Association between gene mutations and certain blood cell indices in patients diagnosed with myelodysplastic neoplasms

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Abstract. Gene mutations play a crucial role in the pathogenesis of myelodysplastic neoplasms (MDS). The present study aimed to assess the association between some gene mutations and certain blood cell indices in patients diagnosed with MDS. The present study was a retrospective cross-sectional study. Patients newly diagnosed with MDS, who underwent next-generation sequencing, and which revealed 51 gene mutations, were enrolled in the present study. The peripheral blood cell indices were recorded before commencing treatment. There were 18 mutations to be found. The *ASXL1* mutation was the most frequently encountered, followed by the *RUNX1, TET2, SF3B1* and *TP53* mutations. Patients with the *U2AF1* mutation had a lower hemoglobin level, those with *BCOR* or *SRSF2* mutations had a higher percentage of peripheral blood blasts, and those with the *SF3B1* mutation had a higher platelet count compared to the group without this mutation. Receiver operating characteristic analysis was performed to determine the optimal cut-off value for hemoglobin level, platelet count and the percentage of peripheral blood blasts. The optimal cut-off value for the hemoglobin level to separate the presence of *U2AF1* mutation was 56.5. The optimal cut-off value for the percentage of peripheral blood blasts to separate the presence of *BCOR* and *SRSF2* mutations was 7.5 and 5.5, respectively. The optimal cut-off value for the platelet count to separate the presence of the *SF3B1* mutation was 228.5. The results also revealed that a hemoglobin level <56.5 g/l, platelet count >228.5 G/l, and a percentage of peripheral blood blasts >7.5 and >5.5% was associated with *U2AF1, SF3B1, BCOR* and *SRSF2* mutations. On the whole, the present study demonstrates that there is an association between gene mutations and blood cell indices in patients diagnosed with MDS. The *U2AF1* mutation is associated with severe anemia, and *BCOR* and *SRSF2* mutations are associated with MDS with increased blast numbers. However, the *SF3B1* mutation is related to a good platelet count.

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Introduction

Myelodysplastic neoplasms (previous terminology, myelodysplastic syndromes; MDS) are characterized by ineffective hemopoiesis, bone marrow dysplasia, cytopenia and an increased risk of leukemic transformation (1). Gene myeloid mutations play a role in the pathogenesis of MDS; thus, these mutations become a contributing factor to the diagnosis, classification and prognosis of patients with the disease (2-5). The minimal diagnostic criteria proposed by the World Health Organization (WHO; from 2001 to 2008) included gene mutations [e.g., splicing factor 3b subunit 1 (*SF3B1*)] in the co-criteria (6). The WHO 2016 classification had used the *SF3B1* mutation as a criterion in the classification of MDS (7). Subsequently, in the WHO 2022 classification, the *SF3B1* and *TP53* mutations were used to classify MDS (8). Therefore, gene mutations play an increasingly critical role in the diagnosis and classification of MDS. Furthermore, previous studies have demonstrated that gene mutations can be considered a key prognostic factor for MDS (9-11). The Molecular International Prognostic Scoring System (IPSS-M), which combines the International Prognostic Scoring System-Revised (IPSS-R) with molecular data including 31 gene mutations, appears to be superior to previous prognostic systems (12-14). However, its disadvantage is its high cost; thus, it is difficult for this new system to be applied in developing countries.

Of note, these gene mutations can also directly influence hematopoiesis due to their involvement in pathogenesis. The *SF3B1* mutation is related to sideroblastic anemia; thus, the WHO 2022 classification determined that the detection of 15% ring sideroblasts may substitute for the *SF3B1* mutation (15). It would be of interest to determine whether it is possible to use blood or bone marrow cell indices to predict the presence

of gene mutations, thus providing reasonable and economical indications. Thus, the aim of the present study was to assess the association between gene mutations and certain cell indices in patients diagnosed with MDS.

Patients and methods

Patients. A retrospective cross-sectional study was conducted at the National Institute of Hematology and Blood Transfusion, Hanoi, Vietnam. Patients newly diagnosed with MDS who had been examined for myeloid genes mutations from January, 2018 to June, 2021 were consecutively recruited in the present study. The study protocol was approved by the Institutional Review Board of the National Institute of Hematology and Blood Transfusion (no. 939/QĐ-HHTM). Patient consent was waived by the committee, since this study was a retrospective observational study. All details of the patients were deidentified.

Next-generation sequencing (NGS). NGS was performed with 51 myeloid gene mutations. The panel included gene groups for DNA methylation, chromatin modification, RNA splicing, cohesin complex, transcription, cytokine receptor/tyrosine kinase, RAS signaling, checkpoint/cell cycle and others (Table I). *SF3B1, TET2, ASXL1* and *DMNT3A* were analyzed using the MiSeq Reagent kit (Illumina, Inc.). Other gene mutations were analyzed using the Hema 50 Panel (Dxome Co., Ltd., Korea).

Data collection. Data from patients, including clinical characteristics, peripheral blood and bone marrow cell indices, as well as cytogenetics report, recorded before starting treatment, were collected from medical record of the patients.

Diagnosis and classification of MDS. The determination of the diagnosis of MDS was based on the proposal of the minimal diagnostic criteria of MDS (5). Patients with MDS were classified according to the WHO 2022 criteria (15). The risk was calculated according to IPSS-M (9,16).

Statistical analysis. Qualitative variables (clinical characteristic, karyotype, cytogenetic risk, type of MDS and IPSS-M) and quantitative variables (hemoglobin, neutrophil count, platelet count, percentage of peripheral blood blast, bone marrow cell count and the percentage of bone marrow blasts) were analyzed according to sex and classification of age (50 years). Comparisons of qualitative variables were performed using the χ^2 test or Fisher's exact test. Comparisons of quantitative variables were performed using an independent samples t-test or the Mann-Whitney U test according to normal or non-normal distribution. The presence of gene mutations was expressed as frequency and percentage. The differences between quantitative variables (hemoglobin, neutrophil count, platelet count, the percentage of peripheral blood blast, bone marrow cell count and the percentage of bone marrow blasts) were compared between two groups according to the presence of each mutation using an independent samples t-test or the Mann-Whitney U test according to normal or non-normal distribution. In variables for which a statistically significant difference was found, receiver operating characteristic (ROC) curve analysis was performed

Table I. Panel of sequencing genes.

No	Gene	Location	No	Gene	Location
1	*ANKRD26*	10p12.1	26	*IDH2*	15q26.1
2	*ASXL1*	20q11.21	27	*IKZF1*	7p12.2
3	*ATM*	11q22.3	28	*JAK2*	9p24.1
4	*BCOR*	Xp11.4	29	*KIT*	4q12
5	*BIRC3*	11q22.2	30	*KRAS*	12p12.1
6	*BLM*	15q26.1	31	*MPL*	1p34.2
7	*BRAF*	7q34	32	*MYD88*	3p22.2
8	*CALR*	19p13.13	33	*NF1*	17q11.2
9	*CBL*	11q23.3	34	*NOTCH1*	9q34.3
10	*CDKN2A*	9p21.3	35	*NOTCH2*	1p12
11	*CDKN2B*	9p21.3	36	*NPM1*	5q35.1
12	*CEBPA*	19q13.11	37	*NRAS*	1p13.2
13	*CREBBP*	16p13.3	38	*PAX5*	9p13.2
14	*CRLF2*	Xp22.33	39	*PRF1*	10q22.1
15	*CSF3R*	1p34.3	40	*PTPN11*	12q24.13
16	*DDX41*	5q35.3	41	*RB1*	13q14.2
17	*DNMT3A*	2p23.3	42	*RUNX1*	21q22.12
18	*ELANE*	19p13.3	43	*SETBP1*	18q12.3
19	*ETV6*	12p13.2	44	*SF3B1*	2q33.1
20	*EZH2*	7q36.1	45	*SRSF2*	17q25.1
21	*FANCA*	16q24.3	46	*TET2*	4q24
22	*FLT3*	13q12.2	47	*TP53*	17p13.1
23	*GATA1*	Xp11.23	48	*U2AF1*	21q22.3
24	*GATA2*	3q21.3	49	*UNC13D*	17q25.1
25	*IDH1*	2q34	50	*WAS*	Xp11.23
			51	*WT1*	11p13

ANKRD26, ankyrin repeat domain containing 26; *ASXL1*, ASXL transcriptional regulator 1; *ATM*, ATM serine/threonine kinase; *BCOR*, BCL6 corepressor; *BIRC3*, baculoviral IAP repeat containing 3; *BLM*, BLM RecQ like helicase; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; *CALR*, calreticulin; *CBL*, Cbl proto-oncogene; *CDKN2A*, cyclin dependent kinase inhibitor 2A; *CDKN2B* cyclin dependent kinase inhibitor 2B; *CEBPA*, CCAAT enhancer binding protein alpha; *CREBBP*, CREB binding protein; *CRLF2*, cytokine receptor like factor 2; *CSF3R*, colony stimulating factor 3 receptor; *DDX41*, DEAD-box helicase 41; *DNMT3A*, DNA methyltransferase 3 alpha; *ELANE*, elastase, neutrophil expressed; *ETV6*, ETS variant transcription factor 6; *EZH2*, enhancer of zeste 2 polycomb repressive complex 2 subunit; *FANCA*, FA complementation group A; *FLT3*, Fms related receptor tyrosine kinase 3; *GATA1*, GATA binding protein 1; *GATA2*, GATA binding protein 2; *IDH1*, isocitrate dehydrogenase [NADP(+)] 1; *IDH2*, isocitrate dehydrogenase [NADP(+)] 2; *IKZF1*, IKAROS family zinc finger 1; *JAK2*, Janus kinase 2; *KIT*, KIT proto-oncogene; *KRAS*, KRAS proto-oncogene; *MPL*, MPL proto-oncogene; *MYD88*, MYD88 innate immune signal transduction adaptor; *NF1*, neurofibromin 1; *NOTCH1*, Notch receptor 1; *NOTCH2*, Notch receptor 2; *NPM1*, nucleophosmin 1; *NRAS*, NRAS proto-oncogene; *PAX5*, paired box 5; *PRF1*, perforin 1; *PTPN11*, protein tyrosine phosphatase non-receptor type 11; *RB1*, RB transcriptional corepressor 1; *RUNX1*, RUNX family transcription factor 1; *SETBP1*, SET binding protein 1; *SF3B1*, splicing factor 3b subunit 1; *SRSF2*, serine and arginine rich splicing factor 2; *TET2*, Tet methylcytosine dioxygenase 2; *TP53*, tumor protein 53; *U2AF1*, *U2* small nuclear RNA auxiliary factor 1; *UNC13D*, Unc-13 homolog D; *WAS*, WASP actin nucleation promoting factor; *WT1*, WT1 transcription factor.

Table II. Cell indices of the patients according to sex and age.

Index	All patients (n=34)	Sex			Age, years		
		Male (n=21)	Female (n=13)	P-value	<50 (n=5)	≥50 (n=29)	P-value
Hemoglobin (g/l), mean ± SD	81.97±15.05	84±13.35	78.64±17.52	>0.05	86.40±10.76	81.21±15.69	>0.05
Platelet count (G/l), median	75.5	83	60	>0.05	78	75	>0.05
Neutrophil count (G/l), median	1.3	1.12	1.41	>0.05	1.41	1.19	>0.05
Peripheral blasts (%), median	1.0	2.0	0.0	>0.05	2.0	0.0	>0.05
Bone marrow cell count (G/l), median	29.46	31.3	20	>0.05	36.8	29.1	>0.05
Bone marrow blast (%), mean ± SD	5.91±5.14	5.95±5.04	5.85±5.52	>0.05	7.2±8.83	5.69±4.91	>0.05

SD, standard deviation.

to separate the significant variables to determine a cut-off value. An area under the curve (AUC) value >0.8 was considered good for separation. The cut-off value was determined based on the coordinates of the curve. The cut cut-off value, the sensitivity (Se) and the specificity (Sp) were selected according to the Youden index (J) as follows: [J=max (Se + Sp -1)] with the highest value. Fisher's exact test was used to examine the association between the presence of the gene mutations and the cut-off value found. Statistical analysis was performed using SPSS 25 software (IBM Corp.). P<0.05 was considered to indicate a statistically significant difference. The bias was controlled as no data were lost. The study reporting conforms to the STROBE guidelines (17).

Results

Patient characteristics. The present study included 34 patients, with 21 males (61.8%) and 13 females (38.2%). The median age of the patients was 66 years (range, 28-81 years). All patients were Vietnamese, of Kinh ethnicity. The peripheral blood and bone marrow cell indices of the patients are presented in Table II. The clinical characteristics of the patients, as well as the classification results (WHO 2022 classification, karyotype, risk of cytogenetics and risk stratification according to the criteria of IPSS-M) are presented in Table III. The common clinical symptom was anemia (97.1%), followed by hemorrhage and infection. There were 3 to 4 patients with hepatomegaly, splenomegaly or lymphadenopathy, which were not massive. A total of 12 patients (35.3%) had comorbidities that included chronic obstructive pulmonary disease, hypertension, diabetes and dyslipidemia. In addition, 10 patients (29.4%) had an abnormal karyotype at the time of diagnosis, of which 2 patients had a complex karyotype (≥3 chromosomal abnormalities), 2 patients had isolated del(5q) and 6 patients had other abnormalities [such as del(20q), -7/del(7q), translocation]. A total of 11 patients were diagnosed with MDS with a low blast count, which accounted for the highest rate (32.4%) and 1 patient was diagnosed with MDS-biT*P53*, accounting for the lowest rate (2.9%); others types included MDS 5q-, MDS-*SF3B1*, MDS-IB1 and MDS-IB2. According to IPSS-M, 9 patients were classified as moderate-high risk, with the highest proportion (26.5%) and no patients were classified as very low risk. No statistically significance differences were found between the males and females, and between patients aged <50 and ≥50 years when these characteristics were compared (P>0.05).

Gene mutation data. NGS was performed to evaluate 51 myeloid gene mutations. A total of 20 patients (58.8%) had mutations. The remaining 14 patients did not have mutations. There were 18 mutations to be detected (Table IV). The ASXL transcriptional regulator 1 (*ASXL1*) mutation (17.6%) was the most commonly encountered, followed by the Runt-related transcription factor 1 (*RUNX1*), Tet methylcytosine dioxygenase 2 (*TET2*) (14.7%), and *SF3B1* and *TP53* mutations (11.8%) (Table IV). The number of gene mutations ranged between 1 to 7 per patient with a mean value of 1.35 (Table V).

Association between mutations and cell indices. As shown in Table VI, patients with the U2 small nuclear RNA auxiliary factor 1 (*U2AF1*) or *TET2* mutation had a lower hemoglobin level than patients without this mutation. In addition, patients with the BCL6 corepressor (*BCOR*) or the serine and arginine rich splicing factor 2 (*SRSF2*) mutation had a higher percentage of peripheral blood blasts than patients without this mutation. Furthermore, patients with the *BCOR* mutation had a higher percentage of bone marrow blasts than those without it. On the other hand, patients with the *SF3B1* mutation had a higher platelet count compared to the patients without it. These differences were statistically significant (P<0.05).

ROC analysis determined that the significant separation only appeared in variables, such as the hemoglobin level, platelet count and peripheral blood blasts, with an AUC value >0.8 and P<0.05 (Table VII). Based on the coordinates of the

Table III: Patients characteristics according to sex and age.

Characteristic	All patients (n=34), n (%)	Sex			Age, years		
		Male (n=21)	Female (n=13)	P-value	<50 (n=5)	≥50 (n=29)	P-value
Clinical factors							
Anemia	33 (97.1)	20	13	>0.05	5	28	>0.05
Hemorrhage	8 (23.5)	4	4	>0.05	1	7	>0.05
Infection	7 (20.6)	3	4	>0.05	2	5	>0.05
Hepatomegaly	4 (11.8)	3	1	>0.05	0	4	>0.05
Splenomegaly	4 (11.8)	4	0	>0.05	0	4	>0.05
Lymphadenopathy	3 (8.8)	2	1	>0.05	0	3	>0.05
Comorbidities	12 (35.3)	7	5	>0.05	2	10	>0.05
Type of MDS							
MDS 5q-	2 (5.9)	1	1		1	1	
MDS *SF3B1*	2 (5.9)	2	0		0	2	
MDS-bi*TP53*	1 (2.9)	1	0		0	1	
MDS low blast	11 (32.4)	6	5	>0.05	1	10	>0.05
MDS-IB1	10 (29.4)	5	5		1	9	
MDS-IB2	8 (23.5)	6	2		2	6	
Karyotype							
Normal	24 (70.6)	14	10		3	21	
Del (5q) isolated	2 (5.9)	1	1	>0.05	1	1	>0.05
Complex karyotype	2 (5.9)	1	1		0	2	
Abnormal (other)	6 (17.6)	5	1		1	5	
Cytogenetic risk							
Very good	1 (2.9)	1	0	>0.05	0	1	>0.05
Good	27 (79.4)	16	11		4	23	
Intermediate	0 (0)	0	0		0	0	
Poor	4 (11.8)	3	1		1	3	
Very poor	2 (5.9)	1	1		0	2	
IPSS-M							
Very low	0 (0)	0	0		0	0	
Low	8 (23.5)	7	1		1	7	
Moderately low	6 (17.6)	2	4	>0.05	2	4	>0.05
Moderately high	9 (26.5)	4	5		1	8	
High	6 (17.6)	4	2		1	5	
Very high	5 (14.7)	4	1		0	5	

MDS, myelodysplastic neoplasms (myelodysplastic syndromes); IB, increased blasts; IPSS-Molecular International Prognostic Scoring System.

curve with the results of calculating the J index, the optimal cut-off values for the hemoglobin level, platelet count and the percentage of peripheral blood blasts were determined with the possible highest values of sensitivity (Se) and specificity (Sp). The cut-off value, the Se and the Sp are presented in Table VII. The optimal cut-off value for the hemoglobin level to separate the presence of the *U2AF1* mutation was 56.5. The optimal cut-off value for the percentage of peripheral blood blasts to separate the presence of the *BCOR* and *SRSF2* mutation was 7.5 and 5.5, respectively. The optimal cut-off value for the platelet count to separate the presence of the *SF3B1* mutation was 228.5. Otherwise, ROC did not determine the separation of the hemoglobin level or the percentage of bone marrow blasts according to the presence of the *TET2* and *BCOR* mutation.

The results of Fisher's exact test indicated that a hemoglobin level <56.5 g/l, a platelet count >228.5 G/l, a percentage of peripheral blood blasts >7.5% and a percentage of peripheral blood blasts >5.5% was associated with the *U2AF1, SF3B1, BCOR* and *SRSF2* mutations, respectively (Table VIII).

Discussion

The development of MDS may be associated with cumulative genetic changes involving hematopoietic stem cells; thus,

Table IV. Frequency of gene mutations.

Pathways	Gene mutations	Frequency	%
Chromatin modification	*ASXL1*	6	17.6
Cohesin complex	*STAG2*	2	5.9
Transcription	*RUNX1*	5	14.7
	BCOR	2	5.9
RNA splicing	*SF3B1*	4	11.8
	SRSF2	3	8.8
	U2AF1	3	8.8
DNA methylation	*TET2*	5	14.7
	IDH1	1	2.9
	IDH2	2	5.9
	DNMT3A	3	8.8
Cytokine receptor/tyrosine kinase	*CSF3R*	1	2.9
	JAK2	1	2.9
	MPL	1	2.9
	KIT	1	2.9
RAS signaling	*NRAS*	2	5.9
Checkpoint/cell cycle	*TP53*	4	11.8
Others	*SETBP1*	1	2.9

ASXL1, ASXL transcriptional regulator 1; *STAG2*, STAG2 cohesin complex component; *RUNX1*, RUNX family transcription factor 1; *BCOR*, BCL6 corepressor; *SF3B1*, splicing factor 3b subunit 1; *SRSF2*, serine and arginine rich splicing factor 2; *U2AF1*, *U2* small nuclear RNA auxiliary factor 1; *TET2*, Tet methylcytosine dioxygenase 2; *IDH1*, isocitrate dehydrogenase [NADP(+)] 1; *IDH2*, isocitrate dehydrogenase [NADP(+)] 2; *DNMT3A*, DNA methyltransferase 3 alpha; *CSF3R*, colony stimulating factor 3 receptor; *JAK2*, Janus kinase 2; *MPL*, MPL proto-oncogene; *KIT*, KIT proto-oncogene; *NRAS*, NRAS proto-oncogene; *TP53*, tumor protein 53; *SETBP1*, SET binding protein 1.

Table V. Distribution of gene mutations in the patients.

Number of gene mutations per patient	No. of patients with this number of mutations	%
0	14	41.2
1	10	29.4
2	1	2.9
3	6	17.6
4	1	2.9
5	1	2.9
6	0	0
7	1	2.9

gene mutations are often detected in patients with MDS (18). Some studies have demonstrated that the majority of patients with MDS (50-90%) have at least one mutation (19-22). In the present study, gene mutations were observed in 58.8% of the patients. In fact, this rate also depended on the panel of NGS, as well as the sample size. The present study demonstrated that the most frequent genetic mutation was the *ASXL1* mutation, followed by *RUNX1, TET2, SF3B1* and *TP53*. Liu *et al* (23) also indicated that the *ASXL1, RUNX1* and *TP53* mutations were common. The *TET2, SF3B1, ASXL1, SRSF2,* DNA methyltransferase 3 alpha (*DNMT3A*) and *RUNX1* mutations were the most commonly observed mutations in the study by Haferlach *et al* (20). In their study, Zhao *et al* (21) suggested that the most prevalent mutations were the *U2AF1, SF3B1, ASXL1, TET2, BCOR, TP53* and *DNMT3A* mutations. In general, it has been indicated that genetic mutations, such as *ASXL1, RUNX1, BCOR, TET2, DNMT3A, SF3B1, SRSF2, U2AF1* and *TP53* are the most common mutations. These mutations also belong to the most known gene groups according to pathways/functions including chromatin modification (*ASXL1*), transcription factors *(RUNX1*), transcriptional regulator (*BCOR*), DNA methylation (*TET2* and *DNMT3A*), RNA splicing (*SF3B1, SRSF2* and *U2AF1*) and tumor suppressor (*TP53*) (24,25).

The accumulation of gene mutations alters hematopoiesis in MDS; thus, features such as cytopenia and bone marrow dysplasia may be associated with the activation of these mutations. Some studies, although a limited number, have indicated this association. Bejar *et al* (19) considered that the *RUNX1, TP53* and *NRAS* mutations were strongly related to severe thrombocytopenia. The *SF3B1* mutation was the most notable one. Martín *et al* (10) claimed that the majority of patients with MDS with ring sideroblasts carried the *SF3B1* mutation. The *SF3B1* mutation is involved in iron transport and causes abnormal iron deposition around the mitochondria to form ring sideroblasts (24). Polprasert *et al* (26) demonstrated that patients with the *SF3B1* mutation had lower hemoglobin levels than those with the wild-type variant, but had normal platelet counts. Stockton *et al* (27) conducted a meticulous study that included numerous mutations and also indicated that patients with the *SF3B1* mutation had anemia and a higher platelet count. In the present study, patients with this mutation also had a higher platelet count. A platelet count >228.5 G/l was associated with the presence of the *SF3B1* mutation. The *U2AF1* mutation, although valuable for consideration, had an ununified effect. Polprasert *et al* (26) hypothesized that it was associated with more severe leukopenia; however, Stockton *et al* (27) indicated that it was related to thrombocytopenia. In the present study, the *U2AF1* mutation was associated with severe anemia. Patients with hemoglobin levels <56.5 g/l had the *U2AF1* mutation. The present study also indicated that a percentage of peripheral blood blasts >7.5 and >5.5% was associated with the presence of the *BCOR* and *SRFS2* mutations, respectively. Otherwise, Stockton *et al* (27) assumed that the *SRFS2* mutation was related to higher hemoglobin levels. There were differences between the results of the studies. However, with the exception of the role of the *SF3B1* mutation in increasing the number of sideroblasts, the mechanisms of gene mutations as regards the genesis of each cell clone are still being investigated.

The present study had certain limitations which should be mentioned: The most notable one was the is small sample size. Although the number of genes for the analysis was 51 genes, it still did not cover all myeloid genetic changes. The present study was only a cross-sectional study; thus, patients were not followed-up to determine their progress or any changes

Table VI. Cell indices according to the presence of some gene mutations.

Index	Gene mutations	Yes	No	P-value
Hemoglobin (g/l), mean ± SD	*U2AF1*	59.33±21.82	84.16±12.69	0.005
	TET2	68.80±20.68	84.24±13.02	0.032
Platelet count (G/l), median	*SF3B1*	335	67	0.004
Peripheral blood blast (%), median	*BCOR*	13	0	0.016
	SRSF2	8	0	0.007
Bone marrow blasts (%), mean ± SD	*BCOR*	13.50±4.95	5.44±4.84	0.029

U2AF1, *U2* small nuclear RNA auxiliary factor 1; *TET2*, Tet methylcytosine dioxygenase 2; *SF3B1*, splicing factor 3b subunit 1; *BCOR*, BCL6 corepressor; *SRSF2*, serine and arginine rich splicing factor 2.

Table VII. ROC analysis of the separation of cell indices according to the presence of some gene mutations.

Gene mutations	Cell indices	AUC	P-value	Cut-off value	Sensitivity (%)	Specificity (%)
U2AF1	Hemoglobin (g/l)	0.87	0.036	56.5	96.8	98.67
SF3B1	Platelet count (G/l)	0.95	0.004	228.5	100	96.67
BCOR	Peripheral blood blasts	0.98	0.026	7.5	100	99.37
SRSF2	(%)	0.94	0.013	5.5	100	98.39

AUC, area under the ROC curve; *U2AF1*, *U2* small nuclear RNA auxiliary factor 1; *SF3B1*, splicing factor 3b subunit 1; *BCOR*, BCL6 corepressor; *SRSF2*, serine and arginine rich splicing factor 2.

Table VIII. Association between cell indices and the presence of some gene mutations.

Gene mutations	Cell indices	P-value
U2AF1	Hemoglobin (g/l) <56.5	0.016
SF3B1	Platelet count (G/l) >228.5	0.002
BCOR	Peripheral blood blasts (%) >7.5	0.011
SRSF2	Peripheral blood blasts (%) >5.5	0.009

U2AF1, *U2* small nuclear RNA auxiliary factor 1; *SF3B1*, splicing factor 3b subunit 1; *BCOR*, BCL6 corepressor; *SRSF2*, serine and arginine rich splicing factor 2.

of the cell clone over time. The present study was conducted in Vietnam, a developing country. Due to the difficulty in accessing novel drugs, as well as the high cost of treatments such as stem cell transplantation, treatment outcome and survival time were difficult to evaluate, so the prognostic role of gene mutations has not been mentioned. In addition, the association between gene mutations and hematopoiesis is very complex, requiring additional valuable tests such as reticulin staining, Prussian blue staining (to detect ring sideroblasts), iron metabolism, etc. for more detailed analyses. These are also limitations of the study.

In conclusion, the present study demonstrates that there is an association between gene mutations and blood cell indices in patients diagnosed with MDS. The *U2AF1* mutation may be related to severe anemia, while the *BCOR* and *SRSF2* mutations may be related to MDS with an increased number of blasts. The *SF3B1* mutation may be related to a good platelet count. Based on the levels of these blood cell indices, the appropriate gene mutations may be considered for examination. However, further research is required in order to determine the association between genetic changes, and changes in blood and bone marrow cells so that a model based on cell indices can be constructed to predict genes. This may promote reasonable genetic testing in patients with MDS. We also hope to carry out studies with large sample sizes and long follow-up periods to be able to determine the time when gene mutations appear based on changes in cell indices.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MPV and QHN conceived and designed the study. QHN, TAT, QCD and DBV participated in data collection and processing.

MPV, QHN, TAT, QCD, DBV, HTN and QKB participated in data analysis and interpretation, as well as in the literature search, and wrote the manuscript. All authors have read and approved the final manuscript. QHN and TAT confirm the authenticity of the raw data.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the National Institute of Hematology and Blood Transfusion (no. 939/QĐ-HHTM). Patient consent was waived by the committee since the present study was a retrospective observational study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that have no competing interests.

References

1. Marques FK and Sabino AP: Myelodysplastic neoplasms: An overview on diagnosis, risk-stratification, molecular pathogenesis, and treatment. Biomed Pharmacother 156: 113905, 2022.
2. Ogawa S: Genetics of MDS. Blood 133: 1049-1059, 2019.
3. Nakajima H: Molecular pathogenesis and treatment of myelodysplastic syndromes. Intern Med 60: 15-23, 2021.
4. Shallis RM, Ahmad R and Zeidan AM: The genetic and molecular pathogenesis of myelodysplastic syndromes. Eur J Haematol 101: 260-271, 2018.
5. Haferlach T: The molecular pathology of myelodysplastic syndrome. Pathobiology 86: 24-29, 2019.
6. Valent P, Orazi A, Steensma DP, Ebert BL, Haase D, Malcovati L, van de Loosdrecht AA, Haferlach T, Westers TM, Wells DA, *et al*: Proposed minimal diagnostic criteria for myelodysplastic syndromes (MDS) and potential pre-MDS conditions. Oncotarget 8: 73483-73500, 2017.
7. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M and Vardiman JW: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 127: 2391-2405, 2016.
8. Garcia-Manero G: Myelodysplastic syndromes: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol 98: 1307-1325, 2023.
9. Bejar R: Clinical and genetic predictors of prognosis in myelodysplastic syndromes. Haematologica 99: 956-964, 2014.
10. Martín I, Such E, Navarro B, Villamón E, Vicente A, Mora E, Pedrola L, Ibáñez M, López-Pavía M, Tormo M, *et al*: Prognostic impact of gene mutations in myelodysplastic syndromes with ring sideroblasts. Blood Cancer J 7: 630, 2017.
11. Maurya N, Mohanty P, Dhangar S, Panchal P, Jijina F, Mathan SLP, Shanmukhaiah C, Madkaikar M and Vundinti BR: Comprehensive analysis of genetic factors predicting overall survival in Myelodysplastic syndromes. Sci Rep 12: 5925, 2022.
12. Ma J, Gu Y, Wei Y, Wang X, Wang P, Song C and Ge Z: Evaluation of new IPSS-Molecular model and comparison of different prognostic systems in patients with myelodysplastic syndrome. Blood Sci 5: 187-195, 2023.
13. Lee WH, Tsai MT, Tsai CH, Tien FM, Lo MY, Tseng MH, Kuo YY, Liu MC, Yang YT, Chen JC, *et al*: Validation of the molecular international prognostic scoring system in patients with myelodysplastic syndromes defined by international consensus classification. Blood Cancer J 13: 120, 2023.
14. Gu S, Xia J, Tian Y, Zi J and Ge Z: A novel scoring system integrating molecular abnormalities with IPSS-R can improve the risk stratification in patients with MDS. BMC Cancer 21: 134, 2021.
15. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, Bejar R, Berti E, Busque L, Chan JKC, *et al*: The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 36: 1703-1719, 2022.
16. Bernard E, Tuechler H, Greenberg PL, Hasserjian RP, Arango Ossa JE, Nannya Y, Devlin SM, Creignou M, Pinel P, Monnier L, *et al*: Molecular international prognostic scoring system for myelodysplastic syndromes. NEJM Evid 1: EVIDoa2200008, 2022.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC and Vandenbroucke JP; STROBE Initiative: The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. J Clin Epidemiol 61: 344-349, 2008.
18. Cook MR, Karp JE and Lai C: The spectrum of genetic mutations in myelodysplastic syndrome: Should we update prognostication? EJHaem 3: 301-313, 2021.
19. Bejar R, Stevenson K, Abdel-Wahab O, Galili N, Nilsson B, Garcia-Manero G, Kantarjian H, Raza A, Levine RL, Neuberg D and Ebert BL: Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med 364: 2496-2506, 2011.
20. Haferlach T, Nagata Y, Grossmann V, Okuno Y, Bacher U, Nagae G, Schnittger S, Sanada M, Kon A, Alpermann T, *et al*: Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia 28: 241-247, 2014.
21. Zhao P, Qin J, Liu W, Quan R, Xiao H, Liu C, Li L, Lv Y, Zhu Q, Wang H, *et al*: Genetic alterations in 47 patients with a novel myelodysplastic syndrome diagnosis at a single center. Oncol Lett 18: 5077-5084, 2019.
22. Yu J, Li Y, Li T, Li Y, Xing H, Sun H, Sun L, Wan D, Liu Y, Xie X and Jiang Z: Gene mutational analysis by NGS and its clinical significance in patients with myelodysplastic syndrome and acute myeloid leukemia. Exp Hematol Oncol 9: 2, 2020.
23. Liu M, Wang F, Zhang Y, Chen X, Cao P, Nie D, Fang J, Wang M, Liu M and Liu H: Gene mutation spectrum of patients with myelodysplastic syndrome and progression to acute myeloid leukemia. Int J Hematol Oncol 10: IJH34, 2021.
24. Saygin C and Godley LA: Genetics of myelodysplastic syndromes. Cancers (Basel) 13: 3380, 2021.
25. Kennedy JA and Ebert BL: Clinical implications of genetic mutations in myelodysplastic syndrome. J Clin Oncol 35: 968-974, 2017.
26. Polprasert C, Kongkiatkamon S, Niparuck P, Rattanathammethee T, Wudhikarn K, Chuncharunee S, Kobbuaklee S, Suksusut A, Lanamtieng T, Lawasut P, *et al*: Genetic mutations associated with blood count abnormalities in myeloid neoplasms. Hematology 27: 765-771, 2022.
27. Stockton SS, Malhotra V, Lu X, Thangavelu M, Albitar M and Cogle CR: Gene mutations in MDS associating with peripheral blood count abnormalities. Blood 126: 1685, 2015.