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ORIGINAL ARTICLE



Plasma fibrinogen levels correlate with prognosis and treatment outcome in patients with non-M3 acute myeloid leukemia

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ABSTRACT

To assess plasma fibrinogen levels as a biomarker to predict the prognosis and treatment outcome in acute myeloid leukemia (AML), a retrospective study of 215 patients with AML excluding M3 was conducted in a single center. Patients were divided into low and high group according to the cutoff value of 3.775 g/L obtained by analyzing the receiver operating characteristic (ROC) curve of fibrinogen at diagnosis. Importantly, overall survival (OS) was markedly better in low fibrinogen group ($p=.006$) as well as disease-free survival (DFS) ($p=.045$). Furthermore, when patients achieved complete remission (CR), the median plasma fibrinogen levels were dramatically decreased in high fibrinogen group but increased in low fibrinogen group. In conclusion, our data suggest that initial plasma FBG levels can be used as an independent prognostic biomarker affecting OS and DFS, as well as a potential parameter reflecting the treatment outcome in patients with non-M3 AML.

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KEYWORDS

Fibrinogen; acute myeloid leukemia; prognosis; biomarker; survival

Introduction

Acute myeloid leukemia (AML) is a malignant hematological stem cell disorder characterized by a clonal expansion of undifferentiated myeloid precursors resulting in impaired hematopoiesis and bone marrow failure. Treatment includes intensive induction therapy, the most common of which is the combination of anthracyclines and cytarabine for chemotherapy, and the use of cytarabine-based chemotherapy or stem cell transplantation for post-remission consolidation [1]. Molecular and cytogenetic changes, the immune status, and other factors in AML patients determine the choice of treatment options and contribute to predict the prognosis [2–6]. The National Comprehensive Cancer Network (NCCN) guidelines state that cytogenetic subgroups are classified as favorable, intermediate, and unfavorable risks [7]. About 50% of patients with AML do not obtain chromosomal abnormalities and present cytogenetically normal AML. Although a larger proportion of patients respond to induction therapy, refractory disease or treatment failure is very common due to relapse of AML [8]. On the other hand, the therapeutic effects of AML patients and early death associated with predictive treatment have

been shown to be linked with a subset of clinical and biological characteristics including advanced age, poor performance, and coexistence conditions.

Fibrinogen is the highest content of all coagulation factors and is the center protein in the coagulation system which is synthesized by hepatocytes and releases into human blood after glycosylation and partial phosphorylation. It has a half-life of 3–4 days and is one of the acute phase reaction proteins [9]. There is increasing evidence that fibrinogen, as an acute glycoprotein traditionally associated with maintenance of hemostasis, is a key factor in inflammation and cancer progression [10]. In the tumor microenvironment, cancer development and progression are thought to be related to fibrinogen-dependent inflammatory responses and tumor matrix formation [11]. Therefore, the results of several clinical studies indicate that high-pretreatment plasma fibrinogen levels are associated with a reduction in overall survival (OS) and disease-free survival (DFS) of solid tumors [12–15]. In hematological malignancies, it has reported that low fibrinogen value commonly occurred in acute promyelocytic leukemia (APL), which is closely related to activate disseminated intravascular coagulation (DIC) [16].

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However, few studies have determined the relationship between plasma fibrinogen values and the prognosis and treatment outcome in patients with non-M3 acute myeloid leukemia.

Therefore, in this study, we analyzed 215 *de novo* non-M3 patients and demonstrated that patients with high initial plasma fibrinogen levels had a shorter OS and DFS than those with low initial plasma fibrinogen levels. In addition, when patients achieved complete remission (CR), median plasma fibrinogen levels were dramatically decreased in patients with high fibrinogen group, and conversely, plasma fibrinogen levels were increased in patients with low fibrinogen group.

Materials and methods

Patient selection

The retrospective study included a total of 215 previously untreated patients aged 14 to 65 years with diagnosed *de novo* AML excluding M3 at the First Affiliated Hospital of Wenzhou Medical University from August 2007 to December 2015. Patients with the history of hematological disorders, therapy-related AML or other carcinomas were excluded. The diagnosis of AML corresponds to the diagnostic criteria of the FAB and the 2008 World Health Organization (WHO) classification of bone marrow tumors [17]. All procedures conformed to the Helsinki Declaration and the study was approved by the Institutional ethics committee.

All patients underwent at least one course of induction chemotherapy and regular follow-up. After initial diagnosis, patients received conventional induction chemotherapy regimen with idarubicin 8–10 mg/m² mostly or daunorubicin 45–60 mg/m² per day on days 1–3 or homoharringtonine 4–6 mg/m² per day on days 1–7 with cytarabine 100 mg/m² per day on days 1–7. CR refers to less than 5% blasts in bone marrow (BM) with neutrophil count $>1 \times 10^9$ /L, peripheral blood PLT count $\geq 100 \times 10^9$ /L, no blasts with Auer rods or the persistence of extramedullary disease and no requirement for transfusion. In our cohort study, 118 patients achieved CR after the first course of induction chemotherapy, other 97 patients received a second course of induction chemotherapy or salvage therapy, and 32 patients failed to achieve CR at least two cycles of chemotherapy finally. After one or two courses of induction chemotherapy, patients who achieved CR underwent high-dose cytarabine-based consolidation treatment. A total of 55 cases (25.58%) underwent hematopoietic stem cell transplantation (HSCT) after induction chemotherapy.

Cytogenetic and molecular mutant studies

Referring to the NCCN 2010 V.1 guidelines, mutation genes detected by the AML molecular prognostic marker include FLT-3, c-KIT, NPM1, and CEBPA. Inv16 or t(16; 16), t(8; 21), or t(15; 17) were categorized to better-risk stratification. Normal cytogenetics with NPM1 mutation in the absence of FLT3-ITD or the isolated biallelic CEBPA mutation were also classified as better-risk status [18]. Normal karyotypes associated with a single ITD mutation, complex karyotype (≥ 3), as well as patients with -5/5q-, -7/7q-, inv (3), 11q23-, except (9; 11), t(3; 3), t(6, 9), or t (9, 22) were defined as poor-risk status. Patients with normal karyotype, +8, t(9;11), other abnormalities or t(8;21), inv16, or t(16; 16) with a c-KIT mutation are in the intermediate-risk status [19].

Statistical analysis

OS was measured by the time from the initial diagnosis date to the time of death or the last follow-up. DFS was defined as the time of CR to the time of relapse or death. Relapse refers to leukemia cells in the BM over 5% after remission, or occurring leukemia lesions outside the BM. OS and DFS were analyzed using Kaplan–Meier curves, which were compared using the log-rank test. Kruskal–Wallis H test or Wilcoxon's rank-sum test for continuous variables and Chi-square test or Fisher's exact test for categorical variables were used to make a comparison among patient clinical characteristics. In addition, Mann–Whitney U test was used to analyze the plasma fibrinogen value before and after remission. Meanwhile, the normality assumption of the baseline date was examined by the Kolmogorov–Smirnov normality test. In this cohort study, fibrinogen levels were measured in all 215 patients, and the receiver operating characteristic (ROC) curve was often used in clinical monitoring to calculate the appropriate fibrinogen values for sensitivity and specificity. For univariate Cox regression analysis, variables with $p < .05$ were progressed to a multivariate analysis using forward stepwise selection analysis. $p < .05$ indicates statistically significant, and all tests were two-tailed. SPSS software (ver. 24.0) was used for statistical analysis.

Results

Patient characteristics

A total of 215 *de novo* non-M3 AML cases were collected in our analysis, including 120 men and 95

Table 1. Baseline characteristics of patients with non-M3 AML.

Characteristics	All patients (n = 215)	Fibrinogen <3.775 g/L (n = 114)	Fibrinogen ≥3.775 g/L (n = 101)	p-value
Median age (years)	40(14–65)	40(14–63)	45(17–65)	.148
Male/Female	120/95	57/57	63/38	.068
Median WBC count ($\times 10^9/L$)	16.12(.38–464)	16.12(.71–262.7)	15.90(.38–464)	.826
Median Hemoglobin (g/L)	82.5(32–153)	79.5(34–153)	77(32–131)	.383
Median Platelets ($\times 10^9/L$)	60.5(2–384)	52.5(5–376)	55(2–384)	.992
Median Prothrombin Activity (%)	79(23–132)	78(23–109)	80(51–132)	.489
Median Prothrombin Time(s)	15.4(11.8–115.2)	15.25(12–115.2)	15.2(11.8–19.4)	.501
Median International Normalized Ratio	1.21(0.86–3.26)	1.20(0.95–3.26)	1.20(0.86–1.62)	.441
Median Thrombin Time(s)	15.85(4.2–36.2)	16.05(4.2–36.2)	15.45(12.7–18.7)	0
Median APTT(s)	39(29.5–79.5)	37.9(30–75.5)	40.25(29.5–55.2)	0
Median ALT(U/L)	34(4–199)	29(7–199)	28.5(4–135)	.470
Median blasts in PB (range), %	49.5(0–99)	58.5(0–99)	59.5(0–98)	.156
Median blasts in BM (range), %	64.8(9–98.8)	64.8(9–98.8)	71.5(12–98)	.889
FAB subtypes, n (%)				
M1	1(0.46)	1(0.87)	0	.348
M2	37(17.21)	20(17.54)	17(16.83)	.908
M4	95(44.19)	51(44.74)	44(43.56)	.914
M5	70(32.56)	37(32.46)	33(32.67)	.981
M6	7(3.26)	3(2.63)	4(3.96)	.596
M7	1(0.46)	1(0.87)	0	.348
Unclassified	4(1.86)	1(0.87)	3(2.97)	.266
Prognostic stratification, n (%)				.159 ^a
Favorable	19(8.84)	13(11.40)	6(5.94)	–
Intermediate	173(80.46)	89(78.07)	84(83.17)	–
Unfavorable	21(9.77)	12(10.53)	9(8.91)	–
Missing	2(0.93)	0	2(1.98)	–
Induction chemotherapy, n (%)				.998
IA	200(93.02)	106(92.98)	94(93.07)	–
DA	4(1.86)	2(1.75)	2(1.98)	–
HA	11(5.12)	6(5.27)	5(4.95)	–
CR ^b , n (%)	183(85.11)	97(85.08)	86(85.14)	.997
Relapse, n (%)	75(34.88)	34(29.82)	41(40.59)	.251
No. of patients who underwent HSCT, n (%)	55(25.58)	35(30.70)	20(19.80)	.158

WBC: white blood cell; APTT: activated partial thromboplastin Time; ALT: alanine aminotransferase; PB: peripheral blood; BM: bone marrow; FAB: French-American-British; HSCT: hematopoietic stem cell transplant; IA: idarubicin and cytarabine; DA: daunorubicin and cytarabine; HA: homoharringtonine and cytarabine.

^aComparison of the two cytogenetic subgroups (favorable versus other).

^bAchieved complete remission (CR) after induction therapy.

women with an average age of 40 years (range: 14–65 years). According to the FAB classification, there were one (.46%) patients with M1, 37 (17.21%) patients with M2, 95 (44.19%) patients with M4, 70 (32.56%) patients with M5, seven (3.26%) patients with M6, one (.46%) patient with M7, and four (1.86%) patients unclassified. In terms of cytogenetic analysis and/or molecular analysis, there are 19, 173, and 21 patients respectively showing favorable, intermediate, and unfavorable karyotypes at the time of initial diagnosis. Other clinical and laboratory characteristics of patients are summarized in Table 1. With the median follow-up time was 31 months (ranging from 0 to 112 months). A total of 106 deaths had been recorded by the time of the last follow-up and the median time to die was 16 months (range from 0 to 52 months).

Optimal values of fibrinogen and association between fibrinogen levels and clinicopathological factors

In the study, the ROC curve of fibrinogen was used to determine the values (Figure 1). The area under the

curve (AUC) of fibrinogen in 14–65 years old patients was .594 (95% confidence interval [CI] = .518–.669), and optimal value was 3.775 g/L, with 56.6% sensitivity and 62.4% specificity, $p = .018$. There were 101 patients with high plasma fibrinogen levels (≥ 3.775 g/L) and 114 patients with low fibrinogen levels (< 3.775 g/L). The association between plasma fibrinogen levels and clinicopathological factors are summarized in Table 1.

Fibrinogen correlates with prognosis and treatment outcome in patients with non-M3 AML

In the prognostic analysis, Kaplan–Meier curve was selected to determine the correlation between plasma fibrinogen levels and survival. The results indicated that the low fibrinogen (< 3.775 g/L) group achieved significantly longer OS compared with the high fibrinogen (≥ 3.775 g/L) group ($p = .006$, Figure 2(A)). Moreover, the analysis of DFS showed a similar tendency between two groups ($p = .045$, Figure 2(B)).

Factors influencing OS and DFS in patients with non-M3 AML were analyzed by the univariate and

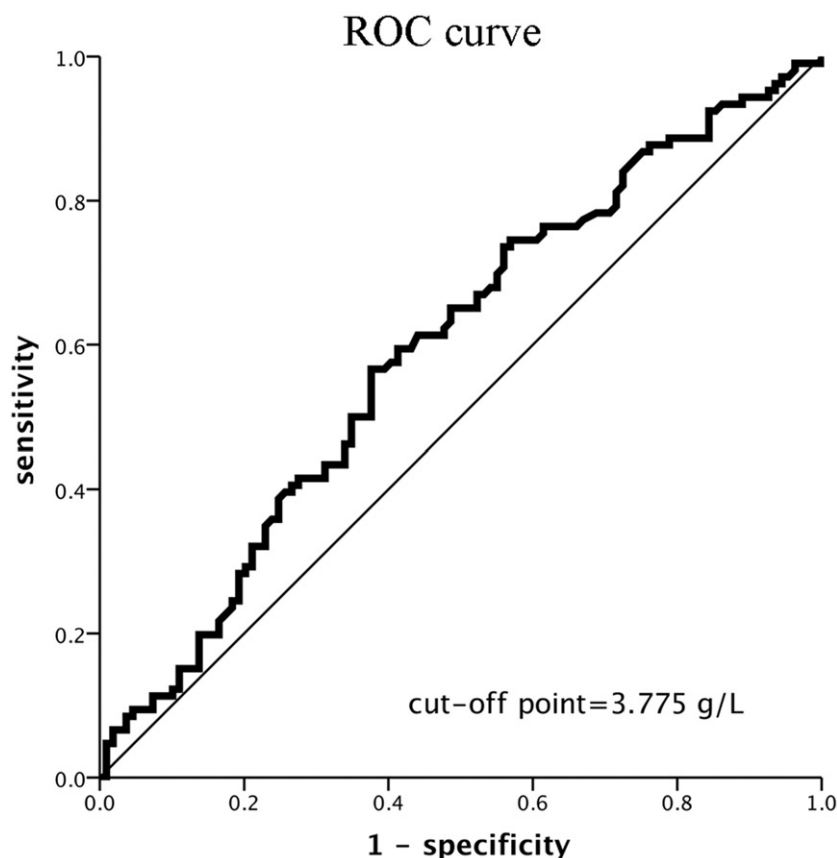


Figure 1. Receiver operating characteristic (ROC) curve analysis of initial plasma fibrinogen levels in non-M3 AML patients.

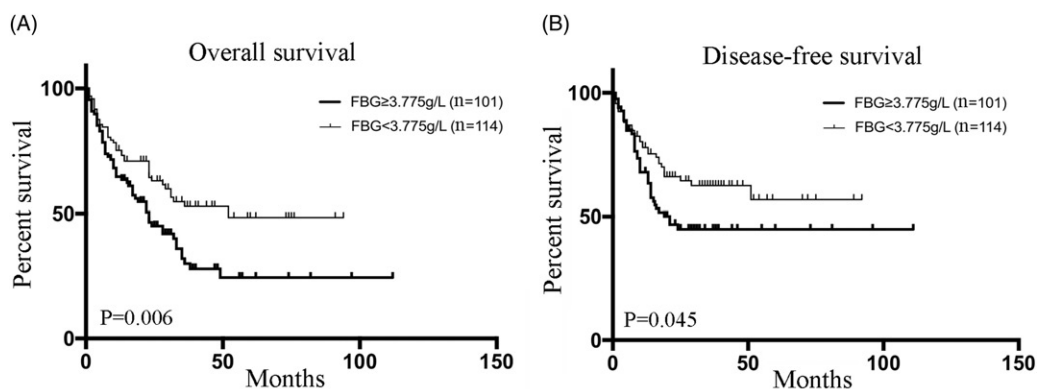


Figure 2. Kaplan–Meier curves are presented for overall survival (A) and disease-free survival (B) between low and high fibrinogen group in non-M3 AML patients.

multivariate cox regression analysis reported in Tables 2 and 3. As shown in Table 2, the significantly prognostic factors for OS were fibrinogen, age, log(WBC) count, hemoglobin count, thrombin time (TT), and activated partial thromboplastin time (APTT) ($p = .007$, $p = .037$, $p = .016$, $p = .015$, $p = .019$, and $p = .033$, respectively). The clinical factors associated with DFS were TT ($p = .014$) and plasma fibrinogen levels ($p = .049$).

The variables with $p < .05$ were selected to conduct a further multivariate cox regression analysis. The results in Table 3 indicates that independent adverse

predictors of OS included the following variables: fibrinogen, age, log(WBC), hemoglobin level and TT ($p = .024$, $p = .023$, $p = .006$, $p = .007$, and $p = .024$, respectively), whereas TT was significantly associated with DFS (OR = 1.119, 95% CI = 1.018–1.230, $p = .02$), other above variables failed to reach a statistical significance. Furthermore, there was a significantly negative correlation between fibrinogen and TT (Table 4). And accumulating evidence has shown that plasma fibrinogen reduction or its structural abnormalities can result in prolongation of TT.

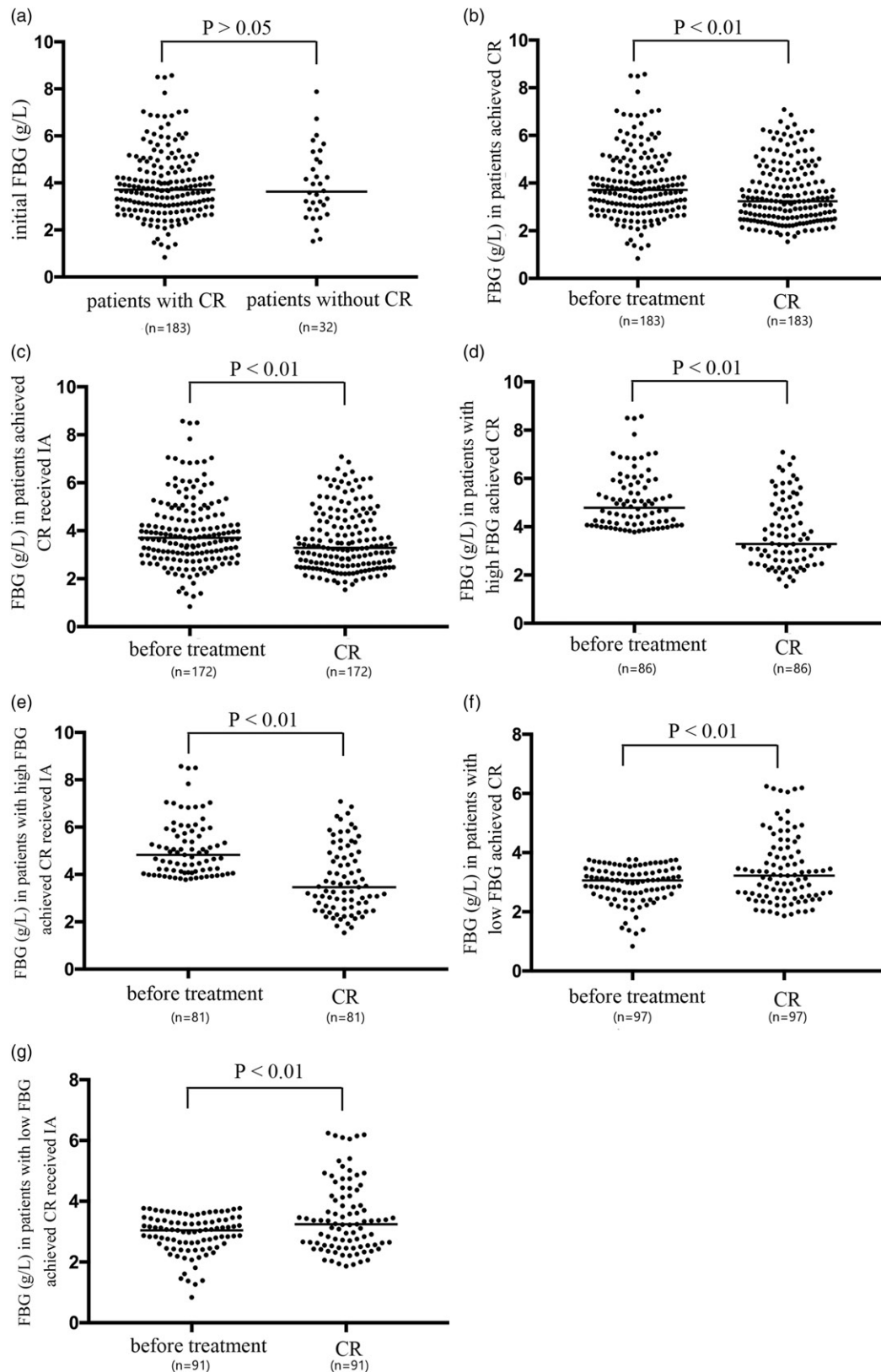


Figure 3. Plasma fibrinogen levels change in non-M3 AML patients when they achieve complete remission. (A) There was no difference in initial plasma fibrinogen levels in patients who achieved complete remission (CR) and did not achieve CR. (B,C) Plasma fibrinogen levels were significantly decreased when patients achieved CR regardless of treatments received or only through IA therapy. (D,E) Plasma fibrinogen levels were dramatically decreased when patients with high initial fibrinogen level achieved CR regardless of treatments received or only through IA therapy. (F,G) Plasma fibrinogen levels were increased when patients with low initial fibrinogen level achieved CR regardless of treatments received or only through IA therapy. Kruskal–Wallis H test was used to test significance between medians of two groups.

Table 2. Univariate analysis of factors influencing OS and DFS in patients with non-M3 AML.

Characteristics	OS			DFS		
	OR	95%CI	p-value	OR	95% CI	p-value
Age	1.509	1.024–2.223	.037	1.257	0.798–1.979	.324
Gender	1.185	0.809–1.737	.383	1.163	0.738–1.834	.515
Log(WBC)	1.438	1.071–1.931	.016	1.185	0.840–1.670	.333
HB (g/L, <100 vs. ≥100)	2.020	1.149–3.546	.015	1.494	0.821–2.724	.188
PLT ($\times 10^9/L$, <30 vs. ≥30)	1.052	0.717–1.543	.793	1.140	0.725–1.795	.569
Median blasts in PB (% , ≥20 vs.<20)	1.272	0.789–2.052	.323	1.063	0.619–1.825	.825
Median blasts in BM (% , ≥60 vs. <60)	1.216	0.815–1.813	.338	1.237	0.741–2.063	.416
TT(s)	1.078	1.012–1.149	.019	1.102	1.020–1.191	.014
APTT(s)	1.030	1.002–1.059	.033	1.028	0.994–1.064	.106
Fibrinogen (g/L, <3.775 vs. ≥3.775)	0.589	0.392–0.868	.007	0.634	0.402–1.000	.049

WBC: white blood cell; HB: hemoglobin; PLT: platelet; PB: peripheral blood; BM: bone marrow; TT: Thrombin Time; APTT: activated partial thromboplastin Time; 95% CI: 95% confidence interval.

Table 3. Multivariate analysis of factors influencing OS and DFS in patients with non-M3 AML.

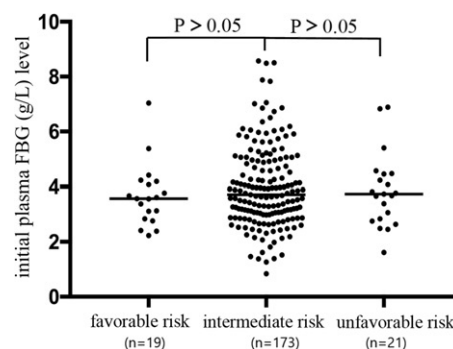
Characteristics	OS			DFS		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.582	1.067–2.347	.023	1.242	0.781–1.972	.359
Log(WBC)	1.530	1.131–2.070	.006	1.188	0.838–1.684	.333
HB(g/L,<100 vs. ≥100)	2.217	1.245–3.949	.007	1.574	0.853–2.903	.147
TT(s)	1.093	1.012–1.182	.024	1.119	1.018–1.230	.020
APTT(s)	1.005	0.974–1.037	.742	1.003	0.966–1.041	.882
Fibrinogen (g/L,<3.775 vs ≥3.775)	0.614	0.402–0.937	.024	0.612	0.369–1.017	.058

WBC: white blood cell; HB: hemoglobin; TT: Thrombin Time; APTT: activated partial thromboplastin Time; 95% CI: 95% confidence interval.

Table 4. The correlations among parameters of patient characteristics.

Characteristics	Fibrinogen (g/L) Correlation coefficient	p-value
Age	0.118	.083
WBC count	–0.060	.379
Hemoglobin(g/L)	–0.070	.304
Thromboplastin Time (s)	–0.241	<.001

There was no significant difference in plasma fibrinogen levels between *de novo* AML patients who achieved CR and did not achieve CR ($p=.955$, Figure 3(A)). In all patients who achieved CR regardless of treatments received or only received IA therapy, plasma fibrinogen levels were significantly decreased when these patients achieved CR (both $p<.01$, Figure 3(B,C)). For *de novo* patients with high initial plasma fibrinogen levels (≥ 3.775 g/L), plasma FBG levels were dramatically decreased when these patients achieved CR regardless of treatments received or only received IA therapy (both $p<.01$, Figure 3(D,E)). On the contrary, in patients with low initial plasma fibrinogen levels (<3.775 g/L), plasma FBG levels were increased when these patients achieved CR through receiving IA, DA, or HA therapy or only receiving IA therapy (both $p<.01$, Figure 3(F,G)). Additionally, there was no correlation between plasma fibrinogen level and the risk stratification of cytogenetics in all patients (Figure 4). Taken together, these results suggested that initial

**Figure 4.** There is no correlation of initial plasma fibrinogen level and risk stratification in non-M3 AML patients. Mann–Whitney U test was used to test significance among medians of fibrinogen level in three groups according to cytogenetic classification.

plasma fibrinogen levels can as an independent prognostic biomarker for OS and DFS and plasma fibrinogen levels can reflect the treatment outcome in patients with non-M3 AML.

DIC correlates with poor prognosis in patients with low fibrinogen levels

As activated DIC leads to decreased fibrinogen levels, we further analyzed whether DIC affects the prognosis of patients with low fibrinogen levels. According to the diagnostic criteria for DIC [20], the DIC scores

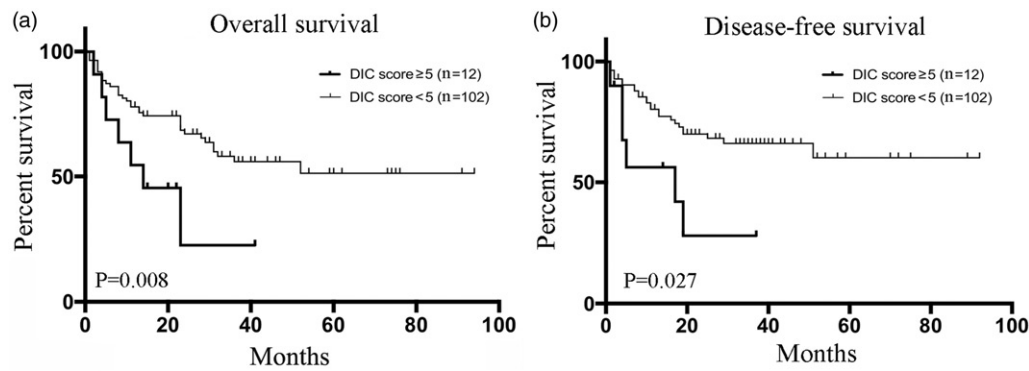


Figure 5. Kaplan–Meier curves are presented for overall survival (A) and disease-free survival (B) between DIC/non-DIC groups in patients with low fibrinogen levels.

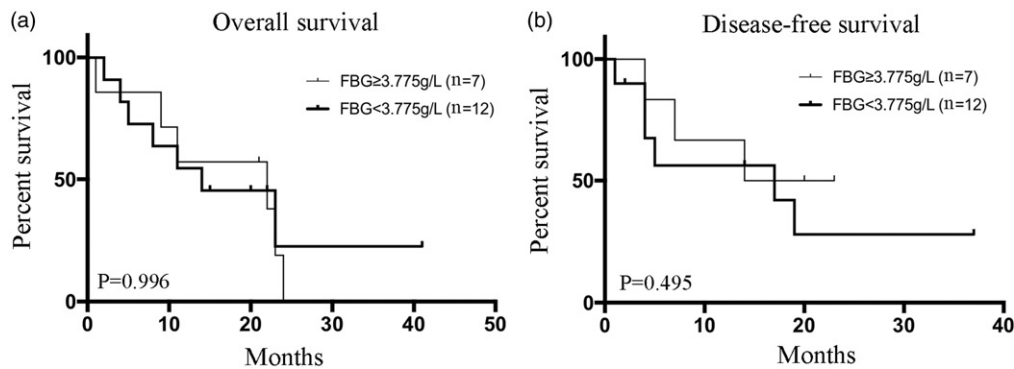


Figure 6. Kaplan–Meier curves are presented for overall survival (A) and disease-free survival (B) between low and high fibrinogen group in patients with overt DIC.

were performed on patients in the low fibrinogen group. Score ≥ 5 points can be diagnosed as DIC. As shown in Figure 5, we performed a survival analysis of OS and DFS in patients diagnosed with or without DIC in low fibrinogen level group. As expected, patients with overt DIC indeed had shorter OS ($p=.008$) and DFS ($p=.027$). In addition, the OS and DFS of patients with overt DIC have no significant difference between the high and low fibrinogen groups (Figure 6).

Discussion

Until now, there is a controversy about the correlation between initial plasma fibrinogen levels and prognosis in hematological malignancies [21,22]. Berger et al. [22] reported that OS and DFS were significantly longer in AML patients with low fibrinogen levels. Conversely, Elmoamly et al. [21] reported that fibrinogen levels had not yet had any prognostic impact on hematological malignancies. In this study, we divided all patients into two subgroups by ROC curve and showed that patients with high initial plasma fibrinogen levels had a shorter OS and DFS than those with low initial plasma fibrinogen levels, similar to the

results in solid tumors [23,24]. Moreover, we also found that the plasma fibrinogen levels were dramatically decreased when patients achieved CR after induction chemotherapy. The early mortality between low and high fibrinogen groups had no difference, inconsistent with two previous studies showing that low fibrinogen levels were associated with an increase in ICU admission and early mortality [25,26]. And our study indicated that the median fibrinogen value increased but still below the cutoff value in patients with low fibrinogen group. This difference may be due to the early adoption of aggressive exogenous fibrinogen replacement therapy for patients with very low fibrinogen at the time of initial diagnosis for the prevention of DIC and other risks. However, for patients with overt DIC in low fibrinogen level group, the survival was shorter despite early fibrinogen replacement therapy.

High initial plasma fibrinogen levels were associated with poor OS and DFS in AML, a possible explanation is that fibrinogen plays a key role in cancer progression by inducing cancer cell proliferation [27,28]. Members of the transforming growth factor- β , fibroblast growth factor, vascular endothelial growth

factor, and platelet-derived growth factor families can directly bind fibrinogen. Therefore, as a reservoir for secreting growth factors, the regulation of fibrinogen/fibrin matrix on cancer cell proliferation also has an effect on inhibition of apoptosis, angiogenesis, and metastasis [29,30]. In addition, fibrinogen cooperates with platelets to construct a network structure that captures tumor cells and enables them to escape host immune surveillance [31,32]. Fibrinogen acts as an important coagulation factor, and its elevated levels can lead to imbalances in the body's coagulation and fibrinolytic systems, resulting in increased blood viscosity and increased platelet aggregation. In addition, the binding of fibrinogen to specific receptors on the surface of neutrophils also promotes leukocyte aggregation and promotes adhesion of leukocytes to endothelial cells, leading to blockage of small vessel lumens and increased incidence of thrombotic events.

Of course, we must admit that our retrospective analysis certainly has limitations. As recruitment was performed in a single institution, election bias might be difficult to be well balanced. Another potentially limiting factor of our study is that the bias caused by HSCT could not be ignored. For there was no difference on the part of patients who underwent HSCT, the study did not give further explanation. Additionally, we analyzed the ROC curve of fibrinogen in patients of all ages, and the curve results showed no statistical significance (data not shown), which may be related to the basic situation of elderly patients over 65 years old. In general, fibrinogen increases with age, but in elderly AML patients over 65 years old, hepatic insufficiency, severe anemia, and other related factors may also affect fibrinogen content. On basis of this single-center and retrospective study, we can further explore the prognostic value of fibrinogen quantification for elderly AML patients by increasing the sample size. Furthermore, D-dimer, as a specific product of the degradation of fibrinogen clots, is considered to be a specific biomarker of fibrin formation and stabilization [33]. D-dimers are generally better at responding to the incidence of thrombotic events, and many studies have indicated that elevated D-dimer values can predict the adverse consequences of different types of carcinoma [34]. To our study, the analysis of the association of D-dimer exactly content with the patient's baseline may need further detection and analysis. Finally, according to our current analysis, there is no correlation between cytogenetic risk stratification and fibrinogen content, and whether it has a correlation with other factors, it all needs to be further explored.

In summary, we demonstrated the relationship between plasma fibrinogen levels at diagnosis and survival in non-M3 AML patients. As a commonly index of coagulation function, plasma fibrinogen level has an independent predictive value for the prognosis of patients with non-M3 AML. Plasma fibrinogen levels can also reflect the treatment outcome after induction chemotherapy in AML patients.

Potential conflict of interest:

Disclosure forms provided by the authors are available with the full text of this article online at <http://10.1080/10428194.2018.1535116>.

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