

Hyperfibrinogenemia as a Poor Prognostic Indicator in Myelodysplastic Syndrome

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Background: Myelodysplastic syndrome (MDS) is a group of heterogeneous myeloid clonal diseases originating from hematopoietic stem cells. It has been demonstrated that fibrinogen (FIB) is associated with disease risk in several cancer types. Coagulation and fibrinolysis problems are widespread in MDS patients. Therefore, FIB might be one of these indicators. We thus examined the role of FIB levels in the prognosis of MDS.

Methods: A cohort of 198 MDS patients were retrospectively analyzed to explore the prognostic value of the plasma FIB levels at diagnosis. Patients were divided into the high FIB group and low FIB group. The prognostic significance of FIB was determined by univariate and multivariate Cox hazard models.

Results: In our cohort, the FIB levels in 198 MDS patients were higher than those in 100 healthy donors (3.9 g/L vs 2.9 g/L, $P < 0.0001$). MDS patients with high FIB levels had significantly shorter overall survival (OS; $P = 0.001$) and decreased leukemia-free survival (LFS; $P = 0.036$). Multivariate cox proportional hazards regression analysis indicated that, in addition to older age, gender, lower HB, poorer karyotype for OS, lower NE, and higher bone marrow blast percentage for OS and LFS, elevated FIB level was also an independent adverse prognostic factor for OS ($P = 0.045$) but not for LFS ($P = 0.188$).

Conclusion: Elevated FIB levels may be associated with mortality risk among MDS patients and could predict disease progress and patient prognosis. Thus, assessment of FIB levels may promote the determination of the prognosis of MDS patients.

Keywords: myelodysplastic syndrome, IPSS-R, prognostic, overall survival, fibrinogen

Background

Myelodysplastic syndrome (MDS) is a group of heterogeneous myeloid clonal diseases originating from hematopoietic stem cells, which was manifested as morphological dysplasia in hematopoietic cells and peripheral cytopenia, and with a high risk of malignant transformation that may lead to secondary acute myeloid leukemia (AML).¹ The prognosis of MDS is extremely heterogeneous. The treatment for MDS is tailored based on risk stratification utilizing different clinical predictive models.² Although the molecular studies refined the prognosis in MDS, the IPSS-R was the most widely used predictive model.³ The IPSS-R was found to be the best predicting system for overall survival.⁴ The scoring system mainly includes the severity of hemocytopenia (anemia, thrombocytopenia, neutropenia, decreased hemoglobin content), increased bone marrow blasts and cytogenetic factors. However, Della Porta MGet al reported that it is very important to incorporate other factors, such as comorbidities, into the treatment decision.⁵ Recently, numerous promising biomarkers have been evaluated as potential prognosis predictors for MDS. For instance, low absolute lymphocyte count (ALC) and absolute monocyte count (AMC) levels, decreased serum ApoA1 levels, as well as an increase in the number of mature monocytes in the bone marrow can predict poor prognosis in MDS.^{6–9} However, none of these markers have been adopted into IPSS-R. In recent

years, it has also been reported that high FIB is a poor prognostic factor in some tumors.^{10–12} However, evidence of the role of FIB in MDS is lacking. Therefore, in this work, we aimed to explore the relationship between FIB level and the prognosis of MDS patients.

Materials and Methods

Patients

Clinical and follow-up data of 198 patients who were newly diagnosed with MDS in Ningbo First Hospital from 2009 to 2019 were collected. Diagnosis and classification of MDS and leukemic transformation were made according to the 2016th WHO classification.¹ Risk stratifications of MDS were made according to IPSS-R.³ All patients received symptomatic and supportive treatment. Among them, 74 patients acquired further treatment, of whom 63 (31.8%) were treated with intensive chemotherapy, 19 (9.6%) with hematopoietic stem cell transplantation (HSCT) and 33 (16.7%) with hypomethylating agents. Peripheral blood samples were collected from 100 normal controls. Healthy donors were defined as those who had not been hospitalized during the past 6 months and had no history of vascular disease, thrombosis, or hemorrhage. 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 were under 18.

Plasma FIB Test

Peripheral venous blood specimens were collected from pretreatment patients. Blood samples were collected using tubes with sodium citrate. The blood specimens were instantly centrifuged and detected within 2 hours based on the manufacturer's protocols. Detection of FIB level was performed using an ACL TOP750 automated coagulation analyzer (Werfen, USA) with proprietary reagents.

Morphology Analysis

Morphology of MDS myeloid cells was 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 analyzed at high power (100 × oil objectives) for the differential count.

Cytogenetic Analysis

BM cells were collected and cultured in RPMI-1640 medium supplemented with 20% newborn calf serum for 24 h. R-banded metaphases and the karyotypes were identified in at least 20 metaphases according to the 2016th International System for Human Cytogenetic Nomenclature (ISCN2016).¹³ 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 16 common genes of MDS including *TP53*, *SRSF2*, *ASXL1*, *NRAS*, *DNMT3A*, *SF3B1*, *IDH1*, *TET2*, *EZH2*, *JAK2*, *CBL*, *ETV6*, *IDH2*, *ZRSR2*, *U2AF1*, and *RUNX1*, was conducted with the next-generation sequencing. The depth of sequencing was 2000 ×. Variants having a variant allele frequency of less than 1% were excluded from the analysis. Multiplex PCR was used to amplify and assemble the sample collection. The Ion Proton platform was used for high-throughput sequencing. Further bioinformatics analysis was conducted using the PolyPhen, HG19, 1000 genomes, COSMIC, ClinVar, and dbSNP databases. Based on the clinical significance, we also classified sequence variations in somatic diseases into four categories: Tier 1, variants with strong clinical significance; Tier 2, variants with potential clinical significance; Tier 3, variants with unknown clinical significance; Tier 4, variants that are benign or likely benign.¹⁴ The Kindstar Global Medical Laboratory (Wuhan, China) completed the gene mutation detection process.

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. 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 the 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 FIB was calculated using the R package (version 4.0.3). The optimal cutoff value was 3.6 g/L. The high FIB level group had FIB > 3.6 g/L, while the low FIB level group had FIB ≤ 3.6 g/L. The *P*-value of < 0.05 was considered statistically significant.

Results

Patient Characteristics

The data of 198 MDS patients consisted of 80 females and 118 males were collected over 10 years period with a median age of 62 years (range 16–89 years). Among these MDS patients, the median duration of follow-up was 16 months, the median OS was 27 months (range 0–125 months), and 29 (14.6%) patients progressed to AML. Based on the 2016th WHO classification, all patients were classified as MDS as follows: 22 (11.1%) of MDS-SLD, 51 (25.8%) of MDS-MLD, 10 (5.1%) of MDS-RS, 52 (26.3%) of MDS-EB1, 45 (22.7%) of MDS-EB2, 5 (1.0%) of MDS-del (5q), 13 (6.6%) of MDS-U. Besides, 169 patients were stratified into IPSS-R risk groups as follows: 9 (5.3%) in the very low-risk group, 34 (20.1%) in the low-risk group, 54 (32.0%) in the intermediate-risk group, 35 (20.7%) in the high-risk group and 37 (21.9%) in the very high-risk group. Of these, the median IPSS-R score was 4.5. Further information was provided in [Table 1](#).

The Relation Between FIB and the Clinical and Laboratory Factors

In our cohort, the FIB was higher in 198 MDS patients than in 100 healthy donors (3.9 g/L vs 2.9 g/L, *P* < 0.0001; [Figure 1](#)). MDS patients were divided into two groups to analyze the correlation between FIB level and the clinical and laboratory characteristics. It showed that, compared with the low FIB group, the high FIB group had significantly higher counts of BM blast (*P* = 0.001) and lower NE (*P* = 0.048), lower HB (*P* = 0.002), higher risk distribution in terms of IPSS-R (*P* = 0.002), higher IPSS-R score (*P* < 0.0001), and higher frequency of leukemia transformation (*P* = 0.048). Besides, the WHO subtype between these two groups had a significant difference (*P* = 0.005). There were no significant differences in other factors between the two groups ([Table 1](#)).

High FIB Was Accompanied by More Frequent Gene Mutations

Mutations of 16 genes were detected in 54 patients, 37 (68.5%) of whom harbored mutations.

The detailed mutation ratios of the 16 genes were as follows: *ASXL1* (17.0%), *TP53* (14.8%), *RUNX1* (11.1%), *SF3B1* (11.1%), *TET2* (11.1%), *DNMT3A* (7.4%), *IDH2* (5.6%), *SRSF2* (5.6%), *NRAS* (1.8%), *EZH2* (5.6%), *CBL* (3.7%), *IDH1* (1.8%), *JAK2* (1.8%), *ZRSR2* (4.0%), *U2AF1* (7.0%) and *ETV6* (0.0%) ([Figure 2](#)). Although the high FIB group harbored higher ratio of gene mutation in comparison with the low FIB group, the difference was statistically insignificant (75.0% vs 61.5%, *P* = 0.287). Among these mutations, the high FIB group showed a higher mutation frequency of *TP53* compared with the low FIB group (25.0% vs 3.8%, *P* = 0.052).

A High FIB Level Was Associated with a Poor Prognosis in MDS

It is observed that a higher level of FIB (> 3.6 g/L) was significantly associated with decreased OS and LFS in MDS patients using the Kaplan-Meier survival analysis and Log rank test. Compared with the low FIB group, the median OS in the high FIB group was significantly shorter (19 months vs 81 months, *P* = 0.001; [Figure 3A](#)). Meanwhile, when it comes to LFS, the high FIB group was remarkably shorter than the low counterpart (*P* = 0.036; [Figure 3B](#)).

Table 1 Comparison Between MDS with Low FIB Group and High FIB Group in 198 MDS Patients

Variable	All Patients	Low FIB Group (n=88)	High FIB Group (n=110)	Statistics	P value
Gender(n)	198				
Male/Female, n	118/80	52/36	66/44	$\chi^2=0.017$	0.897
Age [years, median(range)]	62(16~89)	62(16~86)	61.5(18~89)	Z = -0.074	0.941
BM Blast[% , median(range)]	4.75(0.0~19.5)	3.0(0.0~19.5)	6.5(0.0~19.5)	Z = -3.411	0.001
Peripheral Blood					
NE [$\times 10^9/L$, median(range)]	1.2(0.1~6.9)	1.3(0.2~6.9)	1.1(0.1~6.2)	Z = -1.980	0.048
HB [g/L, median(range)]	7.7(2.2~14.2)	8.8(2.9~14.2)	7.5(2.2~14.2)	Z = -3.044	0.002
PLT [$\times 10^9/L$, median(range)]	52(2~332)	55(6~322)	53.5(2~332)	Z = -0.895	0.371
FIB[g/L, median(range)]	3.9(1.6~9.4)	3.1(1.6~3.6)	4.5(3.7~9.4)	Z = -12.087	<0.0001
2016WHO classification				$\chi^2=18.439$	0.005
MDS-SLD, % (n/n)	11.1% (22/198)	15.9% (14/88)	7.2% (8/110)		
MDS-MLD, % (n/n)	25.8% (51/198)	30.7% (27/88)	21.6% (24/110)		
MDS-RS-SLD, % (n/n)	1.5% (3/198)	3.4% (3/88)	0.0% (0/110)		
MDS-RS-MLD, % (n/n)	3.5% (7/198)	4.5% (4/88)	2.7% (3/110)		
MDS-5q-, % (n/n)	1.0% (5/198)	4.5% (4/88)	0.9% (1/110)		
MDS-EB1, % (n/n)	26.3% (52/198)	22.7% (20/88)	29.1% (32/110)		
MDS-EB2, % (n/n)	22.7% (45/198)	13.6% (12/88)	30% (33/110)		
MDS-U, % (n/n)	6.6% (13/198)	4.5% (4/88)	8.1% (9/110)		
IPSS-R cytogenetic risk group				$\chi^2=8.493$	0.075
Very good, % (n/n)	1.2% (2/169)	2.5% (2/81)	0.0% (0/88)		
Good, % (n/n)	6.2% (104/169)	6.5% (53/81)	5.8% (51/88)		
Intermediate, % (n/n)	2.1% (36/169)	2.0% (16/81)	2.3% (20/88)		
Poor, % (n/n)	4.1% (7/169)	6.2% (5/81)	2.2% (2/88)		
Very poor, % (n/n)	11.8% (20/169)	6.2% (5/81)	17.0% (15/88)		
IPSS-R risk category				$\chi^2=17.200$	0.002
Very low, % (n/n)	5.3% (9/169)	8.6% (7/81)	2.3% (2/88)		
Low, % (n/n)	20.1% (34/169)	30.9% (25/81)	10.2% (9/88)		
Intermediate, % (n/n)	32.0% (54/169)	28.4% (23/81)	35.2% (31/88)		
High, % (n/n)	20.7% (35/169)	17.3% (14/81)	23.9% (21/88)		
Very high, % (n/n)	21.9% (37/169)	14.8% (12/81)	28.4% (25/88)		
IPSS-R score[median(quarter)]	4.5(1.0~10.0)	3.5(1.0~10.0)	5.5(1.5~10.0)	Z = -4.071	<0.0001
Gene mutation, % (n/n)	68.5% (37/54)	61.5% (16/26)	75.0% (21/28)	$\chi^2=1.133$	0.287
Leukemia transformation, % (n/n)	14.6% (29/198)	9.1% (8/88)	19.1% (21/110)	$\chi^2=3.911$	0.048
Complex karyotype, % (n/n)	17.8% (30/169)	12.3% (10/81)	22.7% (20/88)	$\chi^2=3.113$	0.078

Note: P value < 0.05 was considered statistically significant.

Abbreviations: BM, bone marrow; NE, neutrophil; HB, hemoglobin; PLT, platelet; FIB, fibrinogen; 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, MDS unclassifiable; IPSS-R, Revised International Prognostic Scoring System.

In univariate analysis, OS was adversely associated with older age (≥ 60 years; $P < 0.0001$), male ($P = 0.003$), higher-risk IPSS-R cytogenetic ($P = 0.001$), higher BM blast percentage ($> 5\%$) ($P < 0.0001$), higher IPSS-R risk category ($P < 0.0001$), lower HB (< 10 g/dl; $P = 0.006$) and NE ($< 0.8 \times 10^9/L$; $P = 0.005$) counts, and higher FIB level (> 3.6 g/L; $P = 0.001$). LFS was adversely associated with higher BM blast percentage ($> 5\%$; $P < 0.0001$), higher IPSS-R risk category ($P = 0.039$), lower NE ($< 0.8 \times 10^9/L$; $P = 0.001$) count and higher FIB (> 3.6 g/L; $P = 0.036$).

Multivariate analyses showed that older age (≥ 60 years; $P < 0.0001$), male ($P = 0.008$), higher BM blast percentage ($> 5\%$; $P < 0.0001$), higher-risk IPSS-R cytogenetic ($P = 0.032$) were adverse factors and high FIB level was a significant prognostic factor for worse OS ($P = 0.045$). Meanwhile multivariate analyses that included NE, BM blast, IPSS-R risk category, and FIB showed that BM blast percentage ($> 5\%$; $P = 0.001$) was an adverse factor (Table 2). Therefore, elevated plasma FIB level could predict a poor OS independent of the IPSS-R, but not for LFS.

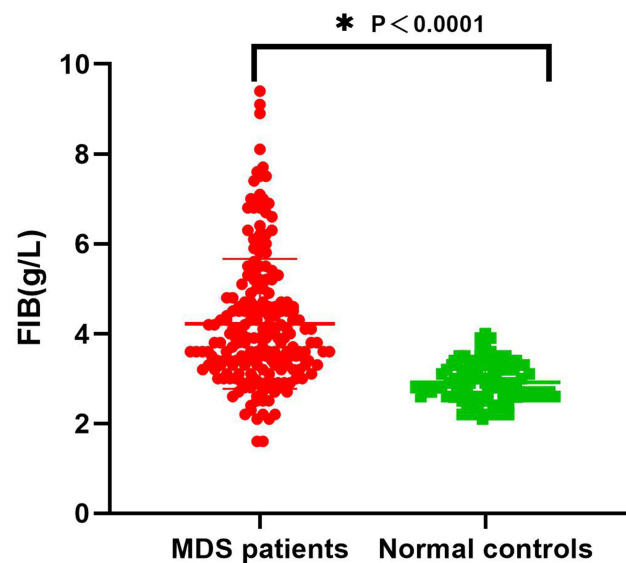


Figure 1 Comparison of plasma FIB between 198 MDS patients and 100 healthy donors. * $P < 0.0001$.

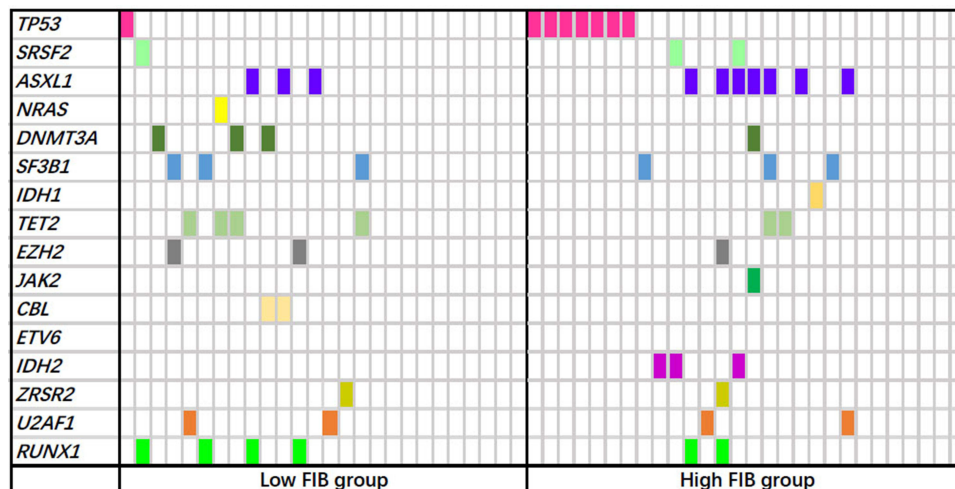


Figure 2 Mutation spectrum of 16 common genes in 54 MDS patients. Each column represents an individual patient sample, and each colored cell represents a mutation of the gene.

Discussion

The above results showed that pretherapy plasma FIB at high level was associated with higher BM blast percentage, higher IPSS-R scores, higher frequency of leukemia transformation, and lower NE, HB, and PLT count. Elevated plasma FIB level correlated with shorter overall survival and leukemia-free survival period, indicating that higher FIB level reflected a poor prognosis in MDS patients. The cox regression analysis revealed that FIB level was an independent OS factor for MDS patients. But not for LFS, and may be associated with the limited number of cases of leukemia conversion lacking.

FIB not only plays a critical role in hemostasis but also is important for tumor biology. FIB is synthesized mainly by liver epithelium upon inflammation. Tumor cells can synthesize and secrete FIB. As an extracellular matrix component, FIB can stimulate cancer cell proliferation and angiogenesis by binding TGF- β , VEGF, PDGF, and FGF-2.¹⁵ Tumor cells are capable of manipulating the microenvironment by endogenously synthesizing and secreting FIB for functions critical to primary tumor growth.¹⁶

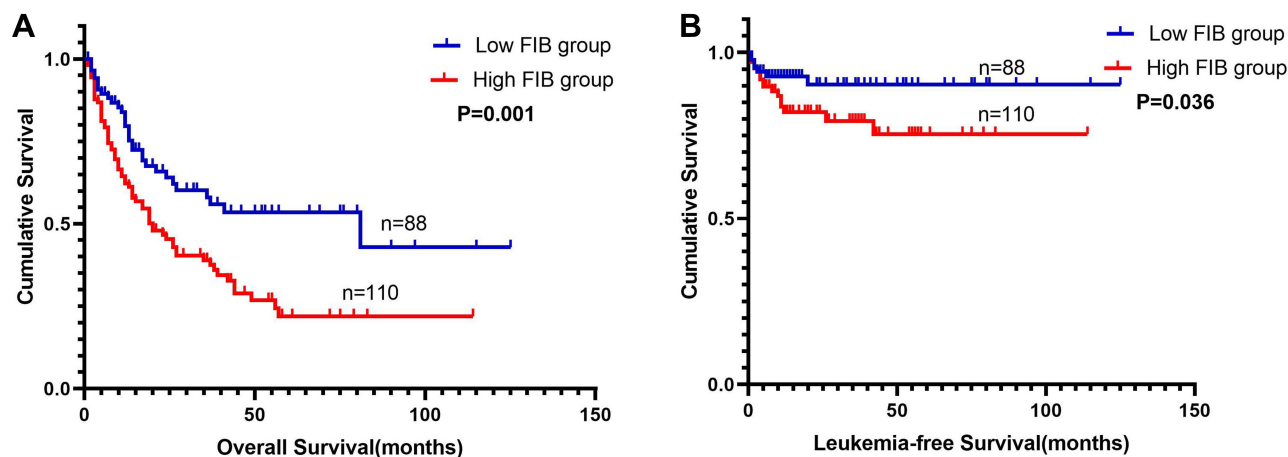


Figure 3 Overall survival and leukemia-free survival according to FIB in MDS. **(A)** Overall survival of 198 patients with primary MDS as stratified by FIB ≤ 3.6 g/L vs FIB > 3.6 g/L ($P = 0.001$). **(B)** Leukemia-free survival of 198 patients with primary MDS as stratified by FIB ≤ 3.6 g/L vs FIB > 3.6 g/L ($P = 0.036$). P value < 0.05 was considered statistically significant.

Recently, considerable attention has been paid to the association between the progression of malignancies and FIB level. Hyperfibrinogenemia is known as a poor prognostic factor in cancer. Several experimental studies have shown that FIB plays a critical role in tumor progression by inducing tumor cell proliferation, EMT, migration, angiogenesis, and hematogenous metastasis.^{17–19} It has been demonstrated that the FIB acts as a reservoir for secreted growth factors that regulate tumor cell proliferation, apoptosis, angiogenesis, and metastasis.²⁰ In some studies, FIB level was significantly associated with clinical tumor stage and patient outcome.²¹ In our study, the WHO subtype was significantly correlated with FIB level. Otherwise, plasma fibrinogen levels are reportedly predictive of a poor prognosis in AML and diffuse large B-cell lymphoma (DLBCL).^{22,23} Reduced Von Willebrand factor cleaving protease ADAMT-13 antigen levels were discovered to be inversely related to MDS prognosis by Castelli R et al²⁴ Although FIB was reported to be a prognostic factor in several malignancies, to the best of our knowledge, there was a study has demonstrated that a high plasma FIB level at diagnosis may be a factor that predicts the prognosis of patients with lower-risk MDS.²⁵ However, whether hyperfibrinogenemia is a prognostic factor in patients with MDS remains unclear. In this study, the FIB level was higher in MDS patients than in healthy donors, which predicted shorter LFS and OS, and was an independent predictor for OS as revealed by cox regression analysis.

It is well known that IPSS-R was widely used in evaluating the prognosis of MDS. Furthermore, FIB could function as an independent prognostic factor of MDS, and 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 also a potential therapeutic target. The mechanisms involved in the association between hyperfibrinogenemia and adverse survival in MDS ultimately remain to be elucidated.

Due to a high degree of heterogeneity, the prognosis of MDS patients may be related to other factors that were not involved in the study. Our statistical analysis showed that primitive patients with elevated FIB level had significantly higher counts of BM blast and higher IPSS-R scores than those with decreased FIB levels. The WHO subtype between the two groups was significantly different. These indicators have been established to be associated with poor prognosis and leukemia transformation.

The research had some limitations. Firstly, various gene mutations were linked to MDS prognosis. However, in our cohort, the number of patients who had received gene mutation analysis was modest, with just 54 instances analyzed. Secondly, the study was a retrospective study, the comorbidities at diagnosis were limited to the information obtained from medical records. Nevertheless, it clearly demonstrated that elevated pretreatment plasma FIB level represents a biomarker of worse survival in patients with MDS. FIB as a prognostic factor could provide convenience for predicting the prognosis of MDS patients and be a useful supplement to IPSS-R. As this study is a retrospective analysis, it is only valid for generating a hypothesis, and the value of FIB should be validated in large prospective trials. Further internal and external validations are needed to clarify the prognostic role of the FIB for MDS patients.

Table 2 Univariate and Multivariate Analyses for Overall Survival and Leukemia-Free Survival in 198 Patients with Primary MDS

Variables	Univariate Analysis for OS		Multivariate Analysis for OS		Univariate Analysis for LFS		Multivariate Analysis for LFS	
	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)
Age≥60(years)	<0.0001	2.200(1.441–3.359)	<0.0001	2.453(1.505–3.998)	0.137	1.755(0.837–3.680)	-	-
Gender(male)	0.003	1.902(1.246–2.905)	0.008	1.941(1.186–3.178)	0.213	1.651(0.750–3.632)	-	-
HB<10g/dl	0.006	2.105(1.233–3.592)	0.126	1.551(0.884–2.721)	0.855	1.083(0.462–2.537)	-	-
NE<0.8×10 ⁹ /L	0.005	1.798(1.194–2.708)	0.214	1.373(0.833–2.264)	0.001	3.315(1.590–6.912)	0.205	1.665(0.757–3.662)
PLT<100×10 ⁹ /L	0.067	1.628(0.967–2.743)	0.134	1.585(0.868–2.896)	0.361	1.568(0.597–4.117)	-	-
BM blast>5%	<0.0001	3.037(2.013–4.581)	<0.0001	2.636(1.600–4.342)	<0.0001	5.781(2.326–14.371)	0.001	5.706(2.027–16.061)
IPSS-R, cytogenetic risk group	0.001	1.376(1.135–1.666)	0.032	1.247(1.020–1.525)	0.039	1.393(1.016–1.910)	0.236	1.217(0.879–1.683)
IPSS-R, risk category	<0.0001	1.827(1.491–2.239)	-	-	<0.0001	2.032(1.414–2.918)	-	-
FIB>3.6g/L	0.001	1.989(1.308–3.025)	0.045	1.641(1.012–2.663)	0.036	2.324(1.028–5.250)	0.188	1.735(0.760–4.043)

Notes: The significant factors in univariate analysis ($P < 0.1$) were used to determine the influence on OS and LFS by multivariate analysis. P value < 0.05 was considered. statistically significant.

Abbreviations: HB, hemoglobin; NE, neutrophil; PLT, platelet; BM, bone marrow; IPSS-R, Revised International Prognostic Scoring System; FIB, fibrinogen.

Abbreviation

MDS, Myelodysplastic syndromes; FIB, Fibrinogen; OS, Overall survival; LFS, Leukemia-free survival; IPSS-R, Revised International Prognostic Scoring System; AML, Acute myeloid leukemia; IPSS, International Prognostic Scoring System; WHO, World Health Organization; BM, Bone marrow; HSCT, Hematopoietic stem cell transplantation; ISCN2016, International System for Human Cytogenetic Nomenclature (2016); ALC, Absolute lymphocyte count; AMC, Absolute monocyte count; 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-EB, MDS with excess blasts; MDS-U, MDS with unclassifiable.

Data Sharing Statement

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.

Ethics Approval and Consent to Participate

All patients were given written informed consent. The project was approved by the Ethics Committee of Ningbo First Hospital (2021RS108) and was in accordance with the Declaration of Helsinki. All co-authors were included in this authorization request to have access to the data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

References

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391–2405. doi:10.1182/blood-2016-03-643544
2. Rami SK, Maria CY, Mohamed AKD, et al. Hypoalbuminemia is an independent prognostic factor for overall survival in myelodysplastic syndromes. *Am J Hematol*. 2012;87(11):1006–1009. doi:10.1002/ajh.23303
3. Greenberg PL, Tuechler H, Schanz J, et al. international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120(12):2454–2465. doi:10.1182/blood-2012-03-420489
4. Bektas O, Uner A, Eliacik E, et al. Comparison of Myelodysplastic Syndrome Prognostic Scoring Systems. *Turk J Haematol*. 2016;33(2):119–126. doi:10.4274/tjh.2014.0455
5. Matteo G. Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. *Haematologica*. 2011;96(3):441–449. doi:10.3324/haematol.2010.033506
6. Jacobs NL, Holtan SG, Porrata LF, et al. Host immunity affects survival in myelodysplastic syndromes: independent prognostic value of the absolute lymphocyte count. *Am J Hematol*. 2010;85(3):160–163. doi:10.1002/ajh.21618
7. Saeed L, Patnaik MM, Begna KH, et al. Prognostic relevance of lymphocytopenia, monocytopenia and lymphocyte-to-monocyte ratio in primary myelodysplastic syndromes: a single center experience in 889 patients. *Blood Cancer J*. 2017;7(3):e550. doi:10.1038/bcj.2017.30
8. Shi C, Gong S, An W, et al. Decreased serum apolipoprotein A1 level predicts poor prognosis of patients with de novo myelodysplastic syndromes. *BMC Cancer*. 2022;22(1):127. doi:10.1186/s12885-022-09248-2
9. An W, Gao P, Ningning W, et al. Elevated mature monocytes in bone marrow accompanied with a higher IPSS-R score predicts a poor prognosis in myelodysplastic syndromes. *BMC Cancer*. 2021;21(1):546. doi:10.1186/s12885-021-08303-8
10. Sheng L, Luo M, Sun X, et al. Serum fibrinogen is an independent prognostic factor in operable nonsmall cell lung cancer. *Int J Cancer*. 2013;133(11):2720–2725. doi:10.1002/ijc.28284

11. Qi Q, Geng Y, Sun M, et al. Hyperfibrinogen is associated with the systemic inflammatory response and predicts poor prognosis in advanced pancreatic cancer. *Pancreas*. 2015;44(6):977–982. doi:10.1097/MPA.0000000000000353
12. Son HJ, Park JW, Chang HJ, et al. Preoperative plasma hyperfibrinogenemia is predictive of poor prognosis in patients with nonmetastatic colon cancer. *Ann Surg Oncol*. 2013;20(9):2908–2913. doi:10.1245/s10434-013-2968-8
13. McGowan-Jordan J, Simons A, Schmid M. *ISCN 2016: An International System for Human Cytogenomic Nomenclature (2016)*. S KARGER AG; 2016.
14. Li MM, Datto M, Duncavage EJ, et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer: a joint consensus recommendation of the association for molecular pathology, American society of clinical oncology, and college of American pathologists. *J Mol Diagn*. 2017;19(1):4–23. doi:10.1016/j.jmoldx.2016.10.002
15. Sahni A, Simpson-Haidaris PJ, Sahni SK, et al. Fibrinogen synthesized by cancer cells augments the proliferative effect of fibroblast growth factor-2(FGF-2). *J Thromb Haemost*. 2008;6(1):176–183. doi:10.1111/j.1538-7836.2007.02808.x
16. Qiu J, Yanping Y, Yunfeng F, et al. Preoperative plasma fibrinogen, platelet count and prognosis in epithelial ovarian cancer. *J Obstet Gynaecol Res*. 2012;38(4):651–657. doi:10.1111/j.1447-0756.2011.01780.x
17. Steinbrecher KA, Horowitz NA, Blevins EA, et al. Colitis-associated cancer is dependent on the interplay between the hemostatic and inflammatory systems and supported by integrin alpha(M)beta (2) engagement of fibrinogen. *Cancer Res*. 2010;70:2634–2643. doi:10.1158/0008-5472.CAN-09-3465
18. Shu YJ, Weng H, Bao RF, et al. Clinical and prognostic significance of preoperative plasma hyperfibrinogenemia in gallbladder cancer patients following surgical resection: a retrospective and in vitro study. *BMC Cancer*. 2014;14:566. doi:10.1186/1471-2407-14-566
19. Staton CA, Brown NJ, Lewis CE. The role of fibrinogen and related fragments in tumour angiogenesis and metastasis. *Expert Opin Biol Ther*. 2003;3:1105–1120. doi:10.1517/14712598.3.7.1105
20. Witsch E, Sela M, Yarden Y. Roles for growth factors in cancer progression. *Physiology*. 2010;25:85–101. doi:10.1152/physiol.00045.2009
21. Pichler M, Dalpiaz O, Ehrlich GC, et al. Validation of the Preoperative Plasma Fibrinogen Level as a Prognostic Factor in a European Cohort of Patients with Localized Upper Tract Urothelial Carcinoma. *J Urol*. 2014;191(4):920–925. doi:10.1016/j.juro.2013.10.073
22. Martin DB, Alexander DH, Katja S, et al. (2017) Increased fibrinogen levels at diagnosis are associated with adverse outcome in patients with acute myeloid leukemia. *Hematol Oncol*. 2017;35(4):789–796. doi:10.1002/hon.2307
23. Niu JY, Tian T, Zhu HY, et al. Hyperfibrinogenemia is a poor prognostic factor in diffuse large B cell lymphoma. *Ann Hematol*. 2018;97:1841–1849. doi:10.1007/s00277-018-3382-x
24. Castelli R, Bergamaschini L, Teatini T, et al. Does outcome/survival of patients with myelodysplastic syndromes should be predicted by reduced levels of ADAMTS – 13? Results from a pilot study. *Clin Lymphoma Myeloma Leuk*. 2020;20(8):e461–e467. doi:10.1016/j.clml.2019.12.016
25. Ogura S, Yonei S, Tanigawa T, et al. Prognostic significance of hyperfibrinogenemia in patients with lower-risk myelodysplastic syndromes. *Ann Hematol*. 2020;99(1):189–191. doi:10.1007/s00277-019-03863-z