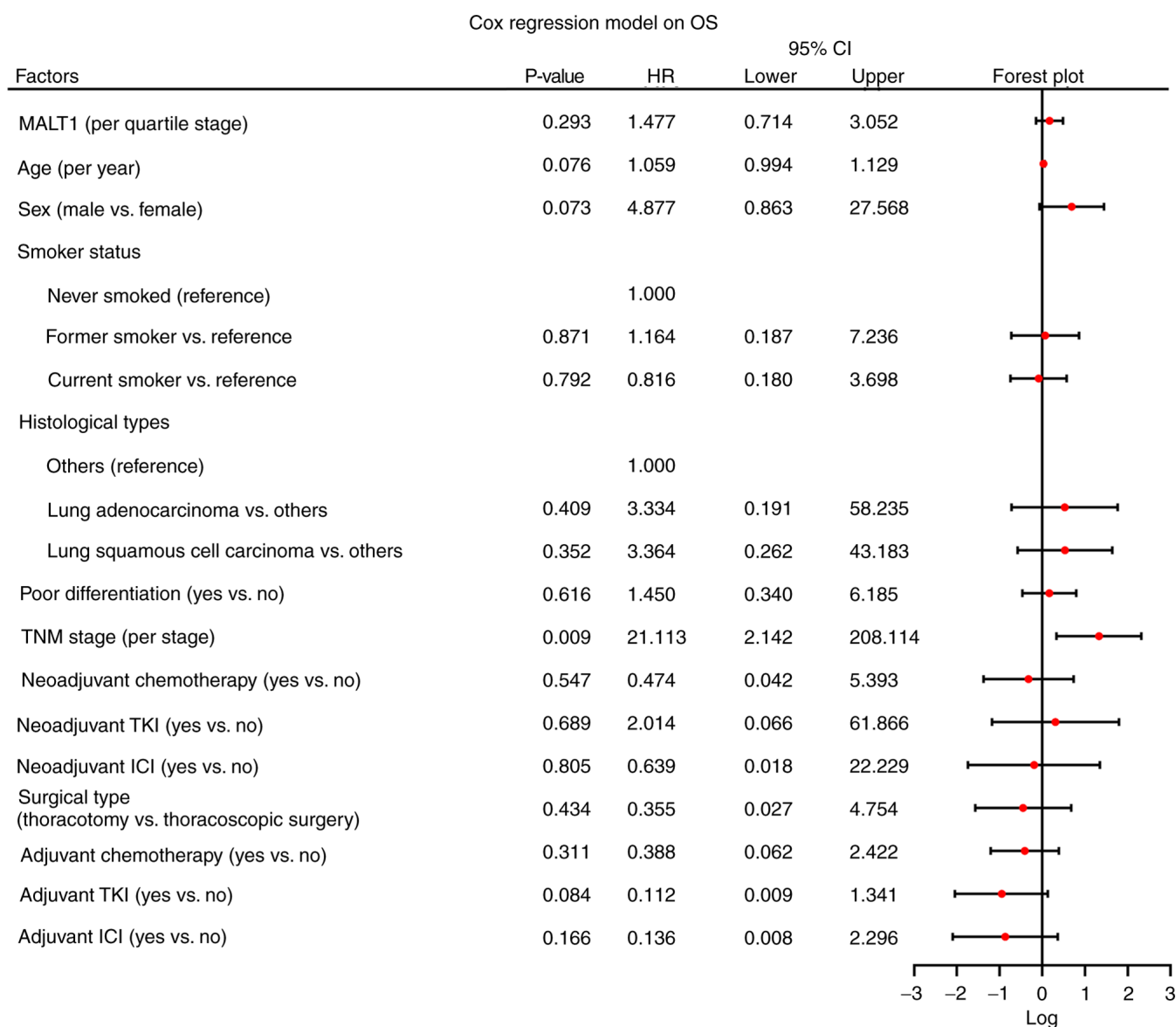


Figure 4. Multivariate Cox analysis for OS. OS, overall survival; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein-1; HR, hazard ratio; TNM, tumor-node-metastasis; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor.

The TIMER database is a comprehensive resource for the systematic analysis of immune infiltrates across diverse types of cancer (25). The TIMER database was used for immune analysis and demonstrated that MALT1 expression levels were correlated with macrophages and CD8⁺ T cells in various types of cancer (Fig. S1C and D). Regarding NSCLC, MALT1 was closely correlated with macrophages (particularly the M1 type) and CD8⁺ T cells in lung adenocarcinoma, but the correlation was lower in lung squamous cell carcinoma.

Discussion

It has been suggested that MALT1 is a significant carcinogenic factor that promotes the initiation and progression of several types of cancer (11-21). More specifically, the role of MALT1 inhibitor as a candidate treatment option for hepatocellular carcinoma, colorectal cancer, chronic lymphocytic leukemia and glioblastoma both *in vivo* and *in vitro*, has

been recently investigated (13,26-28). Due to these functions, MALT1 has attracted increasing attention as a biomarker in different types of cancer. Previous studies demonstrated that MALT1 was upregulated in colorectal cancer, melanoma and lymphomas (16-18). However, the aforementioned studies detected the expression levels of MALT1 in cancerous tissues. Therefore, data on the expression levels of MALT1 in blood samples are lacking. The present study demonstrated that MALT1 was upregulated in blood samples from patients with NSCLC compared with the control group (~3.4-fold). This finding could be due to the possible promoting role of MALT1 in lung cancer (19,20) and its effects on CD8⁺ T-cell functions, immune escape and anticancer immunity (29-31).

Subsequently, the present study also demonstrated that blood MALT1 expression levels were positively associated with N and TNM stages in patients with NSCLC, and showed a notable positive association with poor differentiation and T stage, thus supporting the possible role of MALT1 in

predicting tumor progression or disease burden in patients with NSCLC. These findings could be for the following reasons: i) Previous studies demonstrated that MALT1 could directly activate NF- κ B to promote NSCLC progression, while blood MALT1 levels could also reflect the expression levels of MALT1 in tumor tissues, to a certain extent (32,33); ii) in addition to the NF- κ B signaling pathway, bioinformatics analysis in the Kyoto Encyclopedia of Genes and Genomes predicted that MALT1 could also regulate the C-type lectin, T-cell and B-cell receptor signaling pathways, thus promoting NSCLC progression (34,35); and ii) other studies also suggested that the T-cell receptor signaling pathway, a notable downstream pathway of MALT1, could affect tumor immunity and immune escape to promote NSCLC progression (36-38).

The present study also suggested that blood MALT1 levels may predict the prognosis of patients with NSCLC. Kaplan-Meier curves predicted that the expression levels of MALT1 in the blood of patients with NSCLC were associated with a shorter DFS, while they showed a notable association with worse OS. Further adjustment by multivariate Cox analysis demonstrated that the expression levels of MALT1 could independently predict unsatisfied DFS. The prognostic value of blood MALT1 levels could be due to the following: i) Correlation analysis revealed that MALT1 was associated with advanced tumor conditions, such as N and TNM stages, thus possibly affecting the prognosis of patients with NSCLC; and ii) a large proportion of patients with NSCLC were treated with adjuvant therapies. It has been reported that MALT1 regulates the sensitivity of patients to adjuvant therapies (19,21,39). Therefore, the aforementioned findings could affect the prognosis of patients with NSCLC. Furthermore, the lack of significance regarding the association between MALT1 levels and OS could be due to the fact that OS could be affected by several factors, such as treatment after tumor recurrence, comorbidity and supportive treatment. These factors may weaken the predictive value of MALT1 regarding the prognosis of patients with NSCLC. Furthermore, GEPIA database analysis revealed that MALT1 was not correlated with DFS or OS in lung cancer and the difference between the aforementioned GEPIA data and the present findings may have been due to the fact that tumor tissue was used in GEPIA, while blood samples were used in the present study.

However, the present study had certain limitations. First, the present study only included surgical patients with NSCLC to avoid interference, since the prognosis of advanced cases was far from surgical ones, which limited the generalizability of the study findings. More patients with different types of lung cancer would have been needed to be included to obtain more comprehensive conclusions. Second, the sample size of the present study was relatively small, which may limit the reliability and generalizability of the results. Therefore, more large population-based validation studies are needed to verify the results of the present study. Third, the follow-up time of the present study was relatively short and it was difficult to assess the correlation between blood MALT1 and long-term prognosis. Therefore, longer follow-up studies are needed to verify the long-term prognostic value of blood MALT1 expression levels. Finally, no investigation into the mechanistic relationship between blood MALT1 levels and the development and prognosis of NSCLC was performed, which could be further evaluated in future studies.

In conclusion, the results of the present study suggested that blood MALT1 levels could potentially reflect the stage of lymph node metastasis and predict DFS in patients with NSCLC. This suggests the potential of blood MALT1 to be a prognostic biomarker in patients with NSCLC, which could help facilitate personalized treatment via early identifying prognostic risk stratification. However, future large-scale studies with a longer follow-up duration are needed to further validate the results of the present study.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XZ contributed to the study conception and design. Data collection and analysis were performed by FZ and BW. XP was responsible for the interpretation of data for the present study. XZ and FZ confirm the authenticity of all the raw data. All authors contributed to drafting of article and revising it critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of North Sichuan Medical University (Nanchong, China) approved the present study (approval no. 2024018). Most NSCLC patients and the controls had provided written informed consent, while a waiver was obtained for certain patients with NSCLC who had not provided informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71: 209-249, 2021.
2. Zheng RS, Zhang SW, Sun KX, Chen R, Wang SM, Li L, Zeng HM, Wei WW and He J: Cancer statistics in China, 2016. *Zhonghua Zhong Liu Za Zhi* 45: 212-220, 2023 (In Chinese).

3. Leiter A, Veluswamy RR and Wisnivesky JP: The global burden of lung cancer: Current status and future trends. *Nat Rev Clin Oncol* 20: 624-639, 2023.
4. Qi J, Li M, Wang L, Hu Y, Liu W, Long Z, Zhou Z, Yin P and Zhou M: National and subnational trends in cancer burden in China, 2005-20: An analysis of national mortality surveillance data. *Lancet Public Health* 8: e943-e955, 2023.
5. Chen P, Liu Y, Wen Y and Zhou C: Non-small cell lung cancer in China. *Cancer Commun (Lond)* 42: 937-970, 2022.
6. Yang SR, Schultheis AM, Yu H, Mandelker D, Ladanyi M and Buttner R: Precision medicine in non-small cell lung cancer: Current applications and future directions. *Semin Cancer Biol* 84: 184-198, 2022.
7. Restrepo JC, Duenas D, Corredor Z and Liscano Y: Advances in genomic data and biomarkers: Revolutionizing NSCLC diagnosis and treatment. *Cancers (Basel)* 15: 3474, 2023.
8. Tostes K, Siqueira AP, Reis RM, Leal LF and Arantes L: Biomarkers for immune checkpoint inhibitor response in NSCLC: Current developments and applicability. *Int J Mol Sci* 24: 11887, 2023.
9. O'Neill TJ, Tofaute MJ and Krappmann D: Function and targeting of MALT1 paracaspase in cancer. *Cancer Treat Rev* 117: 102568, 2023.
10. Gomez Solsona B, Schmitt A, Schulze-Osthoff K and Hailfinger S: The paracaspase malt1 in cancer. *Biomedicines* 10: 344, 2022.
11. Zhou B, Mo Z, Lai G, Chen X, Li R, Wu R, Zhu J and Zheng F: Targeting tumor exosomal circular RNA cSERPINE2 suppresses breast cancer progression by modulating MALT1-NF- κ B axis of tumor-associated macrophages. *J Exp Clin Cancer Res* 42: 48, 2023.
12. Vanneste D, Staal J, Haegman M, Driege Y, Carels M, Van Nuffel E, De Bleser P, Saeyns Y, Beyaert R and Afonina IS: CARD14 signaling ensures cell survival and cancer associated gene expression in prostate cancer cells. *Biomedicines* 10: 2008, 2022.
13. Kurden-Pekmezci A, Cakiroglu E, Eris S, Mazi FA, Coskun-Deniz OS, Dalgic E, Oz O and Senturk S: MALT1 paracaspase is overexpressed in hepatocellular carcinoma and promotes cancer cell survival and growth. *Life Sci* 323: 121690, 2023.
14. Minderman M, Lantermans HC, Gruneberg LJ, Cillessen SAGM, Bende RJ, van Noesel CJM, Kersten MJ, Pals ST and Spaargaren M: MALT1-dependent cleavage of CYLD promotes NF- κ B signaling and growth of aggressive B-cell receptor-dependent lymphomas. *Blood Cancer J* 13: 37, 2023.
15. Di Pilato M, Gao Y, Sun Y, Fu A, Grass C, Seeholzer T, Feederle R, Mazo I, Kazer SW, Litchfield K, *et al*: Translational studies using the MALT1 inhibitor (S)-Mepazine to induce treg fragility and potentiate immune checkpoint therapy in cancer. *J Immunother Precis Oncol* 6: 61-73, 2023.
16. Li C, Yu F and Xu W: Early low blood MALT1 expression levels forecast better efficacy of PD-1 inhibitor-based treatment in patients with metastatic colorectal cancer. *Oncol Lett* 26: 329, 2023.
17. Wang Y, Zhang G, Jin J, Degan S, Tameze Y and Zhang JY: MALT1 promotes melanoma progression through JNK/c-Jun signaling. *Oncogenesis* 6: e365, 2017.
18. Tibiletti MG, Martin V, Bernasconi B, Del Curto B, Pecciarini L, Uccella S, Pruneri G, Ponzoni M, Mazzucchelli L, Martinelli G, *et al*: BCL2, BCL6, MYC, MALT 1, and BCL10 rearrangements in nodal diffuse large B-cell lymphomas: A multicenter evaluation of a new set of fluorescent in situ hybridization probes and correlation with clinical outcome. *Hum Pathol* 40: 645-652, 2009.
19. Pan D, Jiang C, Ma Z, Blonska M, You MJ and Lin X: MALT1 is required for EGFR-induced NF- κ B activation and contributes to EGFR-driven lung cancer progression. *Oncogene* 35: 919-928, 2016.
20. Israel L, Gluck A, Berger M, Coral M, Ceci M, Unterreiner A, Rubert J, Bardet M, Ginster S, Golding-Ochsenbein AM, *et al*: CARD10 cleavage by MALT1 restricts lung carcinoma growth in vivo. *Oncogenesis* 10: 32, 2021.
21. Mempel TR and Krappmann D: Combining precision oncology and immunotherapy by targeting the MALT1 protease. *J Immunother Cancer* 10: e005442, 2022.
22. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, Nicholson AG, Groome P, Mitchell A, Bolejack V, *et al*: The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 11: 39-51, 2016.
23. Wang Y, Huang Q and He F: Aberrant blood MALT1 and its relevance with multiple organic dysfunctions, T helper cells, inflammation, and mortality risk of sepsis patients. *J Clin Lab Anal* 36: e24331, 2022.
24. Tang Z, Li C, Kang B, Gao G, Li C and Zhang Z: GEPIA: A web server for cancer and normal gene expression profiling and interactive analyses. *Nucleic Acids Res* 45: W98-W102, 2017.
25. Li T, Fu J, Zeng Z, Cohen D, Li J, Chen Q, Li B and Liu XS: TIMER2.0 for analysis of tumor-infiltrating immune cells. *Nucleic Acids Res* 48: W509-W514, 2020.
26. Qian R, Niu X, Wang Y, Guo Z, Deng X, Ding Z, Zhou M and Deng H: Targeting MALT1 suppresses the malignant progression of colorectal cancer via miR-375/miR-365a-3p/NF- κ B axis. *Front Cell Dev Biol* 10: 845048, 2022.
27. Saba NS, Wong DH, Tanios G, Iyer JR, Lobelle-Rich P, Dadashian EL, Liu D, Fontan L, Flemington EK, Nichols CM, *et al*: MALT1 inhibition is efficacious in both naive and ibrutinib-resistant chronic lymphocytic leukemia. *Cancer Res* 77: 7038-7048, 2017.
28. Liu X, Yue C, Shi L, Liu G, Cao Q, Shan Q, Wang Y, Chen X, Li H, Wang J, *et al*: MALT1 is a potential therapeutic target in glioblastoma and plays a crucial role in EGFR-induced NF- κ B activation. *J Cell Mol Med* 24: 7550-7562, 2020.
29. Flynn SM, Chen C, Artan M, Barratt S, Crisp A, Nelson GM, Peak-Chew SY, Begum F, Skehel M and de Bono M: MALT-1 mediates IL-17 neural signaling to regulate *C. elegans* behavior, immunity and longevity. *Nat Commun* 11: 2099, 2020.
30. Yu JW, Hoffman S, Beal AM, Dykon A, Ringenberg MA, Hughes AC, Dare L, Anderson AD, Finger J, Kasparcova V, *et al*: MALT1 protease activity is required for innate and adaptive immune responses. *PLoS One* 10: e0127083, 2015.
31. Cheng L, Deng N, Yang N, Zhao X and Lin X: Malt1 protease is critical in maintaining function of regulatory T cells and may be a therapeutic target for antitumor immunity. *J Immunol* 202: 3008-3019, 2019.
32. Kingeter LM and Schaefer BC: Malt1 and cIAP2-Malt1 as effectors of NF-kappaB activation: Kissing cousins or distant relatives? *Cell Signal* 22: 9-22, 2010.
33. Chen W, Li Z, Bai L and Lin Y: NF-kappaB in lung cancer, a carcinogenesis mediator and a prevention and therapy target. *Front Biosci (Landmark Ed)* 16: 1172-1185, 2011.
34. Pathan J, Mondal S, Sarkar A and Chakrabarty D: Daboialectin, a C-type lectin from Russell's viper venom induces cytoskeletal damage and apoptosis in human lung cancer cells in vitro. *Toxicon* 127: 11-21, 2017.
35. Luo B, Chu X, Yu P and Tian J: The TCR repertoire diversity and its application in the prevention and treatment of lung cancer. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 38: 939-943, 2022 (In Chinese).
36. Che T, You Y, Wang D, Tanner MJ, Dixit VM and Lin X: MALT1/paracaspase is a signaling component downstream of CARMA1 and mediates T cell receptor-induced NF-kappaB activation. *J Biol Chem* 279: 15870-15876, 2004.
37. Shah K, Al-Haidari A, Sun J and Kazi JU: T cell receptor (TCR) signaling in health and disease. *Signal Transduct Target Ther* 6: 412, 2021.
38. Taniuchi I: CD4 Helper and CD8 Cytotoxic T Cell Differentiation. *Annu Rev Immunol* 36: 579-601, 2018.
39. Li Y, Chen X, Wang Z, Zhao D, Chen H, Chen W, Zhou Z, Zhang J, Zhang J, Li H and Chen C: The HECTD3 E3 ubiquitin ligase suppresses cisplatin-induced apoptosis via stabilizing MALT1. *Neoplasia* 15: 39-48, 2013.

