

Prognostic Significance of Low Serum Apolipoprotein A1 Levels at Diagnosis are Independent Prognostic Factors in De Novo Myelodysplastic Syndrome, and with Higher Frequency of TP53 Mutation

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Abstract

Background: Myelodysplastic syndromes (MDS) is a group of heterogeneous myeloid clonal diseases originating from hematopoietic stem cells. It has been demonstrated that apolipoproteins A1 (ApoA1) is associated with disease risk in many cancer types. However, there is a lack of evidence regarding the link between ApoA1 and MDS. This study was designed to investigate the prognostic value of ApoA1 levels in MDS patients.

Methods: We retrospectively analyzed a cohort of 231 MDS patients to explore the prognostic value of the serum ApoA1 levels at diagnose. Patients were divided into high ApoA1 group and low ApoA1 group. The prognostic significance of it was determined by univariate and multivariate Cox hazard models.

Results: MDS patients with low ApoA1 had significantly shorter overall survival (OS) ($P < 0.001$) along with higher frequency of TP53 mutation ($P = 0.001$). Based on univariate analysis, age (≥ 60 years), gender (male), lower hemoglobin level ($< 10\text{g/dl}$), higher bone marrow blast percentage ($> 5\%$), poorer karyotype and higher IPSS-R score ($P < 0.0001$) were significantly associated with OS. But low ApoA1 had no significantly for Leukemia-free survival (LFS) ($P = 0.359$). Multivariate Cox proportional hazards regression analysis indicated that low ApoA1 level ($\leq 1.02\text{g/L}$) was also an independent adverse prognostic factor for OS in MDS ($P = 0.020$).

Conclusions: Decreased levels of ApoA1 could predict a poor prognosis independent of the IPSS-R and provide a novel evaluation factor for MDS patients.

Background

Myelodysplastic syndromes (MDS), characterized by ineffective hematopoiesis, manifested by morphologic dysplasia in hematopoietic cells and peripheral cytopenia(s), is a group of heterogeneous myeloid clonal diseases originating from hematopoietic stem cells with a high risk of transforming to secondary acute myeloid leukemia (AML) [1]. The prognosis of MDS is extremely heterogeneous, thus the Revised International Prognostic Scoring System (IPSS-R) in 2012 were introduced to risk-stratify MDS patients [2]. The scoring system mainly included the severity of hemocytopenia (anemia, thrombocytopenia, neutropenia, decreased hemoglobin content), increased bone marrow blasts, and cytogenetic factors. Recently, mutations such as TP53, SRSF2, IDH2 and ASXL1 were also demonstrated to predict the prognosis of MDS [3–5].

Tumor microenvironment interacts with tumor cells and plays a crucial role in tumor genesis and development. By mediating complex signaling pathways, it can induce the expression of various pro-inflammatory cytokines, chemokines and angiogenic factors, promote tumor growth, invasion and metastasis, and accelerate tumor progression [6]. MDS has a unique bone marrow microenvironment, and the abnormal bone marrow microenvironment contributes to the proliferation of tumor clones and promotes the occurrence and development of MDS [7]. Evidence for the activation of lipid metabolism in tumor cells can be produced by quantifying the products of lipid metabolism, such as apolipoprotein A1

(ApoA1), in the serum from some cancer patients. Apo plays an important role in regulating lipid balance by binding and transporting triglycerides, total cholesterol and phospholipids, and is widely involved in the occurrence and development of tumors [8]. Apo may be involved in tumorigenesis and development by promoting tumor invasion and metastasis, anti-tumor drug delivery and direct oxidative stress response [9–13]. In the past years, a correlation of ApoA1 levels with disease risk has been observed for many cancer types. It has been also suggested that serum ApoA1 levels were related to the survival rate of a variety of tumors, such as gastric cancer, nasopharyngeal cancer and colorectal cancer [14–16]. However, the prognostic value of serum ApoA1 levels for the overall survival of patients with MDS remains unclear. Therefore, we retrospectively analyzed serum ApoA1 levels at diagnose to accurately delineate meaningful prognostic of MDS patients.

Materials And Methods

Patients

Clinical and follow-up data of 231 patients were collected who were diagnosed of MDS in Ningbo First Hospital from 2009 to 2019. Diagnosis and classification of MDS and leukemic transformation were made according to the 2016 WHO classification [1]. Risk stratifications of MDS were made according to IPSS-R [2]. Almost patients received symptomatic and supportive treatment. 74 patients acquired further treatment, of whom 60 patients (26.0%) were treated with intensive chemotherapy, 19 patients (8.23%) with hemopoietic stem cell transplantation (HSCT) and 31 patients (13.4%) with hypomethylating agents. The patients had no concomitant disease that has been associated with increased serum lipid levels (i. e. diabetes, hyperlipidemia, or metabolic syndrome) and no hormone replacement therapy or use of any drugs known to affect lipid metabolism. Peripheral blood samples from 161 healthy donors served as controls. Approval for the retrospective review of these records was obtained from the Ethics Committee of Ningbo First Hospital and was in accordance with the Declaration of Helsinki. Informed consent was obtained from all adult subjects or parents if subjects are under 18.

Serum ApoA1 test

Peripheral blood was drawn after a strict fasting of at least 6 hours. ApoA1 was measured using turbidimetric immunoassay. The reagents were tested by using Beckman's ApoA1 kit. Follow the instructions, and using automatic biochemical analyzer (Beckman AU5800).

Morphology analysis

Morphology of MDS myeloid cells were observed through Wright-Giemsa stained bone marrow smears. It was evaluated subjectively by light microscopy at low power (10×objectives) for overall quality and distribution, and then was analyzed at high power (100×oil objectives) for differential count.

Cytogenetic analysis

BM cells were collected and cultured in RPMI-1640 medium supplemented with 20% newborn calf serum for 24h. R-banded metaphases and the karyotypes were identified at least 20 metaphases according to the International System for Human Cytogenetic Nomenclature (2016) (ISCN2016) [17]. The karyotypes were grouped into five categories: very good, good, intermediate, poor and very poor according to IPSS-R.

Mutational analysis

Molecular analysis was performed as a part of the routine clinical work-up. Mutational analysis for 14 common genes of MDS including NRAS, DNMT3A, SF3B1, IDH1, IDH2, TET2, EZH2, JAK2, CBL, ETV6, TP53, SRSF2, ASXL1 and RUNX1 were performed with next generation sequencing.

Statistical Analysis

Statistical analyses were performed by SPSS 26.0. OS was calculated from the date of initial diagnosis of MDS to the date of death, last follow-up or acquiring allo HSCT. Leukemia-free survival (LFS) was determined from the date of diagnosis to the date of leukemia transformation, last follow-up or acquiring allo HSCT. OS and LFS were analyzed using the Kaplan-Meier method and compared using the log-rank test. Multivariable analyses were used by Cox proportional hazard regression model. Differences in the distribution of continuous variables between categories were analyzed by Mann-Whitney *U* and categorical variables by Chi-squared test. The cutoff point of ApoA1 was calculated using X-Tile software. The optimal cutoff value was 1.02g/L. The *P* value of < 0.05 was considered statistically significant.

Results

Patients' characteristics

The data of 231 MDS patients including 95 females and 136 males were collected over a 10-year period with a median age of 61 years (range 16-90 years). Among these MDS patients, the median OS was 27 months (range 0-125 months, 95% CI 15.96-38.04 months) and 26 patients (11.3%) progressed to AML. Basing on the 2016 WHO classification, all patients were classified as MDS as follows: 23(10.0%) MDS-SLD, 65(28.1%) MDS-MLD, 17(7.4%) MDS-RS, 61(26.4%) MDS-EB1, 50(21.6%) MDS-EB2, 1(0.4%) MDS-del(5q) including del(5q) alone or with 1 additional abnormality except -7 or del(7q), 14 (6.1%) MDS-U. Besides, 196 patients were stratified into IPSS-R risk groups as follows: 13 (6.6%) very low, 38(19.4%) low, 67(34.2%) intermediate, 42(21.4%) high and 36(18.4%) as very high. Of these, the median IPSS-R score was 4.5(1.0-10.0). Further information was provided in Table1.

Table 1

Comparison between MDS with low ApoA1 group and high ApoA1 group in 231 MDS patients

Variable	All patients	Low ApoA1 group n=126	High ApoA1 group n=105	statistics	P value
Gender(n)	231			$\chi^2=10.072$	0.002
Male/Female, n	136/95	86/40	50/55		
Age [years, median(quartile)]	62(51,73)	63(28,86)	61 (16,90)	Z =-1.842	0.065
BM Blast[% median(quartile)]	4.5(1,9)	6(0,19.5)	3(0,19)	Z =-2.666	0.008
Peripheral Blood					
NE [$\times 10^9/L$, median(quartile)]	1.2(0.7,2.1)	1.1(0,7.4)	1.3(1.1,6.9)	Z =-1.221	0.093
HB [g/L, median(quartile)]	75(62,99)	67(22,142)	88(50,142)	Z =-5.487	≤ 0.001
PLT [$\times 10^9/L$ median(quartile)]	52(28,96)	46(4,332)	61(2,434)	Z =-3.062	0.002
ApoA1[g/L median(quartile)]	1.0(0.82,1.18)	0.84(0.34,1.02)	1.19(1.03,2.36)	Z =-13.081	≤ 0.001
2016WHO classification				$\chi^2=14.575$	0.042
MDS-SLD, % (n/n)	10.0% (23/231)	5.6% (7/126)	15.2% (16/105)		
MDS-MLD, % (n/n)	28.1% (65/231)	26.2% (33/126)	30.5% (32/105)		
MDS-RS-SLD, % (n/n)	2.6% (6/231)	2.4% (3/126)	2.9% (3/105)		
MDS-RS-MLD, % (n/n)	4.8% (11/231)	3.2% (4/126)	6.7% (7/105)		
MDS-5q-, % (n/n)	0.4% (1/231)	0.8% (1/126)	0.0% (0/105)		
MDS-EB1, % (n/n)	26.4% (61/231)	27.8% (35/126)	24.8% (26/105)		
MDS-EB2, % (n/n)	21.7% (50/231)	28.6% (36/126)	13.3% (14/105)		
MDS-U, % (n/n)	6.1% (14/231)	5.6% (7/126)	6.7% (7/105)		
IPSS-R cytogenetic risk group				$\chi^2=2.996$	0.559
Very good, % (n/n)	1.0% (2/196)	1.0% (1/97)	1.0% (1/99)		

Good, % (n/n)	64.3% (126/196)	59.8% (58/97)	68.7% (68/99)		
Intermediate, % (n/n)	20.4% (40/196)	24.7% (24/97)	16.2% (16/99)		
Poor, % (n/n)	5.1% (10/196)	4.1% (4/97)	6.1% (6/99)		
Very poor, % (n/n)	9.2% (18/196)	10.3% (10/97)	8.1% (8/99)		
IPSS-R risk category				$\chi^2=10.777$	0.029
Very low, % (n/n)	6.6% (13/196)	3.1% (3/97)	10.1% (10/99)		
Low, % (n/n)	19.4% (38/196)	4.1% (14/97)	24.2% (24/99)		
Intermediate, % (n/n)	34.2% (67/196)	35.1% (33/97)	34.3% (34/99)		
High, % (n/n)	21.4% (42/196)	23.7% (23/97)	19.2% (19/99)		
Very high, % (n/n)	18.4% (36/196)	24.7% (24/97)	12.1% (12/99)		
IPSS-R score[median(quartile)]	4.5(3.0,6.0)	4.75(1.5-10.0)	3.5(1.0-9.0)	Z =-3.308	0.001
Gene mutation, % (n/n)	62.7% (42/67)	72.4% (21/29)	55.2% (21/38)	$\chi^2=2.068$	0.150
Leukemia transformation, % (n/n)	11.2% (26/231)	12.7% (16/126)	9.5% (10/105)	$\chi^2=0.578$	0.447
Complex karyotype % (n/n)	17.9% (35/196)	21.6% (21/97)	14.1% (14/99)	$\chi^2=1.883$	0.170

Abbreviations: BM, bone marrow; NE, [neutrophil](#); HB, hemoglobin; PLT, platelet; MDS-SLD, MDS with single lineage dysplasia; MDS-MLD, MDS with multilineage dysplasia; MDS-RS-SLD, MDS with ring sideroblasts and single lineage dysplasia; MDS-RS-MLD, MDS with ring sideroblasts and multilineage dysplasia; MDS-EB1, MDS with excess blasts 1; MDS-EB2, MDS with excess blasts 2; MDS-U, unclassifiable; IPSS-R, Revised International Prognostic Scoring System.

Low ApoA1 in relation to clinical and laboratory factors

In our cohort, the ApoA1 level was lower in 231 MDS patients than in 161 healthy donors (1.00g/L vs. 1.33g/L, $P<0.0001$; Figure1). MDS patients were divided into two groups to analyze the correlation between ApoA1 level and clinical and laboratory characteristics. It showed that the low ApoA1 group had

significantly higher counts of BM blast ($P=0.008$) and lower HB ($P=0.001$), lower PLT ($P=0.002$) as well as higher risk distribution in terms of IPSS-R ($P=0.029$) compared with the high ApoA1 group. Also, the WHO subtype between these two groups had a significant difference ($P=0.042$). There were no significant differences in other factors between two groups (Table1).

Low ApoA1 was accompanied with more mutation of TP53

Mutations of 14 genes were detected in 67 patients, 42(62.7%) of whom harbored mutations.

14 genes mutation ratio as follows: ASXL1(14.9%), TP53(11.9%), RUNX1(11.9%), SF3B1(9.0%), TET2(9.0%), DNMT3A (6.0%), IDH2(4.5%), SRSF2(4.5%), NRAS (3.0%), EZH2(3.0%), CBL (3.0%), IDH1(1.5%), JAK2(1.5%) and ETV6(0.0%) (Figure2). The low ApoA1 group harbored higher ratio of gene mutation in comparison with the high ApoA1 group, but the difference was not statistically significant (72.4% vs. 55.3%, $P=0.15$). Among these mutations, the low ApoA1 group showed higher mutation frequency of TP53 compared with the high ApoA1 group (28.0% vs. 0.0%, $P=0.001$).

Low ApoA1 was associated with a poor prognosis

Compared with the high ApoA1 group, the median OS in the low ApoA1 group was significantly shorter (19 months vs 56 months, $P<0.0001$; Figure3A). But when it comes to LFS, the difference was not statistically significant ($P=0.359$; Figure3B).

In univariate analysis, OS was adversely associated with older age (≥ 60 years) ($P<0.0001$), male ($P=0.012$), higher-risk IPSS-R cytogenetic ($P=0.011$), higher BM blast percentage ($>5\%$) ($P<0.0001$), higher IPSS-R score ($P<0.0001$), lower HB($<10\text{g/dl}$) ($P=0.004$) and ApoA1 ($\leq 1.02\text{g/L}$) ($P<0.0001$).

Multivariate analyses showed that older age (≥ 60 years) ($P<0.0001$), higher BM blast percentage ($>5\%$) ($P=0.006$), higher-risk IPSS-R cytogenetic($P=0.006$) were adverse factors and low ApoA1 was a significant prognostic factor for worse OS ($P=0.020$). Meanwhile multivariate analyses included age, gender, IPSS-R score and ApoA1, the data showed that older age (≥ 60 years) ($P<0.0001$), higher IPSS-R score($P<0.0001$) and low ApoA1($P=0.023$) were adverse factors (Table2). Therefore, decreased serum ApoA1 could predict a poor prognosis independent of the IPSS-R.

Table 2

Univariate and multivariate analyses for overall survival in 231 patients with MDS

Variables	Univariate analysis for OS		Multivariate analysis for OS			
	<i>P</i> -value	95%CI	<i>P</i> -value	95%CI	<i>P</i> -value	95%CI
Age≥60(years)	<0.0001	12.522-21.478	<0.0001	0.236-0.588	<0.0001	0.244-0.595
Gender(male)	0.012	14.400-27.600	0.071	0.426-1.036	0.088	0.437-1.060
HB<10g/dl	0.004	15.481-26.519	0.108	0.911-2.562	-	-
NE<0.8×10 ⁹ /L	0.080	12.051-25.949	0.955	0.626-1.556	-	-
PLT<100×10 ⁹ /L	0.098	11.102-34.898	0.200	0.831-2.420	-	-
BM blast≥5%	<0.0001	9.227-18.773	<0.0001	2.016-4.841	-	-
IPSS-R cytogenetic risk group	0.011	23.202-48.798	0.006	1.085-1.636	-	-
IPSS-R score	<0.0001	23.202-48.789	-	-	<0.0001	1.502-2.211
ApoA1≤1.02g/L	<0.0001	12.649-25.351	0.020	0.383-0.921	0.023 (0.020) *	0.389-0.933

Abbreviations: HB, hemoglobin; NE, [neutrophil](#); PLT, platelet; BM, bone marrow; IPSS-R, Revised International Prognostic Scoring System. * Multivariate analyses included age, gender, IPSS-R score and ApoA1.

Discussion

Based on the obtained results, we showed that pretherapy serum ApoA1 at low level was associated with higher BM blast percentage, higher IPSS-R scores, higher TP53 mutation, lower HB, and lower PLT. Decreased serum ApoA1 levels correlated with a shorter survival period, which indicates that lower serum ApoA1 levels reflected a poor prognosis in MDS patients, and Cox regression analysis revealed that ApoA1 level was an independent prognostic factor for MDS patients.

Tumor cells have different metabolic patterns from normal cells, including lipid metabolism. It can be demonstrated that lipids play an important role in the occurrence and development of malignant tumors.

ApoA1 is synthesized predominantly in the liver and the small intestine, which is the predominant protein of plasma HDL [18]. ApoA1 not only participates in fat metabolism by regulating the cholesterol level of cells, but also shows innate immune activity and participates in the occurrence and development of tumors. ApoA1 participates in the immunomodulatory effects of tumor microenvironment by enhancing Treg response [19]. Decreased level of ApoA1 is associated with tumors and has great potential for the early diagnosis, prognosis and therapeutic application of tumors. In the mature immune system, ApoA1 is activated and involved in anti-tumor [20]. A study demonstrated that in the tumor microenvironment, ApoA1 may be work as a potent immunomodulatory agent, altering tumor-associated macrophages from a pro-tumor to an antitumor phenotype. Experimental results in mouse model showed that ApoA1 was transformed from pro-tumor M2 macrophages to anti-tumor M1 phenotypes, and tumors were infiltrated by cytotoxic cells [21]. Lower serum ApoA1 levels even had a practical function to predict the recurrence of breast cancer [22]. Research of nasopharyngeal carcinoma have shown that serum ApoA1 $\geq 1.025\text{g/L}$ is an independent predictor of longer overall survival, no local recurrence and no distant metastasis [23]. In conclusion, ApoA1 inhibits tumor growth and its reduction may lead to tumor progression. Similarly, our study showed that ApoA1 $\leq 1.02\text{g/L}$ is correlated with poor OS and is an independent prognostic factor for survival. However, the role of ApoA1 in carcinogenesis is not well understood. Further, it was demonstrated in our cohort that MDS patients with low ApoA1 harbored higher BM blast percentage, lower HB, lower PLT and especially higher IPSS-R score.

TP53 gene, located in 17p13 chromosomal region is one of the major tumor suppressor genes and often inactivated by deletion and/or mutation in many tumors, including hematologic malignancies [24]. The mutation rate was 5%-10% in MDS [25]. TP53 mutations in MDS are strongly associated with poor treatment outcomes [26]. TP53 is known to play a role in lipid metabolism [27]. Goldstein et al [28] found that the role for TP53 in enhancing lipid catabolism while inhibiting its anabolism. In our cohort, we found that high TP53 gene mutation rate was correlated with the decrease of serum ApoA1 in MDS.

It is well known that IPSS-R was widely used in measuring the prognosis of MDS. Although ApoA1 was reported to be a prognostic factor in several malignancies, to the best of our knowledge, an association between ApoA1 and prognosis of MDS patients has not been reported to date. In this study, the ApoA1 level was lower in MDS patients than in controls, ApoA1 is independent predictor of OS.

Furthermore, ApoA1 could function as an independent prognostic factor of MDS, also it is a common and convenient indicator in pretreatment examination. In addition, this study provides a new idea for the prognostic evaluation of MDS, and provides a potential therapeutic target.

Conclusions

We demonstrated that decreased ApoA1 accompanied with higher frequency of TP53 mutation was associated with a poor prognosis. ApoA1 as a prognostic factor could provide a convenient for measuring the prognosis of MDS patients and be a useful supplement to IPSS-R. Thus, targeting lipid

metabolism might be a promising strategy for therapy. As this study is a retrospective analysis, it is only valid for generating a hypothesis, and the value of ApoA1 should be validated in large prospective trials.

Abbreviations

Myelodysplastic syndromes (MDS)

apolipoprotein A1 (ApoA1)

Overall survival (OS)

Leukemia-free survival (LFS)

Revised International Prognostic Scoring System (IPSS-R)

Acute myeloid leukemia (AML)

International Prognostic Scoring System (IPSS)

World Health Organization (WHO)

Bone marrow (BM)

Hemopoietic stem cell transplantation (HSCT)

International System for Human Cytogenetic Nomenclature (2016) (ISCN2016)

Neutrophil (NE)

Hemoglobin (HB)

Platelet (PLT)

MDS with single lineage dysplasia (MDS-SLD)

MDS with multilineage dysplasia (MDS-MLD)

MDS with ring sideroblasts and single lineage dysplasia (MDS-RS-SLD)

MDS with ring sideroblasts and multilineage dysplasia (MDS-RS-MLD)

MDS with excess blasts (MDS-EB)

MDS with unclassifiable (MDS-U)

Declarations

Ethics approval and consent to participate

All patients gave informed consent. The project was approved by the Ethics Committee of Ningbo First Hospital (2021RS054) and was in accordance with the Declaration of Helsinki. All co-authors were included in this authorization request in order to have access to the data.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from Ningbo First Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Ningbo First Hospital. Cong Shi, the first author, should be contacted if someone wants to request the data from this study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

C.S. and S.G. collected and analyzed data and wrote the manuscript. J.D. analyzed data. Q.M. and G.O. designed research and reviewed the manuscript. C.S. and A.W. followed up with patients by phone. S.Y., D.Z., Y.Z., N.W., C.M., S.S., Y.C., Y.W., X.Z. and Z.H. collected data. All authors read and approved the final manuscript.

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Authors' information

Not applicable.

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Figures

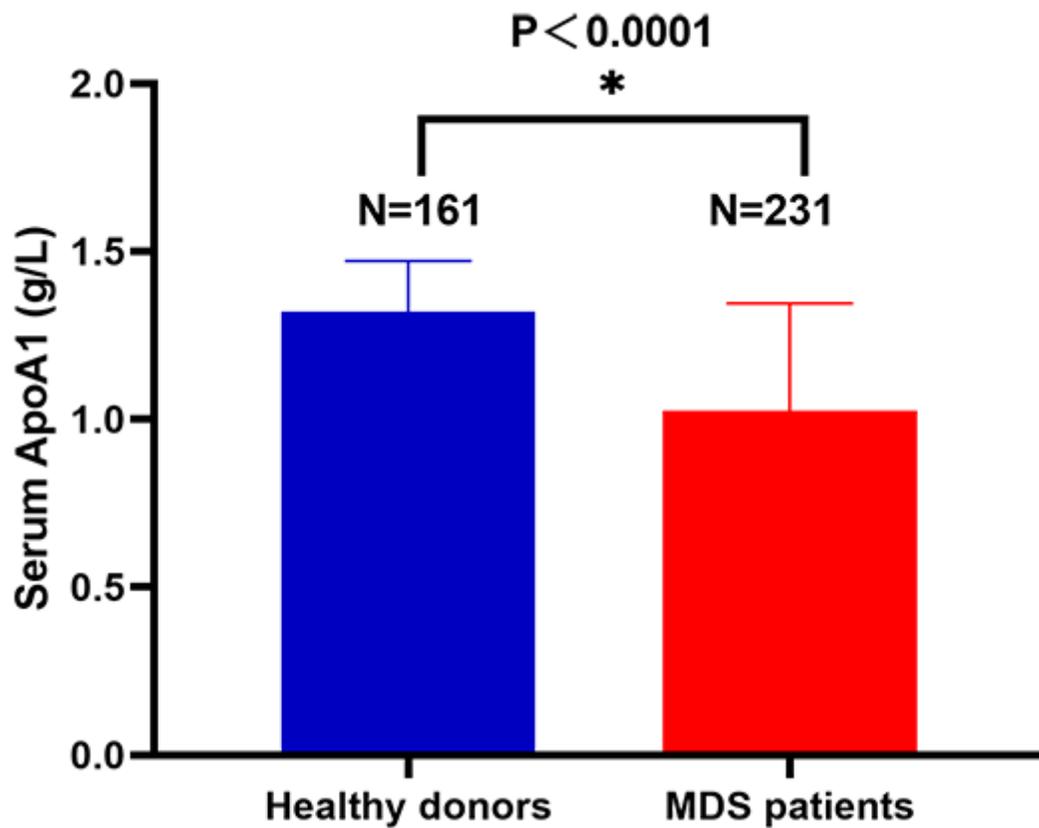


Figure 1

Compare serum ApoA1 between 161 healthy donors and 231 MDS patients.

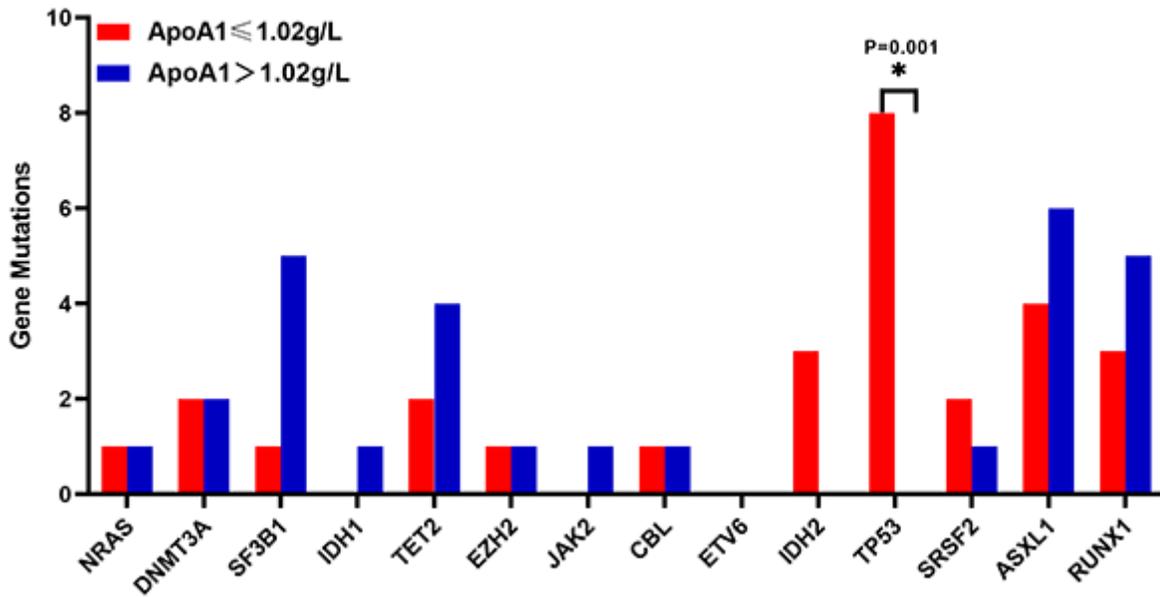


Figure 2

14 common genes of MDS including NRAS, DNMT3A, SF3B1, IDH1, IDH2, TET2, EZH2, JAK2, CBL, ETV6, TP53, SRSF2, ASXL1 and RUNX1.

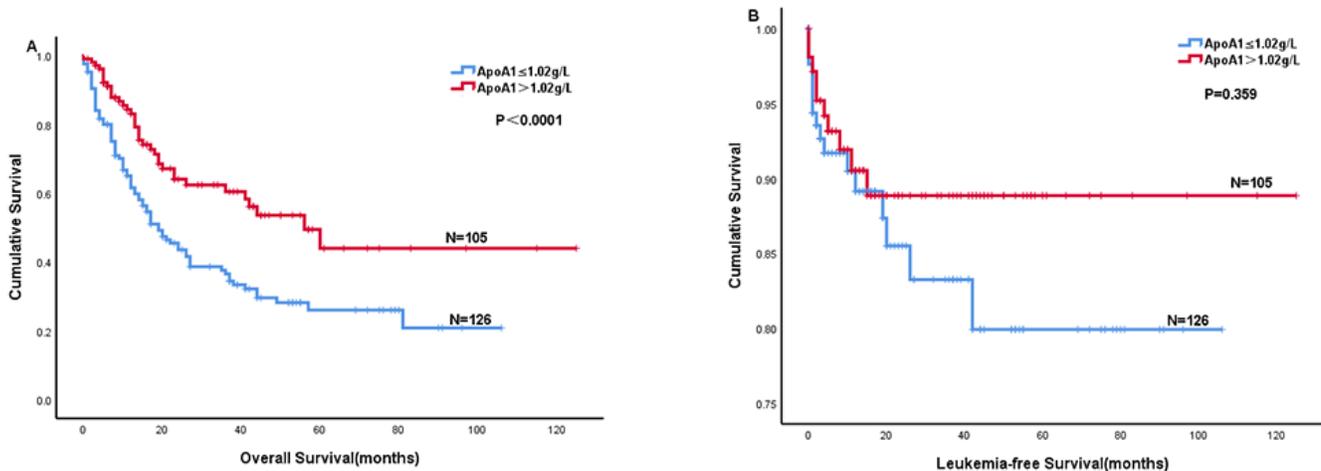


Figure 3

Overall survival and leukemia-free survival according to ApoA1 in MDS (A) Overall survival of 231 patients with primary MDS stratified by ApoA1 ≤ 1.02g/L vs ApoA1 > 1.02g/L (P < 0.0001). (B) Leukemia-free survival of 231 patients with primary MDS stratified by ApoA1 ≤ 1.02g/L vs ApoA1 > 1.02g/L (P = 0.359).