# Clinical Characteristics and Prognosis of 48 Patients with Mutations in Myelodysplastic Syndrome

Yulu Tian#, Ruijuan Zhang#, Linhua Yang*

**Yang L. Clinical Characteristics and Prognosis of 48 Patients with Mutations in Myelodysplastic Syndrome. J Genet Mutat 2018;1(1):6-10.**

Genetic abnormality is one of the important pathogenesis of myelodysplastic syndrome (MDS). Forty-eight patients of MDS were recruited in this study which stratified by the revised International Prognostic Scoring System (IPSS-R). By analyzing 8 gene mutations incidence, correlation with efficacy and prognosis in MDS patients, to understand the significance of gene mutation in MDS. (1) *TET2* showed the highest frequency of mutations (37.5%), followed by *ASXL1* mutations(29.2%), *RUNXL1* and *SRSF2* with the same rate (8.3%) and then *SF3B1, NPM1, DNMT3A, U2AF1* had 2.1%(1/48). Most patients with low risk (low risk and very low risk) group in IPSS-R were ones with *TET2* mutation, which compared with the group without *TET2* mutation, the overall response (OR) was lower (17.6% *vs* 57.1%, P=0.019). Most patients with intermediate risk in IPSS-R were ones with *ASXL1* mutation, which compared with the group without *ASXL1* mutation, the median white blood cell count was higher [3.5(1.5-22.4) × $10^9$/L *vs* 3.1(1.0-9.2) × $10^9$/L, P=0.019], the OR was lower(16.7% *vs* 50.0%, P=0.045), as well as overall survival (OS) of 24 months was lower [(45% ± 17%) *vs* (71% ± 9%), P=0.006]. (2) Except 3 patients lost to follow-up, OR were 42.2% (19/48) after accepting two courses treatment in a total of 48 MDS patients. Regression analysis showed that *TET2* (HR=8.757, P=0.023, 95%CI 1.343-57.093) mutation was an independent prognostic factor for OR. (3) COX regression analysis with high-risk group patients in IPSS-R (HR=14.626, P=0.023, 95%CI 1.459-146.633) and *ASXL1* (HR=3.315, P=0.023, 95%CI 1.180-9.309) mutation were independent prognostic factors for OS.

**Conclusion**

In a total of 48 MDS patients, the frequency of *TET2* and *ASXL1* mutation was higher, the subgroup with *TET2* mutation might have a poor curative effect, *ASXL1* mutation was one of factors shorter OS, especially in intermediate and low risk MDS patients.

**Keywords:** *Genetic abnormality; Myelodysplastic syndrome; Gene mutation; Peripheral blood cell count; Bone marrow biopsy; Cytogenetics; cytometry*

**Abbreviations**: *MDS: Myelodysplastic Syndrome; OR:* Overall Response; *OS:* Overall Survival; CR: The Sum of Complete Remission; PR: Partial Remission; mCR: Bone Marrow Complete Remission; HI: Hematological Improvement

Myelodysplastic syndrome is a highly heterogeneous hematopoietic disorder characterized by ineffective hematopoiesis and high risk of secondary acute myeloid leukemia. The correct diagnosis of MDS remains a challenge as it can be difficult to distinguish MDS from its benign and malignant mimickers, current prognostic scoring systems consider karyotypic abnormalities and certain clinical features to stratify patients with MDS into risk groups. However, because of karyotype of MDS can change over time, the heterogeneous hematopoietic disorder will be poorly sensitive by karyotype analysis, as well as, approximately 80% of MDS patients with more than one gene mutation (1-3) and about 2/3 of these mutations are seen in patients with a normal karyotype (4,5).

Some frequently occurring gene mutations have a prognostic value independent of IPSS (2,5). Studies had shown that the overall survival of patients with MDS carrying one or more mutated genes such as *TP53, RUNX1, ASXL1, EZH2*, or *ETV6* is similar to the next highest IPSS-R risk group (2). In addition, the overall survival of 1/3 of the patients with mutations in the intermediate-risk is similar to the next highest risk group (3), according to the NCCN guidelines, combined with patient gene mutation status, IPSS-R intermediate risk patients may consider choosing a treatment regimen with a higher or lower risk stratification that will benefit long-term survival in this group of patients. Meanwhile, the corresponding mutations targeted drugs are constantly trying clinical applied. Therefore, the study of gene mutations has become increasingly prominent in the accurate diagnosis, prognostic and therapeutic efficacy prediction.

In the recent discoveries, more than 40 kinds of gene mutations have been detected and are closely related to the pathogenesis of MDS, which are mainly classified in eight functional groups, DNA methylation (*TET2, DNMT3A, IDH1/2*), chromatin modification (*ASXL1, EZH2*), RNA-splicing machinery (*SF3B1, SRSF2, ZRSR2, U2AF1, U2AF2*), transcription factor (*TP53, RUNX1*), signal transduction/kinases (*FLT3, JAK2*), RAS pathway (*KRAS, NRAS, CBL, NF1, PTPN11*), cohesin complex (*STAG2, CTCF, SMC1A, RAD21*), DNA repair (*ATM, BRCC3, DLRE1C, FANCL*) (7). Only 6 genes are consistently mutated in ≥ 10% of MDS patients: *TET2, ASXL1, SF3B1, SRSF2, DNMT3A*, and *RUNX1* (3,4). In this study, we retrospectively analyzed the clinical features, efficacy and prognosis of patients with *TET2* and *ASXL1* mutation in MDS.

*TET2* was identified with micro-deletions at 4q24, which encode a α-ketoglutalate dependent oxygenases, involved in conversion of 5-methylcytosin to 5-hydroxymethylcytosine, and that loss of *TET2* function by gene mutation was associated with dysregulated DNA methylation (7). Somatic *TET2* mutations have been found in 11%-26% of patients with MDS, 37%-44% of patients with MDS/MPN, and 11%-24% of patients with *sAML* (8,9). The prevalent studies show that prognostic impact of *TET2* mutations has always been controversial, but in a recent large-scale study (10), a total of 1494 patients from nine studies were subjected to meta-analysis, found that *TET2* mutations have no prognosis impact on OS of patients with MDS (HR 1.13, 95% CI: 0.81–1.5).

*ASXL1* encodes a chromatin-binding protein involved in epigenetic regulation in hematopoietic cells and recruiting *PRC2* to specific loci (11,12). *ASXL1* mutation were originally identified by Gelsi-Boyer et al. (13) in MDS with del20q11 through sequencing of the focal deletion in MDS. In mouse model, *ASXL1* mutation caused progressive, multilineage cytopenias, dysplasia with increased numbers of hematopoietic stem/progenitor cells, and occasional progression to overt leukemia similar to that of human MDS (14,15). *ASXL1* is common in MDS (14-21%), and is found to be associated with worsened OS among MDS patients transforming to AML independently of other clinical features, including age, cytogenetics and cytopenias (16).

## PATIENTS AND METHODS

**Patients**

From July 2011 to April 2017, 48 patients with MDS confirmed by detection

*Department of Hematology, The Second Hospital of Shanxi Medical University, Taiyuan, China*

*Correspondence: Dr Yang L, Department of Hematology, The Second Hospital of Shanxi Medical University, Taiyuan, China, Tel: +86 351 652 8781; Email: yanglh5282@163.com*
*Yulu Tian and Ruijuan Zhang contributed equally*

*Received: March 05, 2018, Accepted: March 29, 2018, Published: April 05, 2018*

of peripheral blood cell count, myeloid cell morphology, peripheral blood cell classification, NAP, bone marrow biopsy, multi-parameter flow cytometry, cytogenetics and molecular biology Patients and all patients with MDS gene mutation results and clinical features.

### Method

According to the Revised International Prognostic Scoring System (IPSS-R) (17), patients in the low-risk MDS group were given supportive therapies such as hematopoietic stimulation, blood transfusions and immunomodulation. Patients in the high-risk group were given demethylation, acetylation and chemotherapy, refractory or ineffective treatment of patients with clinical trials or hematopoietic stem cell transplantation.

### Assessment of treatment response

Efficacy assessment in patients with MDS according to the efficacy criteria of International Working Group (IWG) 2006 (18), OR is the sum of complete remission (CR), partial remission (PR), bone marrow complete remission (mCR) and hematological improvement (HI).

### Follow-up

By telephone and outpatient clinic visits, from October 2015 to April 2017, three patients were lost to follow-up, with a median follow-up of 13.5 (1-71) months. OS is defined as the time from diagnosis to death or until the end of follow-up. Leukemia free survival (LFS) is from diagnosis to acute myeloid leukemia time.

### Statistical analysis

SPSS 21.0 software was used for statistical analysis. The clinical features were expressed in terms of median (percentage) and percentage. Chi-square or Fisher exact test and Mann-Whitney U test were used in the univariate analysis. Multivariate analysis of efficacy was performed by Logistic regression and survival using COX regression, using Kaplan-Merei method drawn survival curves. Statistical significance was set at $P < 0.05$(2-sided).

## RESULTS

### Clinical characteristics

Among 48 patients with MDS, there were 27 males (56.3%) and 21 females (43.7%) with a median age of 67 (42-82) years. 26 patients (54.2%) were MDS with excess blast (*MDS-EB*), 16 patients (33.3%) were MDS with multiple lineage dysplasia (*MDS-MLD*), 3 cases (6.3%) of MDS with simple lineage dysplasia (*MDS-SLD*), 2 cases (4.2%) of MDS with isolated del(5q) and 1 case (2%) was MDS unclassified (*MDS-U*). During the follow-up, 7 cases (14.6%) were diagnosed with MDS-EB progressed to acute myelogenous leukemia (AML). According to the IPSS-R group, 3 patients (6.2%) were in very low risk group, 7 patients (14.6%) in low risk group, 20 patients (41.7%) in intermediate risk group, 12 patients (25.0%) in high risk group and 6 patients in very high risk group (12.5%).

### The distribution of genetic mutations in MDS

All people were detected with 8 MDS-related mutations, including 37.5% (18/48) *TET2*, 9.2% (14/48) *ASXL*, and 8.3% (4/48) *RUNX1, SRSF2, and SF3B1, NPM1, DNMT3A and U2AF1* accounted for 2.1% (1/48) respectively.

*TET2* mutations were found in 44.4% (8/18) of MDS-EB patients, 33.3% (6/18) of MDS-MLD patients, 11.1% (2/18) of MDS-SLD patients, MDS-U and MDS with isolated del (5q) accounted for 5.5% (1/18) respectively. The distribution of *ASXL1* mutation was 50.0% (7/14) in MDS-EB and 28.5%(4/14) in MDS-MLD, MDS-SLD, MDS-U and MDS with isolated del(5q) accounted for 7.1% (1/14) respectively.

Patients with MDS were divided into three groups according to IPSS-R: A group was low-risk and very low-risk group, B group was intermediate risk group and C group was high risk and very high risk group. The *TET2* mutation rates in the three groups were 60.0%(6/10), 30.0%(6/20) and 33.3%(6/18), respectively. The prevalence of *ASXL1* mutation in three groups were 20.0% (2/10), 40.0%(8/20) and 22.2%(4/18), respectively. *NPM1* and *DNMT3A* only showed positive mutation in C group, accounted for 5.5% (1/18) respectively. *U2AF1* and *SF3B1* were positive mutation in 5% (1/20) of B group (Figure 1).

The OR of patients with *TET2* mutation was lower compared to those without (17.6% *vs.* 57.1%, p=0.019). Four patients with the *TET2* mutation received decitabine therapy, of which 3 patients (75%) reached OR, fifteen patients without *TET2* mutation received decitabine, of which 8 patients (53.3%) reached OR. There was no significant difference between the two

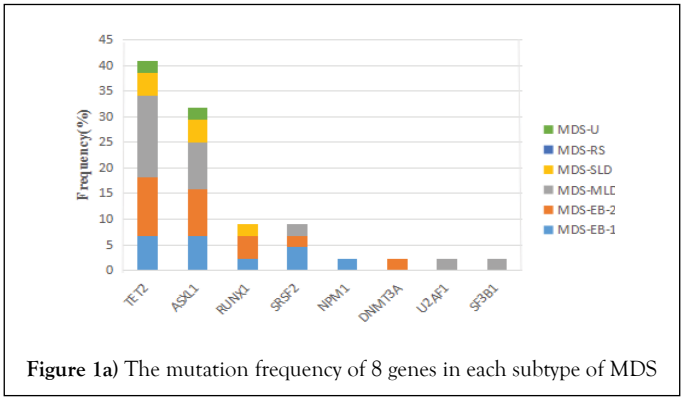


**Figure 1a)** The mutation frequency of 8 genes in each subtype of MDS

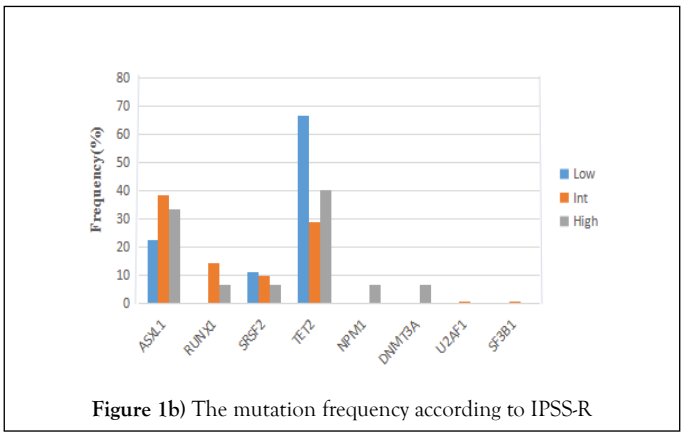


**Figure 1b)** The mutation frequency according to IPSS-R

groups responsed to decitabine ($\chi 2$=0.608, P=0.603). *ASXL1* mutation patients achieved higher white blood cell count [3.5(1.5-22.4) $\times 10^9$/L *vs.* 3.1(1.0-9.2) $\times 10^9$/L without *ASXL1* mutation patients, P=0.019], lower OR (16.7% *vs.* 50.0%, p=0.045) and shorter overall survival at 24 months [45% ± 17% *vs.* 71% ± 9%, P=0.006] (Table 1, 2).

### Treatment response

Among 48 MDS patients, 3 patients were lost to follow-up, analysis of the treatment response after remaining patients received two courses of treatment. The patients reached OR had lower proportion of bone marrow blasts [ 2 (0-15)% vs. 9 (0-16)% in without reached OR patients, P=0.006],

**Table 1**

**Characteristics of MDS patients with and without *TET2* mutation**

| Characteristic | *TET2* Mutation positive (n=18) | *TET2* Mutation negative (n=30) | P |
|---|---|---|---|
| Sex, n (%) | | | |
| Male | 11 (61.1) | 16 (53.3) | 0.599 |
| Female | 7 (38.9) | 14 (46.7) | - |
| Median age (year)(range) | 79 (51-82) | 52 (42-57) | 0.19 |
| Diagnosis, n (%) | - | - | 0.295 |
| EB | 8 (44.4) | 18 (60.0) | - |
| Non-EB | 10 (55.6) | 12 (40.0) | - |
| White blood cell count ($\times 10^9$) (range) | 3.6 (2.3-8.9) | 3.2 (2.3-4.0) | 0.546 |
| Hemoglobin (g/L)(range) | 68 (49.0-116.0) | 97 (71.5-129.0) | 0.184 |
| Platelet count ($\times 10^9$)(range) | 339 (23-444) | 28 (15-239) | 0.089 |
| WT1 (10-4×ABL)(range) | 1050 (174-1462) | 48 (1-4307) | 0.424 |
| Bone marrow blast cell count (%)(rang) | 4.2 (0-13.5) | 8.0 (0-10.0) | 0.81 |
| IPSS-R risk group, n (%) | - | - | 0.493 |
| Low/Intermediate | 6 (71.4) | 13 (58.9) | - |
| High | 12 (28.6) | 17(41.1) | - |

| | | | |
|---|---|---|---|
| Treatment, n (%) | - | - | 0.073 |
| Decitabine ± Chemotherapy | 4 (22.2) | 15 (50.0) | - |
| Support treatment | 14 (77.8) | 15 (50.0) | - |
| Treatment Response, n (%) | - | - | 0.019 |
| OR | 3 (17.6) | 16 (57.1) | - |
| Non-OR | 14[a] (82.3) | 12[b] (42.9) | - |
| 24-month OS | 48%±17% | 54% ± 13% | 0.527 |
| Progress to AML, n (%) | - | - | 1.000 |
| Y | 3 (16.7) | 5 (16.7) | - |
| N | 15 (83.3) | 25 (83.3) | - |

a: One patient had unknown curative effect; b: Two patients had unknown curative effect; Low/Intermediate risk group were very-low risk and low-risk and intermediate-risk group; High risk group were very high-risk and high-risk group

**Table 2**

**Characteristics of MDS patients with and without *ASXL1* mutation**

| Characteristic | *ASXL1* mutation-positive (n=14) | *ASXL1* mutation-negative (n=34) | P |
|---|---|---|---|
| Sex, n (%) | | | |
| Male | 8 (57.1) | 19 (55.9) | 0.936 |
| Female | 6 (42.9) | 15 (44.1) | |
| Median age (year)(rang) | 71 (42-82) | 63 (42-80) | 0.229 |
| Diagnosis, n (%) | | | 0.710 |
| EB | 7 (50.0) | 19 (55.8) | |
| Non-EB | 7 (50.0) | 15 (44.2) | |
| White blood cell count(×10$^9$)(rang) | 3.5 (1.5-22.4) | 3.1 (1.0-9.2) | 0.019 |
| Hemoglobin (g/L)(rang) | 82.9 (49.0-129.0) | 81.5 (31.0-134.2) | 0.427 |
| Platelet count (×10$^9$)(rang) | 60 (5-418) | 33 (4-444) | 0.447 |
| *WT1* (10-4×ABL)(rang) | 345.5 (0-4307.0) | 19.9 (0-12789.0) | 0.067 |
| Bone marrow blast cell count (%) (rang) | 4.8 (0-15.0) | 1.3 (0.2-6.8) | 0.544 |
| IPSS-R risk group, n (%) | | | 0.412 |
| Low/Intermediate | 10 (71.4) | 20 (58.9) | |
| High | 4 (28.6) | 14 (41.1) | |
| Treatment, n (%) | | | 0.100 |
| Decitabine ± Chemotherapy | 3 (21.4) | 16 (47.1) | |
| Support treatment | 11 (78.6) | 18 (52.9) | |
| Treatment response, n (%) | | | 0.045 |
| OR | 2 (16.7) | 17 (50.0) | |
| Non-OR | 10[a] (83.3) | 16[b] (50.0) | |
| 24-month OS | 45%±17% | 71%±9% | 0.006 |
| Progress to AML, n (%) | | | 0.776 |
| Y | 2 (14.3) | 6 (17.6) | |
| N | 12 (85.7) | 28 (82.4) | |

patients diagnosed as EB (42.2% vs. 69.2% in non-EB patients, P=0.069), with *ASXL1* mutation patients (10.5% vs. 38.5% in without *ASXL1* mutation patients, P=0.036) and with *TET2* mutation patients (15.8% vs. 87.5% in without *TET2* mutation patients, P=0.009) were more likely to achieved OR. Multivariate analysis showed *TET2* mutation (HR 8.757, P=0.023, 95%CI 1.343-57.093) is an independent factor affecting OR (Table 3).

**Survival and disease progression factors**

In the univariate analysis, OS was associated with *ASXL1* mutation (P=0.043), quantification of *WT1* (P=0.006), diagnosis of EB (P=0.091) and high-risk patients (P=0.001), multivariate analysis showed *ASXL1* mutation (HR 3.315, P=0.023, 95% CI 1.180-9.309) and the high-risk group (HR 14.626, P=0.023 95% CI 1.459-146.633) was an independent prognostic factor affecting OS (Table 4); Analysis of factors influencing the progressed of the disease showed that patients with a higher proportion of bone marrow blasts were more likely to progress to AML [11 (6-14.5)% *vs.* 3 (0-16)%, P=0.007], however, the proportion of bone marrow blast cell was not an independent factor affecting the disease progression.

In 48 patients with MDS, these data indicated that the *TET2* mutation did

**Table 3**

**Univariate and multivariate analyses for treatment response**

| Variables | Univariate analysis | Multivariate analysis | |
|---|---|---|---|
| | *P* | *P* | *HR (95%CI)* |
| Sex | 0.027 | | |
| Median age | 0.32 | | |
| Diagnosis | 0.069 | 0.968 | 0.943 (0.560-15.923) |
| White blood cell count | 0.53 | | |
| Hemoglobin | 0.318 | | |
| Platelet count | 0.904 | | |
| *WT1* | 0.473 | | |
| Bone marrow blast cell count | 0.006 | 0.106 | 1.253 (0.954-1.645) |
| IPSS-R risk group | 0.109 | | |
| *ASXL1* mutation | 0.036 | 0.285 | 2.744 (0.431-17.47) |
| *TET2* mutation | 0.009 | 0.023 | 8.757 (1.343-57.093) |
| Treatment | 0.227 | | |

**Table 4**

**Multivariate analyses for overall survival**

| Variables | *OS* | | |
|---|---|---|---|
| | HR | *95%CI* | *P* |
| Bone marrow blast cell count | 0.998 | 0.843~1.182 | 0.982 |
| Diagnosis (EB/Non-EB) | 0.323 | 0.019~3.686 | 0.323 |
| IPSS-R | 14.626 | 1.459~146.633 | 0.023 |
| *WT1* | 1 | 1.000~1.000 | 0.431 |
| *ASXL1* mutation | 3.315 | 1.180~9.309 | 0.023 |

not significantly affect the OS of MDS patients (P=0.527), compared to the without *ASXL1* mutation patients. The patients with *ASXL1* mutation had lower OS rate (P=0.006); According to IPSS-R stratification, the OS was no significant difference between with and without *TET2* mutation cases as well as *ASXL1*(P=0.556 and 0.687, respectively) in high risk group; The OS was no significant difference between with and without *TET2* mutation cases in intermediate and low risk group (P=0.104), but the OS of *ASXL1* mutation cases was significantly lower than those without *ASXL1* mutation in intermediate and low risk group (P <0.001).

A total of 48 MDS patients, with *TET2, ASXL1* mutation cases and respective without mutation cases difference was not statistically significant in *LFS* (P=0.520 and 0.210, respectively), as well as those in high risk group (P=0.782 and 0.984, respectively), also, there was no significant difference in the with and without of *TET2, ASXL1* mutation cases between intermediate and low risk group (P=0.083 and 0.210, respectively) (Figure 2).

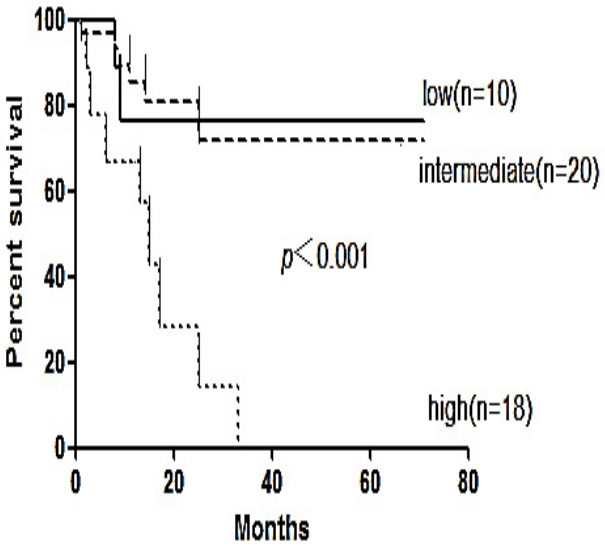


**Figure 2a)** Contraction of novel prognosis evaluation system for OS

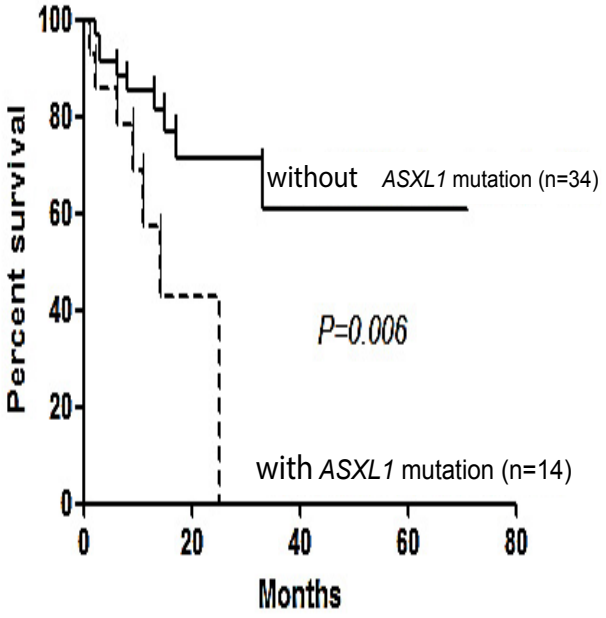


**Figure 2b)** Contraction of novel prognosis evaluation systems for OS

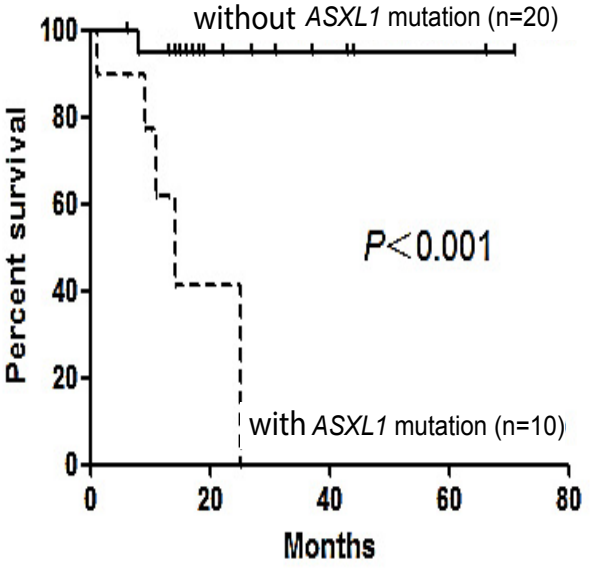


**Figure 2c)** Contraction of novel prognosis evaluation system for OS

Figure 2a) Kaplan-Meier survival analysis is shown for these groups (low, intermediate and high) according to IPSS-R; Figure 2b) Kaplan-Meier survival analysis is shown for with and without *AXL1* mutation in total 48 cases of MDS; Figure 2c) Similarly, Kaplan-Meier survival analysis is shown for with and without *AXL1* mutation in low and intermediate MDS cases.

## DISCUSSION

MDS is mainly based on cytopenia, dysplastic morphological and clonal hematopoiesis diagnosis, but the atypical MDS diagnosis is still difficult, due to only 50% of MDS patients' clonal abnormality can be detected by conventional chromosomal and FISH technology.

However, the combination of molecular biology technology clonal abnormality can be increased to 80-90%, so reducing the difficulty of diagnosis and treatment of MDS (19). In summary, the gene mutations in the diagnosis of MDS play an important role. It has been confirmed that more than 40 kinds of gene mutations are related to MDS (3, 20). There are mainly 4 types of gene mutations in clinical practice, including cytokine signaling, DNA methylation, histone modifications and spliceosome.

The eight gene mutations in this study, DNA methylation and histone modification genes are the main types of mutations. *TET2* showed the highest frequency of mutations (37.5%), followed by *ASXL1* mutations (29.2%), which was slightly higher than that of *TET2* (12-26%) and *ASXL1* (15-29%) gene mutation rate reported by foreign literature (9,21). *TET2* and *ASXL1* gene mutations were the highest in MDS-EB patients, accounting for 44.4% (8/18) and 50.0% (7/14) respectively, followed by high prevalence in MDS-MLD patients, 33.3 (6/18) and 28.5% (4/13) , respectively. In the IPSS-R stratification, the *TET2* and *ASXL1* gene mutations were distributed in all stratification groups. However, there were the highest mutation rates of *TET2* gene mutation in low-risk group and *ASXL1* gene in intermediate-risk group [60.0 %(6/10), 40.0% (8/20) , respectively].

Lin et al (4) analyzed relationship between *TET2* gene mutation and prognosis in 46 MDS/AML patients that showed *TET2* mutation is an independent factor to shorten the Leukemia-free survival, especially in MDS-EB2 and very high-risk subgroup were significantly affected ( HR 4.52 and 7.81, respectively). During the progression of MDS to AML, the amount of *TET2* clones showed a tendency of gradual expansion, but had no significant effect on the overall survival of MDS patients. Also, most studies (2,22,23) concluded that *TET2* mutations do not affect the long-term and progression-free survival of patients with MDS. In our study, *TET2* mutation was not associated with overall survival and Leukemia-free survival in patients with MDS (P=0.527 and 1.000, respectively).

In the current study, we found that the mutation of *SF3B1* is an independent predictor of prognosis in MDS (19). However, no consensus has been reached on the prognosis of MDS in other types of gene mutations. Wu et al (23) analyzed the reproducible gene mutations in 304 MDS patients revealed that MDS patients with *ASXL1* mutations had older median age, higher IPSS-R score, often accompanied with complex karyotype and lower platelet and hemoglobin count, the above factors are the main reasons for the short overall survival of these patients.

In our paper, the results showed that high risk group (HR 14.626, 95% CI 1.459-146.633) and with *ASXL1* mutation (HR 3.315, 95% CI 1.180-9.309) were independent prognostic indicators of overall survival of MDS. Further analysis of patients with *ASXL1* mutation and without *ASXL1* mutation patients' clinical characteristics, and found that with *ASXL1* mutation patients had higher white blood cell count [3.5 (1.5-22.4) × $10^9$/L *vs.* 3.1 (1.0-9.2)×$10^9$/L, P=0.019]. Lower ORR after 2 courses of treatment (16.7% *vs.* 50.0%, P=0.045), they were the major factors in shortening overall survival. At the same time, there was a significant difference (P=0.006 and <0.001, respectively) in the overall survival between MDS patients with and without *ASXL1* mutation in total of MDS patients and low and intermediate-risk IPSS-R groups. Therefore, it is suggested that MDS patients with low-risk group with *ASXL1* mutation should choose a more aggressive treatment.

MDS as a type of malignantly clonal hematopoietic stem cell abnormal disease, treatment efficacy is poor in some patients, owing to primary body resistance drug, but the mechanism of resistance rarely reported. Study (24) reported that MDS patients with *TET2* mutation had a better response to demethylating agents, therefore, this part of patients with prolonged survival. In this paper showed that with *TET2* mutation (HR 8.787, 95% CI 1.343-57.093) was an independently adverse prognostic factor for OR. Compared to without *TET2* mutation group, the *TET2* mutation patients achieved higher OR 75% (3/4) after treated with demethylating agents, but the two groups with no significant difference($\chi 2$=0.608, P=0.603).

## CONCLUSION

The 8 genetic mutations analyzed in this study showed the highest frequency of *TET2* mutations and the second highest frequency of *ASXL1* mutations. The higher the degree of malignancy in MDS disease, the more abnormal gene clones. OS of MDS patients with *ASXL1* mutations is short, especially in patients with low and intermediate risk of IPSS-R, with *ASXL1* mutation patients with worse prognosis, MDS low-risk patients with *ASXL1* mutations recommended more aggressive treatment.

## REFERENCES

1. Bejar R, Stevenson KE, Caughey BA, et al. Validation of a prognostic model and impact of mutations in patients with lower-risk myelodysplastic syndromes J Clin Oncol.2012;30: 3376-3382.
2. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med. 2011;364: 2469-2506.

3. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesion in 944 patients with myelodysplasic syndromes[J]. Leukemia. 2014;28:241-247. DOI: 10.1038/leu.2013.336.
4. Cazzola M, Della Porta MG, Malcovati L. The genetic basis of myelodysplasia and its clinical relevance. Blood. 2013;122:4021-4034.
5. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological im-plications of driver mutations in myelodysplastic syndromes. Blood. 2013; 122:3616-3627.
6. Ganguly BB, Kadam NN. Mutations of myelodysplastic syndromes (MDS): An update. Mutat Res Rev Mutat Res..2016;769:47-62.
7. Tung-Liang L, Yasunobu N, Hsiao-Wen K, et al. Clonal leukemic evolution in myelodysplastic syndromes with *TET2* and IDH1/IDH2 mutations Haematologica..2014;99:28-31.
8. Kohlmann A, Grossmann A, Klein H.U, et al. Next-generation sequencing technology reveals a characteristic pattern of molecular mutations in 72.8% of chronic myelomonocytic leukemia by detecting frequent alterations in *TET2* CBL, RAS, and RUNX1. J Clin Oncol. 2010;28:3858–3865.
9. Smith AE, Mohamedali AM, Kulasekararaj A, et al. Next-generation sequencing of the *TET2* gene in 355 MDS and CMML patients reveals low-abundance mutant clones with early origins, but indicates no definite prognostic value. Blood. 2010;116:3923–3932.
10. Zhen G, Shao-kai Z, Zhe Z, et al. Prognostic significance of *TET2* mutations in myelodysplastic syndromes: A meta-analysis Leuk Res. 2017;58:102-107.
11. Abdel-Wahab O, Adli M, LaFave LM, et al. *ASXL1* mutations promote myeloid transformation through loss of PRC2-mediated gene repression. Cancer Cell. 2012; 22:180-193.
12. Davies C, Yip BH, Fernandez-Mercado M, et al. Silencing of *ASXL1* impairs the granulomonocytic lineage potential of human CD34+ progenitor cells. Br J Hematol. 2013;160: 842-850.
13. Gelsi-Boyer V, Trouplin V, Adelaide J, et al. Mutations of polycomp-associated gene *ASXL1* in myelodysplastic syndromes and chronic myelomonocytic leukemia. Br J Haematol. 2009;145: 788-800.
14. Abdel-Wahab O, Gao J, Adli M, et al. Deletion of *ASXL1* results in myelodysplasia and severe developmental defects in vivo. J Exp Med. 2013;210:2641-2659.
15. Inoue D, Kitaura J, Togami K, et al. Myelodysplasti syndromes are induced by histone methylation-altering *ASXL1* mutations. J Clin Invest. 2013;123:4627-4640.
16. Thol F, Friesen I, Damm F, et al. Prognostic significance of *ASXL1* mutations in patients with myelodysplastic syndromes. J Clin Oncol. 2011;29:2499-2506.
17. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89:2019-2088.
18. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodyslpasia. Blood. 2006;108: 419-425.
19. Zhijian X. The precise diagnosis of myelodysplastic syndromes. Chin J Hematol. 2015;36:361-362.
20. Raphael I, Olivier K, Pharm D, et al. Somatic mutations and epigenetic abnormalities in myelodysplastic syndromes. Clinical Heamatology. 2013;26:355-364.
21. Feng X, Ling-Yun W, Qi H, et al. Exploration of the role of gene mutations in myelodysplastic syndromes through a sequencing design involving a small number of target genes. Scientific reports. 2017;21:43113.
22. Langemeijer SM, Kuiper RP, Berends M, et al. Acquired mutations in *TET2* are common in myelodysplastic syndromes. [J]. Nat Genet. 2009; 41:838-842.
23. Wu L, Song L, Xu L, et al. Genetic landscape of recur- rent *ASXL1*, U2AF1, SF3B1, SRSF2 and EZH2 mutations in 304 Chinese patients with myelodysplastic syndromes. Tumor Biol. 2016;37:1-8.
24. Jennifer JJ, Sinha AU, Zhu N, et al. Haploinsufficiency of Dnmt1 impairs leukemia stem cell function through derepression of bivalent chromatin domains. Genes Dev. 2012;26: 344-349.