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Can plasma fibrinogen level predict bone marrow fibrosis?

Yildiz IPEK, Ayse Nilgun KUL

Department of Hematology, Kartal Lutfi Kirdar City Hospital, Istanbul, Turkey

Corresponding Author: Yildiz IPEK
E-mail: dryildizipek@hotmail.com

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ABSTRACT

Objective: We aimed to assess the possible relationship between plasma fibrinogen level and bone marrow fibrosis (BMF) grades in patients who had undergone bone marrow (BM) biopsy for any reason.

Patients and Method: This retrospective cohort study included 106 participants aged 18 years and over who had undergone simultaneous BM biopsy and circulatory fibrinogen level measurement during 2020 and 2021 at our center. BMF grade was measured by the modified Bauermeister grading system (MBGS). Participants were divided into two groups according to MBGS as those without BMF and those with BMF.

Results: Fifty-eight male were included in our study, and the median age of the patients was 63 (range: 19-97) years. Fibrinogen (p=0.004) and lactate dehydrogenase (LDH) (p=0.030) levels were significantly higher in the fibrosis group. Multiple regression revealed that high fibrinogen (≥359) and high LDH (≥238) were independently associated with a higher likelihood of fibrosis presence (adjusted for age and sex); however, diagnostic analyses revealed low accuracy.

Conclusion: High plasma fibrinogen and LDH levels were found to be independently associated with the presence of BMF. However, it was also evident that neither of these parameters could be used for diagnostic purposes.

Keywords: Bone marrow fibrosis, Plasma fibrinogen, Lactate dehydrogenase, Modified Bauermeister grading system

1. INTRODUCTION

Bone marrow fibrosis (BMF) is a histopathological process known for abnormal excess deposition of reticulin or collagen fibers in the BM. A number of malignant and non-malignant conditions and diseases can cause BMF [1, 2]. Although, studies have examined whether the severity and type of fibrosis are associated with disease prognosis, the results are inconsistent [2]. The presence of reticulin fibers alone, which is characteristic of mild fibrosis, does not appear to be associated with disease severity or comorbidities. However, an increase in collagen fibers, which indicates worse BMF, has been associated with the severity of primary disorders [2, 3]. BMF level and likelihood has been associated with disease severity or treatment response in various diseases, including chronic myeloid leukemia (CML) [4], myelodysplastic syndrome (MDS) [5].

Fibrinogen is a hexameric plasma glycoprotein produced in hepatocytes that contributes to various processes, including inflammation, atherogenesis, and thrombogenesis [6]. The coagulation system not only carries out blood clotting, but also contributes to various processes, including inflammation and tissue repair [7]. One of the most important functions of fibrinogen is its contribution to wound healing, particularly since fibrinogen is suggested to influence the development of healthy wound healing or fibrotic scarring [8]. Imbalances in wound healing mechanisms can lead to excessive scar formation and organ fibrosis [7]. Studies have shown that fibrinogen plays diverse roles in the fibrosis of various organs such as the kidney [6], liver [9], pancreas [10], skin [8], muscle [11], lung [12] and oral submucosa [13]. Even, fibrinogen is considered to be a useful biomarker for diseases in which fibrosis plays an important role in the pathogenesis, such as idiopathic pulmonary fibrosis and liver fibrosis [14, 15]. Therefore, fibrinogen may also contribute to BMF development in various diseases. However, to our knowledge, there is no study examining the role of fibrinogen in BMF and the relationship between plasma fibrinogen level and BMF grade.

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Since fibrinogen measurement can be performed from blood samples, it is evident that possible associations with BMF presence or its severity could yield a method for diagnosing BMF without the need for BM biopsy (BMB), which is an invasive technique. Therefore, we aimed to assess the possible relationships between plasma fibrinogen level and BMF grades in patients who had undergone BM biopsy (BMB) due to any cause.

2. PATIENTS and METHODS

Study Design and Ethics

This was a single-centered, retrospective cohort study carried out at Kartal Dr. Lutfi Kirdar City Hospital. The study was started after ethics committee approval was obtained from Clinical Research Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital. Since the study was retrospective, obtaining written informed consent from the participants was not required. All information were recorded anonymously.

Study Population and Power Analysis

The study included 106 participants aged 18 years or older who had undergone BMB for any indication and simultaneous fibrinogen level measurement in our hospital during 2020 and 2021. Exclusion criteria were as follows: being younger than 18 years old, pregnancy, having additional malignancy other than the primary hematological disease, and history of rheumatological or autoimmune disease, liver or kidney failure, organ transplantation, acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL). Patients with a history of infection within the two weeks before BMB and those with any history of fibrosis in any other organ were also excluded from the study. Severe BMF is usually seen in cases of primary myelofibrosis. Therefore, in order to define the relationship between fibrosis and fibrinogen, patients with other bone marrow diseases showing different degrees of BMF were also included in this study.

According to descriptive statistics from the study by Yu et al. [16], which demonstrated an effect size of 0.549, we performed power analysis and found that a sample size of 106 patients achieved 81% power according to the two-sided 0.05 significance level (Hintze J., 2011, PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

Data Collection

The demographic features including age and gender, indications for BMB, laboratory results, and the histopathological findings of patients were collected retrospectively from the electronic database of our hospital.

Laboratory Analysis

Patients' blood samples were obtained from the antecubital vein after 8 hours of fasting immediately before BMB. Fibrinogen (mg/dL), D-dimer (ng/mL), lactate dehydrogenase (LDH; U/L), C-reactive protein (CRP) (mg/L), white blood cell (WBC) count ($x10^3$), hemoglobin (g/dL), platelet count ($x10^3$), prothrombin time (PT) (sec), activated partial thromboplastin time (aPTT) (sec), and international normalized ratio (INR) were measured in the clinical chemistry department of our hospital via use of routine devices and routine techniques.

Pathological Assessment-BMB Grading

Iliac BMB samples were sent to the pathology unit of XXX for examination. BMF grade was determined according to the modified Bauermeister grading system (MBGS) [17] by qualified pathologists. MBGS is a system that classified the degree of BMF according to reticulin staining and collagen fibrosis in BMB specimens. Grade 0: lack of reticulin fibers, Grade 1: sporadic areas of fine individual fibers and presence of fine fiber network, Grade 2: fine fiber network present throughout the section without any coarse fibers, Grade 3: presence of diffuse fiber network with scattered coarse fibers without mature collagen (negative trichrome staining), Grade 4: presence of diffuse coarse fiber networks with areas of collagenization (positive trichrome staining) [17]. Participants were divided into two groups according to MBGS class; those without BMF (Grade 0 and 1, non-fibrosis group) and those with BMF (Grade 2 and 3 and 4, fibrosis group).

Statistical Analysis

All analyses were performed on SPSS v25 (IBM, Armonk, NY, USA) with a significance threshold of <0.05 (p value). For the normality check, the Kolmogorov-Smirnov test was used. Data are given as mean ± standard deviation or median (1st quartile – 3rd quartile) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. Normally distributed variables were compared with the independent samples *t*-test; whereas the Mann-Whitney *U* test was used for non-normally distributed variables. Chi-squared tests were used to compare distributions of categorical variables. Prediction performances were assessed by using Receiver Operating Characteristic (ROC) curve analysis. Optimal cut-off points were determined by using Youden index. Multiple logistic regression analysis was performed to evaluate the BMF prediction performance of variables by adjusting for age and sex.

3. RESULTS

Fifty-eight male and 48 female patients were included in our study, and the median age of the patients was 63 (IQR: 48 – 70) (range: 19 – 97) years. The indications for BMB, laboratory results, and distribution of fibrosis grades according to MBGS are summarized in Table I.

There were 53 patients in the non-fibrosis group and 53 patients in the fibrosis group. Median age was 61 (IQR: 46 – 70) years in the non-fibrosis group, and 64 (IQR: 55 – 70) years in the fibrosis group (p = 0.200). Sex distribution was also similar in the two groups (p = 0.329). The percentage of patients without hematological malignancy in the non-fibrosis group was significantly higher (p=0.001), while the number of patients with chronic myeloproliferative disorders (CMPDs) was significantly higher in the fibrosis group (p=0.001). Fibrinogen (p = 0.004) and LDH (p = 0.030) levels were significantly higher in the fibrosis group, but there was no significant difference between the two groups in terms of other laboratory parameters (Table II, Figure 1, and Figure 2).

Table I. *Summary of patients' characteristics and laboratory measurements*

Age	63 (48 – 70)
Sex	
Male	58 (54.7%)
Female	48 (45.3%)
Diagnosis	
Normal	22 (20.8%)
Lymphoma	10 (9.4%)
MM	33 (31.1%)
CML	3 (2.8%)
Chronic MPDs	17 (16.0%)
CLL	2 (1.9%)
MDS	15 (14.2%)
AA	4 (3.8%)
Fibrinogen	349 (289 – 392)
D-dimer	1190 (485 – 3010)
LDH	217 (178 – 335)
CRP	3.17 (2.06 – 6.26)
WBC (x10^3)	5.52 (3.88 – 8.20)
Hemoglobin	11.00 ± 2.39
Platelet (x10^3)	177 (73 – 259)
PT	14.05 (13.1 – 14.9)
aPTT	30.62 ± 4.33
INR	1.08 (0.98 – 1.21)
Modified Bauermeister Grading System	
0	3 (2.8%)
1	50 (47.2%)
2	27 (25.5%)
3	24 (22.6%)
4	2 (1.9%)

Data are given as mean ± standard deviation or median (1st quartile – 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. MM: Multiple myelom, CML: Chronic myeloid leucaemia, MPDs: Myelodysplastic syndromes, CLL: Chronic lymphocytic leukemia, MDS: Myelodysplastic syndrome, AA: AA amyloidosis, LDH: Lactate dehydrogenase, CRP: C-reactive protein, WBC: White blood cell, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio

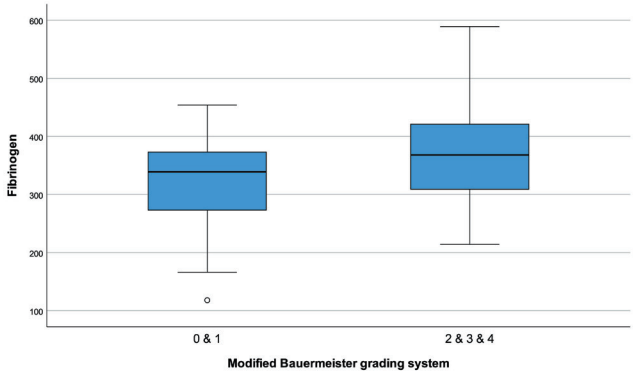

Figure 1. *Fibrinogen levels with regard to bone marrow reticulin*

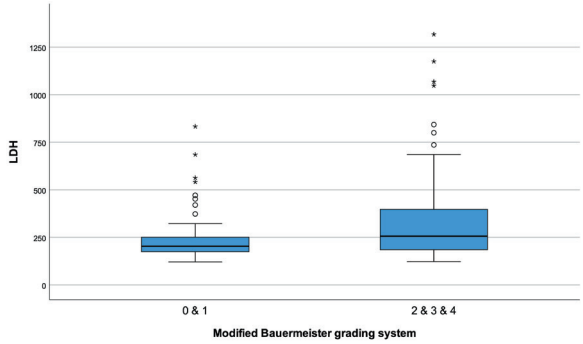

Figure 2. *LDH levels with regard to bone marrow reticulin*

Table II. *Summary of patients' characteristics and laboratory measurements with regard to bone marrow reticulin*

	Modified Bauermeister Grading System		
	0 & 1 (n=53)	2 & 3 & 4 (n=53)	p
Age	61 (46 – 70)	64 (55 – 70)	0.200
Sex			
Male	26 (49.1%)	32 (60.4%)	0.329
Female	27 (50.9%)	21 (39.6%)	
Diagnosis			
Normal	20 (37.7%)	2 (3.8%)	**0.001**
Lymphoma	5 (9.4%)	5 (9.4%)	
MM	17 (32.1%)	16 (30.2%)	
CML	1 (1.9%)	2 (3.8%)	
Chronic MPDs	3 (5.7%)	14 (26.4%)	
CLL	0 (0.0%)	2 (3.8%)	
MDS	5 (9.4%)	10 (18.9%)	
AA	2 (3.8%)	2 (3.8%)	
Fibrinogen	339 (273 – 373)	368 (309 – 421)	**0.004**
D-dimer	1145 (485 – 2685)	1295 (660 – 3010)	0.830
LDH	203 (174 – 251)	256 (185 – 397)	**0.030**
CRP	3.00 (1.37 – 6.70)	3.40 (2.50 – 5.73)	0.197
WBC (x10^3)	5.61 (3.88 – 7.96)	5.41 (3.90 – 9.10)	0.665
Hemoglobin	11.43 ± 2.52	10.56 ± 2.19	0.060
Platelet (x10^3)	178 (70 – 243)	160 (78 – 271)	0.924
PT	13.8 (13 – 14.7)	14.2 (13.1 – 16.1)	0.219
aPTT	30.32 ± 3.94	30.93 ± 4.71	0.472
INR	1.09 (0.98 – 1.19)	1.08 (0.98 – 1.28)	0.497

Data are given as mean ± standard deviation or median (1st quartile – 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. MM: Multiple myeloma, CML: Chronic myeloid leucaemia, MPDs: Myelodysplastic syndromes, CLL: Chronic lymphocytic leukemia, MDS: Myelodysplastic syndrome, AA: AA amyloidosis, LDH: Lactate dehydrogenase, CRP: C-reactive protein, WBC: White blood cell, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio

In ROC curve analysis, a cut-off value of ≥359 for fibrinogen revealed a sensitivity of 56.6% and a specificity of 73.6% for the identification of patients in the fibrosis group (AUC: 0.662, 95% CI: 0.559 – 0.765). For LDH level, a cut-off value of ≥238 had a sensitivity of 56.6% and a specificity of 71.7% in predicting patients with fibrosis (AUC: 0.622, 95% CI: 0.515 – 0.730) (Table III, Figure 3).

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Table III. *Performance of the variables to predict patients with mild/severe fibrosis (Modified Bauermeister grading system 2-4)*

	Fibrinogen	LDH
Cut-off	≥ 359	≥ 238
Sensitivity	56.6%	56.6%
Specificity	73.6%	71.7%
Accuracy	65.1%	64.2%
PPV	68.2%	66.7%
NPV	62.9%	62.3%
AUC (95.0% CI)	0.662 (0.559 – 0.765)	0.622 (0.515 – 0.730)
p	**0.004**	**0.030**

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals, LDH: Lactate dehydrogenase

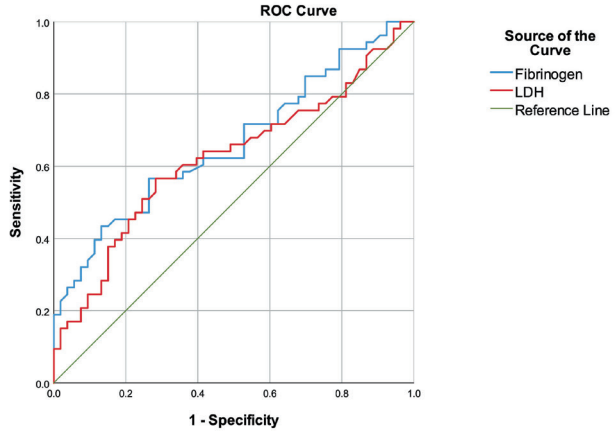

Figure 3. *ROC curve of the variables to predict bone marrow fibrosis*

We performed multiple logistic regression analysis to evaluate the BMF prediction performance of the variables by adjusting for age and sex. Patients with high fibrinogen (≥ 359) had 3.084-fold higher likelihood to have BMF compared to those with low fibrinogen after adjusting for age and sex (OR: 3.084, 95% CI: 1.303 – 7.299; p = 0.010). Patients with high LDH (≥ 238) had a 2.865-fold higher likelihood for BMF compared to other patients after adjusting for age and sex (OR: 2.865, 95% CI: 1.214 – 6.761; p = 0.016) (Table IV).

Table IV. *Significant predictive factors of the bone marrow fibrosis, multiple logistic regression analysis*

	β coefficient	Standard Error	p	Exp(β)	95.0% CI for Exp(β)	
Age	0.015	0.015	0.324	1.015	0.986	1.045
Sex, female	-0.332	0.433	0.443	0.717	0.307	1.676
Fibrinogen (≥ 359)	1.126	0.440	**0.010**	3.084	1.303	7.299
LDH (≥ 238)	1.053	0.438	**0.016**	2.865	1.214	6.761
Constant	-1.617	0.951	0.089	0.198		
Dependent variable: Modified Bauermeister GS 2-4; Nagelkerke R^2=0.213						

CI: Confidence interval, GS: Grading system, LDH: Lactate dehydrogenase

4. DISCUSSION

A large number of benign and malignant diseases may cause an increase in reticulin or collagen fibers in the BM. The reason for this abnormal fiber increase in the BM stroma has not been clarified. The clinical consequences of increased fibers (either reticulin or collagen) may differ [18]. The literature reports that the amount of reticulin increase in the BM rarely correlates with the severity of causative disease; however, increased collagen fiber levels often correlate strongly with abnormal blood counts and the severity of the causative disease [19-22]. Reticulin fibers accumulate more commonly in BMF; however, it is difficult to detect the presence and severity of fibrosis by measuring reticulin level via a noninvasive method. In this study, we aimed to assess whether plasma fibrinogen level could be a diagnostic tool that could predict BMF. Univariate analyses showed that high fibrinogen and LDH levels were significantly associated with the presence of BMF. Multiple logistic regression also supported the association of fibrinogen and LDH elevation with BMF, and demonstrated these variables to be independent risk factors associated with BMF after adjusting for age.

BMF can occur in many hematological and non-hematological, benign or malignant diseases. However, it can be seen at different degrees even in the absence of diseases or conditions directly associated with BMF. While collagen fibrosis is exceedingly rare in the BM of healthy individuals, reticulin staining of various grades can be observed in around 70% of BM samples [17]. The most common malignant diseases in which generalized BMF is seen are chronic idiopathic myelofibrosis (MF), CML, AML, ALL, MDS, lymphomas and metastatic tumors [23]. Non-malignant causes of BMF include endocrine disorders, autoimmune diseases, vitamin D deficiency and infections (HIV, tuberculosis) [1, 2, 23]. The identification of BMF is vital in some diseases. For example, in CML, BMF is an important factor associated with post-transplant therapeutic efficacy and prognosis [20]. Additionally, BMF grade is an indicator of treatment failure in CML [24], and BMF development during the course of MDS has been associated with worse outcomes [5]. In a study of 301 patients with MDS, patients with grade 2 and 3 BMF were shown to have shorter overall and leukemia-free survival than those with grade 0 or 1 BMF [5]. One study evaluating CLL patients showed that those with high-grade BMF (grades 2 and 3) had worse 5-year overall survival rate than those with grade 0-1 BMF [25]. However, identifying the presence of BMF necessitates BM aspiration and pathological examination with special dyes. Although BMB is known to be a safe procedure, pain at the biopsy site, discomfort, bleeding, hematoma, gluteal artery pseudoaneurysm, and infection are the most common complications [26, 27].

Various studies have explored possible parameters that can replace the need for biopsy for the detection of BMF. It has been shown that latent and active transforming growth factor-β (TGF-β) is increased in BM plasma as well as in the serum of patients with hairy cell leukemia who have BMF, and the concentration of active TGF-β is associated with the degree of reticulin fibrosis. That is, serum TGF-β may allow for noninvasive assessment of BMF in general [28]. Also,

measurement of serum procollagen III peptide (PIIINP) is another recommended biochemical marker for the diagnosis of reticulin fibrosis. One study showed that 35 participants with CMPD had higher PIIINP levels than 35 healthy volunteers, and that PIIINP levels correlated with the degree of reticulin fibrosis; however, PIIINP levels were not associated with collagen fibrosis [29]. Interleukin (IL)-8, IL-2R and lipocalin-2 are other cytokines that have been suggested to be involved in the pathophysiology of BMF, especially among patients with MF [30]. Genetic studies assessing JAK2 V617, MPL and CALR gene mutations have suggested possible associations with BMF [1]. However, their routine diagnostic value has not been consistent [30]. In the present study, we examined the relationship between plasma fibrinogen level and BMF. Our results were promising, as demonstrated by elevated fibrinogen and LDH levels in patients with BMF. In multiple regression, we found that high fibrinogen and LDH were independent risk factors for BMF after adjusting for age and sex. However, ROC analyses revealed relatively low sensitivity, specificity, PPV and NPV values in predicting BMF.

Reticulin and/or collagen production are associated with adventitial reticular cells, perisinusoidal adventitial cells, periarterial adventitial cells, adipocytes, and endosteal cells, which are fibroblastic BM cells in the stroma [31]. Fibroblasts are in close association with collagen fibers and respond to many fibrogenic factors such as interleukin (IL)-6, IL-12, IL-8, TNFα, IFNy, TGFβ, bFGF, VEGF and TGFβ1 [32]. Most of these profibrotic, angiogenic, and proinflammatory factors are stored and released by the α-granules of megakaryocytes [33]. Abnormal deposition of reticulin and collagen in the BM stroma is associated with abnormalities in the number and/or function of megakaryocytes and platelets, and thus the cytokines released from these cells [18]. The reason for the close relationship between fibrosis and neoplastic proliferation of abnormal megakaryocytes has not been explained. Few studies have examined the mechanism by which abnormal megakaryocytes exert their effects on collagen-producing cells [34, 35]. Also, it was shown that fibrinogen may participate in the development of fibrosis by triggering the expression of TGF-β1 and by activating cellular signaling pathways [6]. This complex relationships between fibrinogen, megakaryocytes, platelets, and fibroblasts make it difficult to clarify the role of each cell. While the contribution of fibrinogen to other organ fibrosis is established, its role in BMF is unclear. In a genetic study, it was determined that many extracellular matrix components, including increased expression of fibrinogen, are altered during the development of MF [36]. In a case report, the fibrinogen level of a patient with TAFRO syndrome (a rare systemic inflammatory disease characterized by thrombocytopenia, pleural effusion, fever, renal dysfunction, reticulin fibrosis of the BM, and organomegaly) was reported to be high (fibrinogen: 434 mg/dL) together with somewhat elevated D-dimer level (22.5 μg/mL) [37]. However, prior studies do not demonstrate the relationship between BMF and fibrinogen.

Fibrinogen is a 340 kDa glycoprotein that is mainly synthesized by hepatocytes and has many biological functions [38, 39]. During tissue maintenance, fibrinogen and fibrin matrix elements are associated with re-epithelialization, vascularization and collagen deposition, possibly explaining relationships with BMF [40]. Fibrinogen is also a main acute phase protein and its concentration in plasma is often used as a marker for systemic inflammation [9]. It has been observed that different components of the coagulation system, including fibrinogen, play an important role in the development of tissue fibrosis. In a mice study, in vitro experiments showed that fibrinogen was a potent mitogen that promoted renal fibroblast expansion [7]. In this study, it was showed that fibrinogen deficiency confers significant protection from interstitial damage, attenuated collagen deposition, and limited interstitial cell proliferation, a hallmark of fibrosis. It was concluded that fibrinogen increases renal fibrosis by triggering resident fibroblast proliferation [7]. Another study demonstrated that nephropathy patients with high serum fibrinogen had higher renal tubular atrophy and interstitial fibrosis [6]. Additionally, studies have shown a possible role for fibrinogen in the early phase of acute inflammation associated with pulmonary fibrosis [41, 42]. A study investigating the role of fibrinogen in dystrophic muscle fibrosis demonstrated that fibrinogen stimulated collagen production in fibroblasts, while TGFβ produced due to fibrinogen potentiated collagen accumulation [11]. Such results provide evidence for the profibrotic effects of fibrinogen deposition which have been demonstrated in other disease states [10]. Therefore, fibrinogen, whose role is evident in the fibrosis of various organs, is likely to play a role in BMF as well. By investigating the mechanisms involving fibrinogen in the fibrosis of these organs, its role can be clarified and new parameters can be obtained to facilitate easier diagnosis of BMF.

There are some limitations in our study. The fact that the study was retrospective and single-center made it difficult to add new data and limited the assessment of results from other perspectives. Although potential mechanisms by which fibrinogen could be associated with BMF were examined in the light of the literature, this study could not evaluate the mechanisms of this effect, but aimed to elucidate a possible relationship between circulatory fibrinogen level and BMF. Since the number of patients with Grade 0 and Grade 4 BMF were very low, we had to categorize patients into two groups with respect to the results of MBGS (fibrosis versus non-fibrosis). However, it is evident that this dichotomization may have led to inaccuracy. We believe studies that can assess fibrinogen and BMF levels in a higher number of patients are warranted.

Conclusion

In conclusion, high plasma fibrinogen and LDH levels were found to be associated with the presence of BMF. It was shown that the elevation of these each of these two parameters were independent risk factors for the presence of BMF (adjusted for age and sex). Clarifying the role of fibrinogen in the development of BMF and demonstration of higher levels of accuracy with respect to BMF grades may yield a new and non-invasive approach to the identification of BMF development. Possible advantages of such an approach include early diagnosis and better management.

Compliance with Ethical Standards

Ethical approval: The study was started after ethics committee approval was obtained from Clinical Research Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital (Date: 10.11.2021, No: 2021/514/213/2).

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Conflict of Interest: The authors have no conflicts of interest to declare.

Author Contributions: YI and ANK: Concept and design of the study, YI: Data acquisition, ANK: Statistical analysis, YI and ANK: Literature YI and ANK: Drafting and Writing. Both authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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