

KMT2D and TP53 mutation status improve the prognostic value of the International Prognostic Index (IPI) stratification in ENKTL patients

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Extranodal NK/T-cell lymphoma nasal type (ENKTL) is a subtype of T cell lymphoma with poor prognosis. In this study, we designed a new prognostic model specifically for ENKTL to improve the risk stratification. In 29 ENKTL patients, we screened mutations in 9 ENKTL-associated genes using next-generation sequencing (NGS). We have found that mutated *KMT2D* was associated with the inferior overall survival (OS) and progression free survival (PFS) and *KMT2D* or *TP53* mutations were associated with a higher mortality rate. Moreover, the difference in PFS among different stratifications was not significant using the International Prognostic Index (IPI) alone but was significant after the mutation status of *KMT2D* and *TP53* were incorporated into the IPI model, forming a harmonious risk stratification reflecting the clinical features and genetic information of ENKTL. In summary, we demonstrate that the prognostic value of the IPI system can be enhanced by integrating the status of genetic mutations.

Key words: ENKTL, IPI, risk stratification, NGS, gene profile, KMT2D

Extranodal NK/T cell lymphoma (ENKTL) is a subtype of non-Hodgkin's lymphoma (NHL), characterized by a cytotoxic phenotype and is associated with Epstein-Barr virus (EBV) infection [1]. ENKTL is an aggressive disease with an incidence of about 5–18% of NHL [2] and most commonly occurs in East Asia and Latin America [3]. Although the survival time of patients has been improved by chemoradiotherapy and autologous stem cell transplantation, the risk of relapse and drug resistance is still high [4]. At present, optimal treatment strategies and prognosis for patients with ENKTL have not been fully defined [5].

The International Non-Hodgkin's Lymphoma Prognostic Factors Project proposed a prognosis model based on clinical characteristics, including age, tumor stage, serum lactate dehydrogenase (LDH) concentration, performance status, and the number of extranodal disease sites for NHL [6]. Although the above international prognostic index (IPI) has been widely used for both predicting prognosis and selecting therapeutic options in patients with aggressive NHL, it has not been widely used in ENKTL because of the inhomogeneous distribution found for this disease. More than half of ENKTL patients were stratified at low risk according to the IPI classification [7], leading to inaccurate prognoses. Moreover, clinical features do not fully reflect the

biological characteristics of ENKTL. Therefore, it is urgent to identify new prognostic indicators to further improve the IPI classification to better stratify and guide the treatment of ENKTL patients.

Recently, many studies have shown that gene mutations are associated with the classification and prognostic evaluation of lymphoma [8–10]. For example, *ARID1A* and *EP300* gene mutations detected by next-generation sequencing (NGS) improved IPI score accuracy and improved prognosis of follicular lymphoma [11]. NGS can simultaneously carry out sequence analysis of hundreds of thousands or millions of short DNA molecules, in high throughput formats with high sensitivity and relative quantification [12]. Moreover, a recent multicenter laboratory evaluation showed that NGS was highly consistent and repeatable [13]. However, the prognostic value of genetic mutations has not been entirely assessed in ENKTL populations. We retrospectively investigated a cohort of ENKTL patients by NGS and detected mutations in nine candidate genes highly associated with ENKTL pathogenesis and prognosis. We aimed to improve the risk stratification of ENKTL patients by integrating gene mutations into IPI classifications, providing more prognostic information for personalized therapeutic strategies.

Patients and methods

Patients. We retrospectively reviewed a total of 29 patients with primary ENKTL at 4th Hospital of Hebei Medical University from August 2010 to November 2016. Review, analysis, and publication of the data from this study were approved by the ethics committee of Hebei Medical University. Informed consent for the collection of medical information was obtained from all patients. The data collected at diagnosis included patient age, gender, Ann Arbor stage [14], Eastern Cooperative Oncology Group performance status (ECOG PS), regional lymph node quantification, extranodal sites, B symptoms, complete blood count, serum LDH, biochemical profile, bone marrow examination, and computed tomography scanning. The diagnosis and clinical stage of all patients were determined according to the 2008 WHO classification scheme of hematopoietic and lymphoid tissue tumors [15]. The 29 patients were all treated by at least 2 courses of asparaginase based chemotherapy (CT) alone or combined with field radiotherapy (RT) after diagnosis with ENKTL.

Next generation sequencing. In this study, we designed a small panel of ENKTL-related genes including *ARID1A*, *KMT2D*, *TP53*, *MGA*, *STAT3*, *EP300*, *ASXL3*, *DDX3X* and *STAT5B* for deep sequencing to investigate gene mutation status in our ENKTL patient cohort. Genomic DNA from paraffin-embedded tissue was isolated with QIAamp DNA FFPE kit (Qiagen, CA, USA) according to the manufacturer's instructions. Primers for the nine genes for NGS were custom-designed and synthesized by Yuanqi Bio-Pharmaceutical Co., Ltd. (Shanghai, China). The main steps of NGS were as follows: a genomic DNA (gDNA) library was prepared using the TruSeq Nano DNA Library Preparation Kit (Illumina, San Diego, CA, USA). The gDNA was sheared into fragments by sonication and ligated at both ends with indexed paired-end adaptors (Covaris, Woburn, MA, USA). Then the adapter-ligated gDNAs were purified and used as templates in a ligation-mediated PCR for 8 cycles to enrich target genes. Paired-end DNA was sequenced on a HiSeq X (Illumina, San Diego, CA, USA). Data analysis was performed using Illumina bcl2fastq software, version 2.15.

Risk stratification scoring system for ENKTL. IPI scores were calculated based on clinical features including age, tumor stage, LDH concentration, performance status, and the number of extranodal disease sites. Scores for our new classification were calculated by combining the IPI score with a factor based on *KMT2D* and *TP53* mutation status. Details were as follows: wild-type was assigned '0', mutant was assigned '1', and the score = sum (IPI score + *KMT2D* + *TP53*). We defined three categories to establish the new integrated system: low risk (0–1 point), intermediate risk (2–3 points) and high risk (4–6 points).

Statistical analysis. All data were analyzed using IBM SPSS statistics software (Version 20.0, SPSS Inc., USA). The treatment effect on overall survival (OS) rate and progres-

sion-free survival (PFS) rate was determined by Kaplan Meier curves. $P < 0.05$ was considered statistically significant.

Results

Clinical features of ENKTL patients. We recruited a total of 29 patients with primary ENKTL for this study at the Fourth Hospital of Hebei Medical University from August 2010 to February 2017. The median age was 46 years (range 25–73 years), with 24 (82.8%) being male and 5 (17.2%) female (Table 1). According to the Ann Arbor standard, 19 patients were in phases I/II and 10 patients were in phases III/IV. We recorded abnormal clinical features including lactate dehydrogenase (LDH, threshold 250 U/l), Ki67 (threshold 70%), albumin (ALB, threshold 40 g/l) and absolute lymphocyte count (ALC, threshold $1.1 \times 10^9/l$) as follows: increased LDH and Ki67 in 44.8% and 24.1% of patients, respectively; decreased ALB and ALC in 48.3% and 44.8% of patients, respectively. According to the IPI classification, we found 14, 8, 4 and 3 ENKTL patients with low, low-to-intermediate, intermediate-to-high and high risk, respectively. Seventeen patients received chemotherapy plus radiotherapy and 12 patients received chemotherapy alone. After treatment, 16 patients achieved a complete response (CR) or partial response (PR), while 13 patients remained with progressive disease (PD). At the end of follow-up, 11 patients died due to disease progression or other causes.

Correlation between clinical characteristics and OS. The OS of patients in phases I/II (78.9%) was significantly higher than for those in phases III/IV (20%, $p = 0.002$, Figure 1A). OS rates of patients that received RT plus CT and CT alone were 76.5% and 33.3%, respectively ($p = 0.012$, Figure 1B). In addition, we found that levels of Ki67 (Figure 1C), LDH (Figure 1D), ALB (Figure 1E) and ALC (Figure 1F) correlated to OS and the differences of OS were statistically significant between patients with normal clinicopathological characteristics and those with abnormal data (Figure 1). Increased Ki67 and LDH, as well as decreased ALB and ALC resulted in lower OS in these ENKTL patients.

Gene mutation rates. Among the 29 ENKTL patients, we found mutation rates of 34.48%, 31.03%, 24.13%, 24.13%, 24.13%, 17.24%, 17.24%, 6.89% and 6.89% for *ARID1A*, *KMT2D*, *TP53*, *MGA*, *STAT3*, *EP300*, *ASXL3*, *DDX3X* and *STAT5B* genes, respectively (Figure 2). The *KMT2D* mutation rate was significantly lower in low and low-to-intermediate risk patients than in intermediate-to-high and high risk patients (18.18% vs 71.43%, $p < 0.05$, data not shown) according to their IPI score. However, we found no significant differences in the mutation rates of the other 8 genes between patients with low and high risk.

Associations between *KMT2D* or *TP53* mutation and mortality. Mortality was 75% (6/8) for patients with *KMT2D* mutations whereas mortality was 9.5% (2/21) for patients with wild-type *KMT2D*, and the difference was statistically significant ($p < 0.01$). Similarly, we found significant

Table 1. Clinical characteristics of 29 ENKTL patients.

Characteristics	No.	Percentage
Age		
≤60	24	82.8
>60	5	17.2
Gender		
Male	24	82.8
Female	5	17.2
Ann Arbor stage		
I/II	19	65.5
III/IV	10	34.5
B symptom		
With	20	69.0
Without	9	31.0
Bone marrow involvement		
With	12	41.4
Without	17	58.6
ECOG PS		
0–1	26	89.7
≥2	3	10.3
Regional lymph nodes involvement		
With	16	55.2
Without	13	44.8
Extranodal sites		
<2	22	75.9
≥2	7	24.1
LDH		
<250 U/L	22	75.9
≥250 U/L	7	24.1
IPI (score)		
Low risk (0–1)	14	48.3
Low-to-intermediate risk (2)	8	27.6
Intermediate-to-high risk (3)	4	13.8
High risk (4–5)	3	10.3
Ki67		
<70%	16	55.2
≥70%	13	44.8
ALC		
<1.1×10 ⁹ /L	13	44.8
≥1.1×10 ⁹ /L	16	55.2
ALB		
<40 g/L	14	48.3
≥40 g/L	15	51.7
Treatment		
CT+RT	17	58.6
CT	12	41.4
Treatment effect		
CR+PR	16	55.2
PD	13	44.8

ECOG PS, Eastern Cooperative Oncology Group performance status; ALC, absolute lymphocyte count; ALB, albumin; LDH, lactate dehydrogenase; IPI, International Prognostic Index; CT, chemotherapy; RT, radiotherapy; CR, complete response; PR, partial response; PD, progressive disease. Bold fonts denote the clinical parameters for IPI risk stratification.

differences in PFS and OS between patients with *KMT2D* mutations and those with wild-type *KMT2D* (Figure 3). We also found significant differences in mortality ($p=0.036$) between patients with *TP53* mutations and wild-type (71.43% vs 27.27%, data not shown). In order to avoid an imbalanced IPI classification effect, we assessed the difference of mortality between *KMT2D* mutation and wild-type patients in low and low-to-intermediate risk patients. Statistical results indicated that *KMT2D* mutations also increased mortality in low and low-to-intermediate risk patients (data not shown). In 22 low and low-to-intermediate risk patients, 3 of 4 patients with *KMT2D* mutations died whereas only 2 died in 18 patients with wild-type *KMT2D* ($p=0.0058$). Although mortality was increased in all patients with *TP53* mutations, the difference of mortality was not significant between patient cohorts with *TP53* mutation and wild-type in low and low-to-intermediate risk patients.

Integrated System combines *KMT2D* and *TP53* mutations with the IPI score. The difference in PFS was not significant among 4 risk stratifications ($p=0.0824$, Figure 4A) but OS differed significantly (Figure 4B) according to IPI classification. To devise a more accurate system, we incorporated *KMT2D* and *TP53* gene mutations into the IPI system as risk factors (a gene mutation is defined as a point). This modification resulted in a redistribution of patients: 13, 9 and 7 patients moved to low, intermediate and high risk groups, respectively. The difference in PFS was significant ($p=0.0094$) and the new classification showed a homogeneous distribution of patients (Figures 4C and 4D). In order to better assess the improvement of risk stratification integrated with gene mutations, we compared the proportions and OS rates of patients among different risk stratifications between IPI scores and our integrated system (Figure 5). According to IPI classification, the OS rates of low, low-to-intermediate, intermediate-to-high and high risk patients were 78.6%, 62.5%, 0%, and 33.3%, respectively. For low-to-intermediate and intermediate-to-high risk groups in the IPI classification, patients with wild-type alleles were reported by our integrated classification to the intermediate risk stratification, while patients with mutations in both genes were resorted to the high risk group. Patients in the intermediate-to-high and high risk groups patients with mutations were reclassified to the high risk group by our integrated system. The OS rates of low, intermediate and high risk patients were 84.6%, 55.6%, and 14.3% respectively in our integrated system, which formed a harmonious classification with the precise prognosis of ENKTL patients.

Discussion

ENKTL is also called angiocentric T-cell lymphoma because tumor cells in this disease are derived from natural killer cells and cytotoxic T cells. At present, ENKTL is the most common subtype of T cell lymphoma in China [16]. However, the outcome of therapeutic interventions for

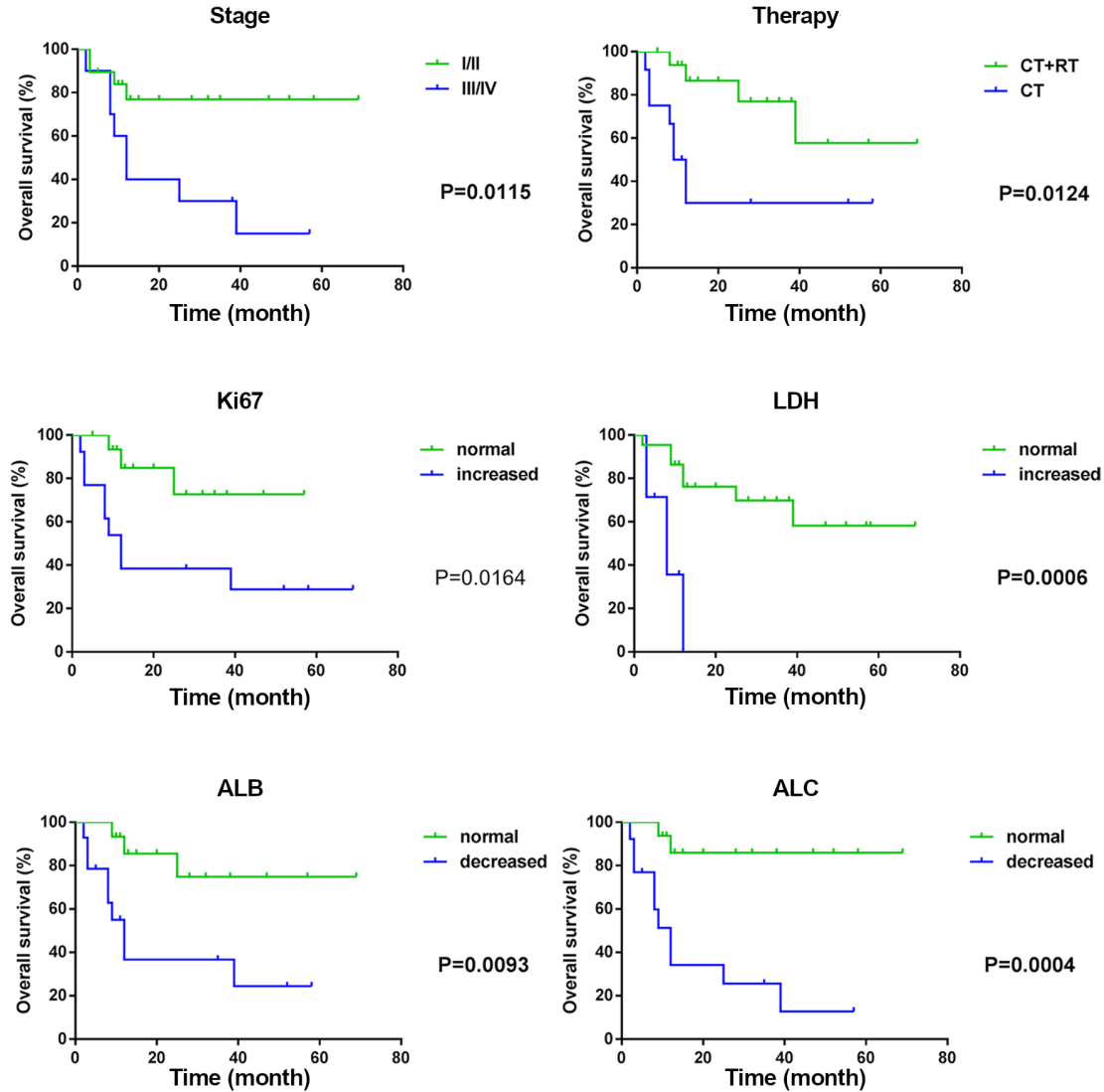


Figure 1. Kaplan-Meier plots of Overall Survival (OS) in patients: comparisons of various clinical characteristics.

ENKTL is generally poor and prognosis varies among patients [17]. Conventional risk stratification for NHL is not specific for ENKTL. In this study, we established a new prognostic model based on the existing IPI system for NHL by incorporating genetic mutation status for a more precise stratification in ENKTL patients.

According to the IPI score designed for NHL, only 24.1% of 29 ENKTL patients in our cohort were placed in the intermediate-to-high and high risk stratification. This formed an imbalanced classification that did not reflect the high degree of malignancy in ENKTL, suggesting that the IPI score needed improvement to better evaluate ENKTL prognoses. In this study, we found that the status of selected genetic mutations was a powerful factor when incorporated into IPI scores to improve ENKTL patient prognoses.

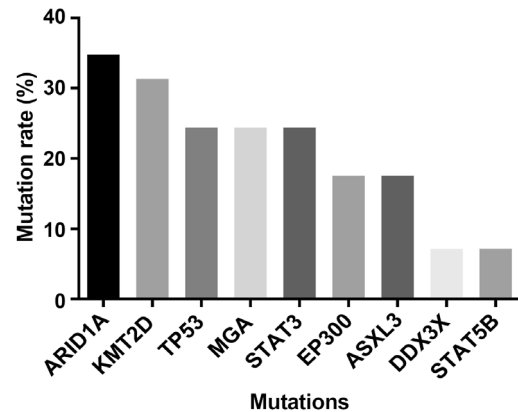


Figure 2. Mutation rates of 9 genes evaluated by NGS in 29 patients with ENKTL.

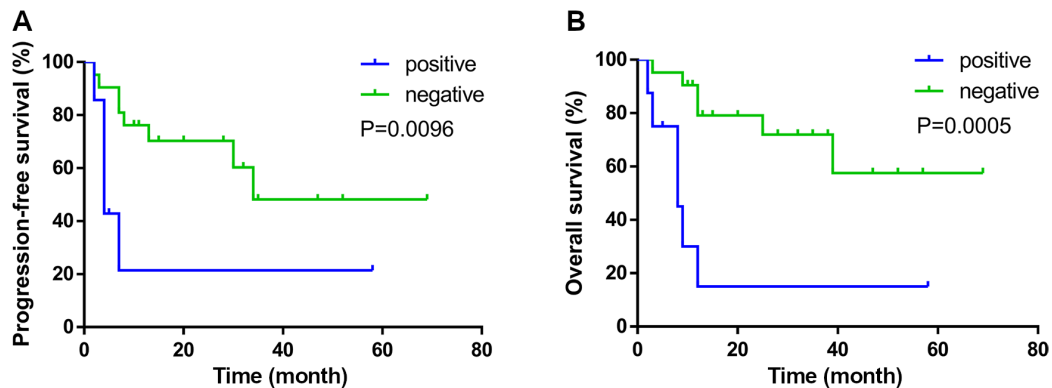


Figure 3. Progression-Free Survival (PFS) and Overall Survival (OS) of patients with mutant and wild-type *KMT2D*.

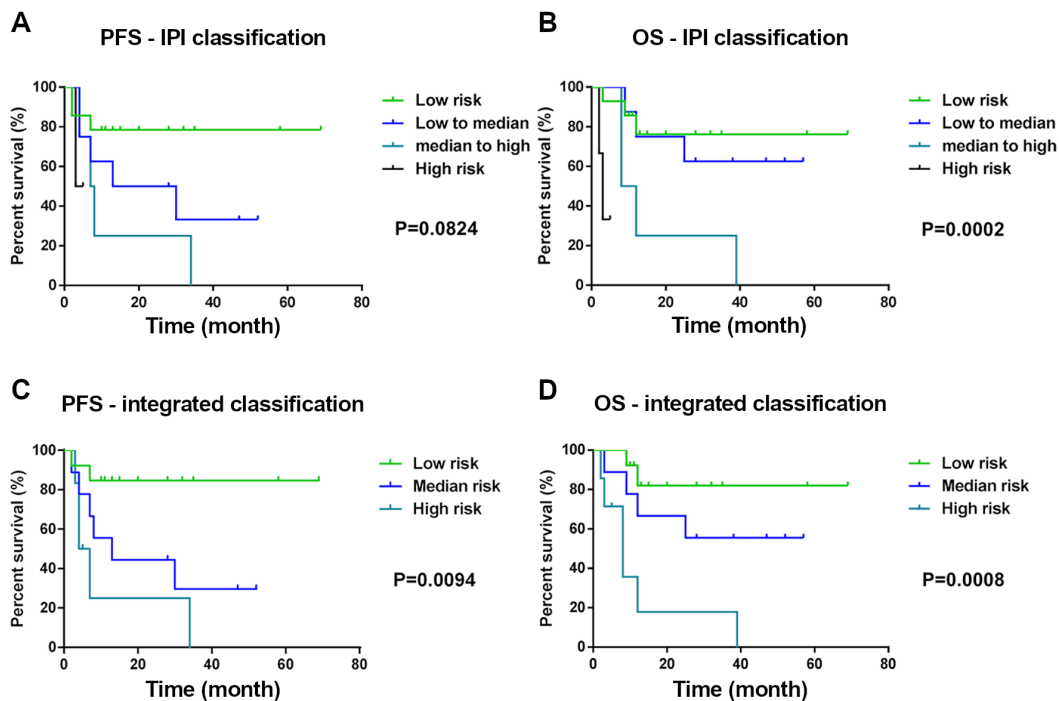


Figure 4. PFS and OS of ENKTL patients: comparison of risk classification method by stratification category. A) PFS using IPI categories. B) OS using IPI categories. C) PFS using our integrated classification categories. D) OS using our integrated classification categories.

A growing number of studies have shown that numerous genetic mutations are associated with the occurrence and development of ENKTL [18–20]. However, it has been difficult to investigate gene profiles of ENKTL patients because of their low incidence. In recent years, the sensitivity and specificity of NGS techniques have been greatly improved and many gene mutations can be detected simultaneously by a specifically assigned gene panel [21]. In this study, we investigated mutations in a small panel of genes frequently associated with ENKTL, including *ARID1A*, *KMT2D*, *TP53*, *MGA*, *STAT3*, *EP300*, *ASXL3*, *DDX3X*, and *STAT5B*. Our

NGS results showed that except for *DDX3X* and *STAT5B*, the mutation rates of the genes were all over 10%, consistent with a report by Choi et al. [22]. The high mutation rate for *KMT2D* in intermediate-to-high and high risk patients suggested that mutant *KMT2D* may more accurately be placed in a high risk stratification and predict poor prognosis. Ardeshir-Larijani et al. [23] reported that patients with mutant *KMT2D* had a significantly lower median OS and PFS compared with patients with wild-type *KMT2D* in NSCLC. Consistent with this report, we also found that *KMT2D* mutant-positive ENKTL patients in our cohort

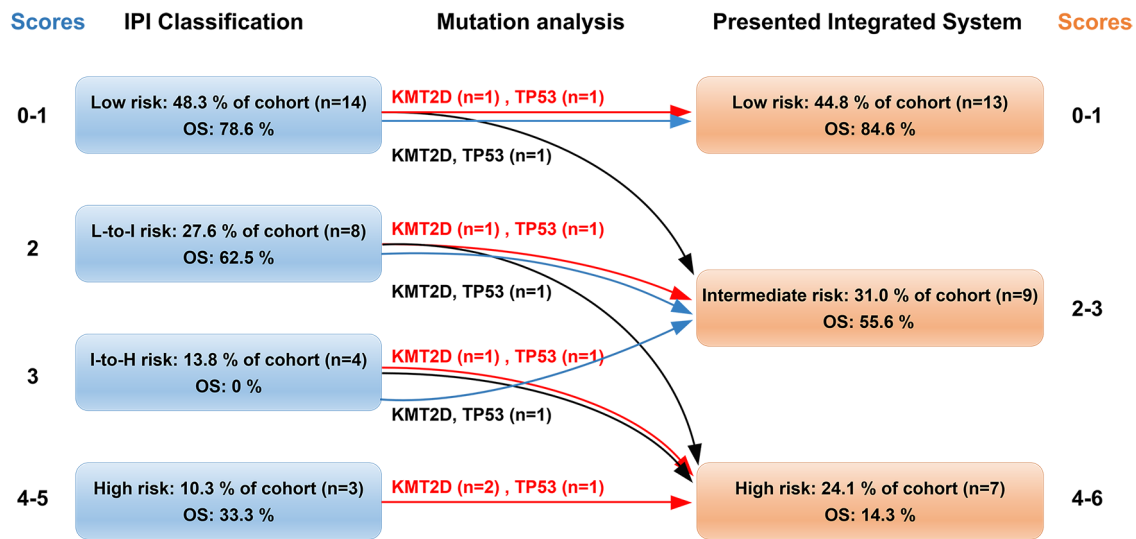


Figure 5. Effect of mutation profiling on conventional IPI risk stratification. Patients with markedly poor prognoses are reassigned into more appropriate risk groups according to their mutation profiles. Red arrows denote patients with either a mutant *KMT2D* or *TP53* gene. Black arrows denote patients with both mutant *KMT2D* and *TP53* genes. Blue arrows denote patients with wild-type genes. L-to-I, low-to-intermediate; I-to-H, intermediate-to-high.

had a lower median OS and PFS. Ortega-Molina et al. [24] showed that *KMT2D* mutations could promote lymphoma development due to enhanced proliferation and impaired terminal differentiation and *KMT2D* deficiency was sufficient to trigger B cell malignancy in mice. Our results showed that *KMT2D* may be an independent high risk prognostic factor for ENKTL patients. However, the prognostic value of *KMT2D* mutations in ENKTL needs to be further investigated in a larger cohort of patients. *KMT2D* (formerly known as *MLL2*) encodes a catalytic lysine methyltransferase containing SET domain, which has the activity to methylate H3K4 and is an important component of the polyprotein complex that plays a role in gene regulation and embryonic development [25–28]. Abnormal expression of *KMT2D* has been shown to be associated with multiple tumors, such as breast cancer, colon cancer [29], prostate cancer and gastric cancer [30, 31]. Several studies reported that *KMT2D* acted as a tumor suppressor gene in non-Hodgkin lymphoma [32–34]. It was reported that *KMT2D* deficiency resulted in attenuated cancer cell proliferation and defective cell migration in medulloblastoma cancer [35]. It was reported that *KMT2D* acted as a tumor suppressor gene, leading to changes in the epigenetic landscape of cancer precursor cells, which promotes the proliferation of mice B cells. Thus the eradication of *KMT2D*-deficient cells may be a rational therapeutic strategy for lymphoma [36]. In studies of DLBCL and follicular cell lymphoma, data showed that 89% of FL and 23–32% of DLBCL have *KMT2D* gene mutations, which mostly occur in the early stage of tumor formation. Most of the mutations are nonsense mutations and code shift mutations, which lead to the inactivation of the *KMT2D* gene [32–34]. Korean researchers also found mutations of the *KMT2D* gene

in ENKTL through the whole exon sequencing technology, counted for about 17.6%, most of which were nonsense mutations. They also found that the mutations caused the loss of gene function through RNA sequencing, suggesting that epigenetic factor mutations may play a role in the pathogenesis of ENKTL [20].

TP53 is a well-known tumor suppressor gene, which encodes a protein P53 to regulate the expression of corresponding target genes in response to various cellular stress, thus inducing regulation of DNA repair, apoptosis, senescence, and DNA repair and metabolism [37, 38]. Majority of *TP53* mutations are missense mutations, and the encoded mutant P53 proteins not only exerts a negative effect on wild-type p53 and inhibits its function as a tumor suppressor [39, 40], but also exhibits new carcinogenic functions including promoting cell proliferation, the evasion of apoptosis, metabolic changes, migration, and so on [41–43]. Clinical studies have demonstrated that mutations in the tumor suppressor gene *TP53* predicted poor prognosis in hematopoietic tumors and ENKTL [10, 37, 44, 45]. However, in our study *TP53* mutation status only predicted increased mortality but had no significant effect on PFS and OS. Additional studies with significantly more patients may be required to establish the predictive value of *TP53* mutation status in ENKTL. Nevertheless, for our cohort of ENKTL patients, incorporating the IPI score with *KMT2D* and *TP53* mutation status, produced a new scoring system that could predict a patients' prognosis more precisely.

In conclusion, we identified a new prognostic stratification system by combining the IPI classification for NHL with ENKTL-relevant genetic mutations, resulting in a significant improvement in risk stratification. Additional studies

with significantly more patients are warranted to validate the clinical relevance of this integrated system for ENKTL, which should provide great insight into disease management of ENKTL and our understanding of ENKTL biology.

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