Pretransplant Serum Fibrinogen Level may be a Predictive Marker on Chronic Graft-Versus-Host Disease (cGVHD) in Patients Having Undergone Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT)

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ABSTRACT

Inflammatory processes play an important role in the pathophysiology of cGVHD. Serum fibrinogen is a proinflammatory protein with a wide range of functions in inflammation. But its role in GVHD is unclear. The aim of this study was to evaluate the predictive impact of pre-transplantation fibrinogen levels on cGVHD in allo-HSCT recipients. We retrospectively analyzed 249 patients with hematologic diseases undergoing allo-HSCT from 10/10 HLA-matched donors. Serum high fibrinogen levels at the time of HSCT (day 0) were significantly associated with cGVHD development in univariate analyses (OR 2.01, p= 0.012) and multivariate analyses (OR 1.003, p= 0.037). There was no significant association between fibrinogen levels and overall survival, disease-free survival and, acute GVHD (p> 0.05). This is the first report demonstrating the association between high fibrinogen levels and increased cGVHD occurrence.Further studies are warranted and may identify the efficacy of fibrinogen as a predictive marker on cGVHD in allo-HSCT recipients.

Keywords: Allogeneic Hematopoietic Stem Cell Transplantation, Fibrinogen, Inflammation, Chronic Graft-Versus-Host Disease

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains a cornerstone curative therapy for high-risk hematological malignancy and severe immune deficiencies.[1] Although this therapeutic approach has demonstrated good rates of success for disease eradication, life-threatening complications such as severe acute graft-versus-host disease (aGVHD) or chronic graft-versus-host disease (cGVHD) and infections remain as major problems after HSCT.[2-4]

cGVHD is a multisystem inflammatory disease characterized by tissue fibrosis. The treatment outcome of allogeneic hematopoietic stem cell transplantation (HSCT) for hematological disorders was determined by two major factors: transplant-related morbidity or mortality (TRM) and disease relapse. cGVHD represents the major cause of procedural morbidity and nonrelapse mortality.[5,6]

Depending on the type of transplantation, patient age, immunosuppression, and underlying disorders 35-50% of transplanted patients develop cGVHD.[7-10] Patients developing severe cGVHD have a mortality risk of about 25-35% due to immune-mediated specific organ damage and/or concomitant infections.[8,11-14]

Because of this, doctors try to reduce the occurrence and severity of GVHD before and after transplantation and take every precaution to prevent GVHD. Predicting patients at high risk of developing cGVHD might allow early therapeutic interventions and, thereby, prevent long-term complications.

Serum fibrinogen level may be a predictive marker for the risk of occurrence of cGVHD.

Fibrinogen is a soluble 340-kDa glycoprotein synthesized by hepatocytes in the liver[15] and one of the most important coagulation factors. In pathological conditions, such as after injury, or disease associated with vascular disruption, infection, or inflammation, the blood concentration of fibrinogen increases severalfold.[16] It is a modest acute-phase reactant. So, fibrinogen is a pro-inflammatory protein. Coagulation factors play important biological roles not only in hemostasis but also in reproduction, tissue repair, and inflammatory responses related to infection or disease.[17]

Evidence shows that there is some connection between fibrinogen and the development of inflammation.[17] And chronic inflammation is a risk factor in the occurrence of cGVHD.[18] Additionally, IL-6 is a pleiotropic cytokine that is released after the induction of macrophage activation by fibrinogen.[19] IL-6 signaling results in phosphorylation of STAT3, which is critical for the generation of cGVHD.[20,21]

To date, no studies have demonstrated the predictive value of serum fibrinogen levels on cGVHD in patients undergoing allo-HSCT. We, therefore, retrospectively analyzed the pretransplant fibrinogen levels to investigate the relationship between elevated fibrinogen levels and cGVHD and to evaluate the predictive value of fibrinogen on cGVHD.

PATIENTS and METHODS

Patients

The records of 249 patients who underwent allo-HSCT from 10/10 HLA-matched donors due to hematological diseases at Erciyes University Hematology Transplant Center, between the years of 2003-2016, were retrospectively reviewed. Pretransplantation (the day of HSCT, day 0) serum fibrinogen was available for 249 patients. The cut-off value was 350 mg/dl. At our institution, serum fibrinogen levels between 180-350 mg/dl are considered within the normal range.

Patients were divided into 2 groups; patients with pretransplant fibrinogen levels lower than ≤ 350 mg/dl and higher than 350 mg/dl. This study was approved by the local ethics committee of Erciyes University (Approval number: 2021/399).

Transplantation Procedures and Prophylaxis Strategy:

HSCT was performed according to standard transplantation procedures. Myeloablative conditioning (MAC) consisted of cyclophosphamide/total body irradiation (TBI) or cyclophosphamide/busulfan. Reduced-intensity conditioning (RIC) consisted of fludarabine/busulfan, fludarabine/melphalan, or fludarabine/low dose TBI. For GVHD prophylaxis, patients received methotrexate plus cyclosporine A. Patients with a matched unrelated donor additionally received anti-thymocyte globulin (ATG).

In the first 4 weeks of the post-transplant period, antibacterial (moxifloxacin 1 × 400 mg/day) and antiviral (valacyclovir 1 × 500 mg/day) prophylactic regimens were administered. For antifungal prophylaxis, fluconazole 2 × 200 mg/day was given in the post-transplant period until the 75th day following the transplant. Trimethoprim and sulfamethoxazole treatment were given at a dose of 160 mg and 800 mg, respectively, twice a day, twice weekly for pneumocystis jirovecii prophylaxis after the engraftment was achieved until 180. Patients were followed by weekly visits for the first month and biweekly for 3 months.

Definition of Transplant-Related Variables

For transplantation-associated risk stratification patients with acute leukemia in first or second complete remission (CR) and patients with myelodysplastic syndrome (MDS) were considered to be a standard risk.[22] All other patients were graded as being at high risk. Gender mismatch between donor and host was graded as high risk in the case of female donors with male recipients, and all oth-

Table 1. Patient characteristics

Variables	n (%)
Age, years (< 40 / ≥ 40)	174 (69.9)/75 (30.1)
Gender (male / female)	153 (61.4)/96 (38.6)
Diagnosis	
Acute leukemia	175 (70.3)
Lymphoproliferative diseases	17 (6.8)
Other diseases	57 (22.9)
Sex mismatch (standard risk/high risk)	183 (73.5)/66 (26.5)
Risk group (standard risk / high risk)	166 (66.7)/83 (33.3)
Time to transplant	
(< 12 months / ≥ 12months	184 (73.9)/65(26.1)
Conditioning regimen	
MAC	168 (72.4)
RIC	64 (27.6)
HLA matched	
Related	219 (82)
Unrelated	3 (1.1)
CD 34+count, 106/kg, median (range)	7.1 (2.7-16)
Fibrinogen level at HSCT	
Median in mg/dl (range)	311 (7.1-1003)
Neutrophil engraftment, d, median (range)	15 (8-61)
Missing	14 (5.6)
Platelet engraftment, d, median (range)	11 (4-64)
Missing	12 (4.8)
Infection (yes)	185 (74.3)
Acute GVHD (yes)	35 (14.1)
Chronic GVHD (yes)	83 (33.3)
GVHD (yes)	112 (45)
DFS, d, median (range)	365 (4-4320)
OS, d, median (range)	520 (4-4320)
Peri-transplant mortality (yes)	7 (2.8)
Early-transplant mortality (yes)	26 (10.4)

DFS: Disease-Free Survival; GVHD: Graft-Versus-Host Disease; HLA: Human Leukocyte Antigen; OS: Overall Survival; d: day; MAC: Myeloablative; Conditioning; RIC: Reduced Intensity Conditioning

ers were considered a standard risk.[23] GVHD was graded according to standard clinical criteria.[24,25]

Statistical Analysis

In statistical analysis, we used the Mann-Whitney U test for continuous variables between the two groups. Pearson Chi-Square test and Fisher Freeman Halton test were used for comparison of categorical data. Survival and mortality probabilities were estimated using the Kaplan-Meier method, and comparisons were performed using the log-rank test. Moreover, univariate and multivariate logistic regression analyses were applied to identify the most significant risk factors on GVHD. Also, odds ratios were given with 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant.

RESULTS

Patients Characteristics

Patients' characteristics are listed in Table 1. There were 249 patients enrolled in our study. 153 (61.4%) of the patients were male, and 96 (38.6%) were female. One hundred seventy-four patients (69.8%) were below the age of 40, 75 (30.1%) were above 40. Most patients were transplanted for acute leukemia (70.3%), with fewer patients transplanted for lymphoproliferative diseases (6.8%), myelodysplastic syndrome (2%), and other diseases (20.9%). For risk classification; 83 patients (33.3%) were defined as high versus 166 (66.7%) standard risk.

Most patients received a myeloablative conditioning regimen (72.4%). Two hundred nineteen patients were transplanted from 10/10-HLA-matched related donors while three patients had an unrelated 10/10-HLA-matched donor. The time-to-transplant period was less than 12 months in 184 (73.9%) patients and more than 12 months in 65 (26.1%) of the patients. The median time for neutrophil engraftment was 15 days (range, 8-61 days) and 11.00 days (range, 4-64 days) for platelet engraftment. The median level of fibrinogen level at the time of HSCT was 311 mg/dl (range, 7.1-1003 mg/dl).

We divided these patients into two groups according to the level of plasma fibrinogen. The concentration of plasma fibrinogen greater than 350 mg/dl was described as hyperfibrinogenemia. Applying this cutoff value to these patients, 87 (34.9%) patients had a higher level of fibrinogen while 162 (65.1%) patients had fibrinogen levels below the cut-off.

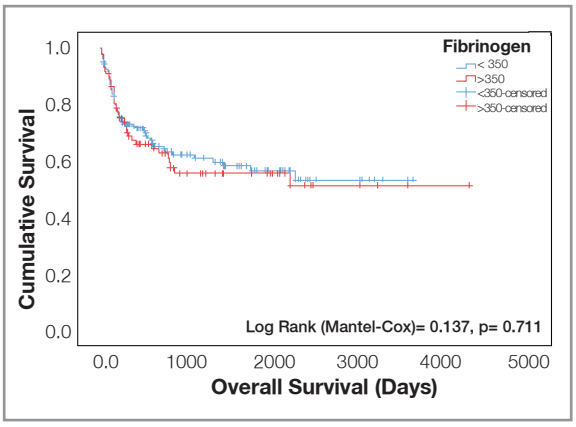

Figure 1. Patients with pre-transplant serum fibrinogen levels > 350 mg/dl did not have a significant difference in OS compared with those with pre-transplant serum fibrinogen levels ≤ 350 mg/dl (p= 0.71)

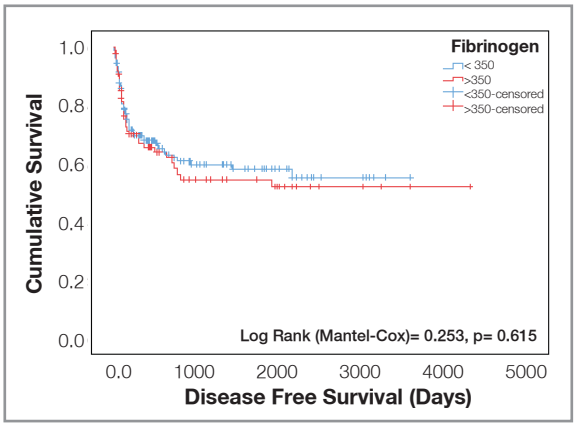

Figure 2. Patients with pre-transplant serum fibrinogen levels > 350 mg/dl did not have a significant difference in DFS compared with those with pretransplant serum fibrinogen levels ≤ 350 MG/DL (p= 0.61)

In the posttransplant evaluation; infections were the leading complication in the recipients 185 (74.3%) of the patients had at least ≥1 episode of infectious events. GVHD was the second common complication in the post-transplant period. A total of 35 (14.1%) patients had acute GVHD while chronic GVHD was diagnosed in 83 (33.3%) of the patients. A total of 94 patients (37.8%) died during the posttransplant follow-up. A total of 26 patients (10.4%) died in the first 30 days after transplantation (early transplant mortality), while 7 patients (2.8%) died within the first 100 days after transplantation (peritransplant mortality). Fifty-three patients (21.3%) relapsed in the posttransplant period. OS and DFS were 520 days (range, 4 - 4320) and 365 days (range, 4 - 4320), respectively.

The Association of OS and DFS with Elevated Serum Fibrinogen Levels

Pretransplant elevated fibrinogen levels were not significantly associated with the OS (p= 0.71) and DFS (p= 0.61) (Figüre 1 and Figüre 2).

The association of elevated serum fibrinogen levels prior to transplantation with GVHD: Univariate and multivariate analysis showed that patients with elevated serum fibrinogen levels > 350 mg/dl displayed significantly increased development of chronic cGVHD compared with those whose value was ≤ 350 mg/dl (univariate OR= 2.01, 95% CI: 1.16 - 3.47, p= 0.012; multivariate OR= 1.003, 95% CI: 1 - 1.006, p= 0.037). Multivariate, as well as univariate analyses, are shown in Table 2. We concluded that elevated serum fibrinogen levels prior to allo-SCT are an independent risk factor for cGVHD.

Risk factors for cGVHD in the univariate analysis were sex mismatch [patients with high risk had significantly increased cGVHD risk compared to with standard risk (OR= 2.33, 95% CI: 1.14 - 4.79, p= 0.02)], other diseases [patients with other diseases had a lower risk compared with patients with acute leucemia (OR 0.43, 95% CI: 0.20 - 0.88, p= 0.025)], time to transplant interval [patients who had undergone allo-HSCT more than 12 months from diagnosis (≥ 12 months) had lower risk compared to with those who had undergone allo-HSCT within 12 months from diagnosis (< 12 months) (OR 0.45, 95% CI: 0.23 - 0.88, p= 0.021)], risk status [patients with high transplantation associated risk had significantly increased cGVHD risk compared to with standard transplantation associated risk (OR 1.79, 95% CI: 1.03 - 3.10; p= 0.038)], conditioning regimens [patients who have been treated with RIC regimen a had lower risk compared with patients who have been treated with MAC regimen (OR= 0.22, 95% CI: 0.10 - 3.10; p= 0.49)].

Risk factors for cGVHD in the multivariate analysis were conditioning regimens [patients who have been treated with RIC regimen had a lower risk compared with patients who have been treated with MAC regimen (OR= 0.34, 95% CI: 0.14 - 0.8; p= 0.013)], age [patients who were older than 40 years

Table 2. Univariate and multivariate analysis of parameters for cGVHD

Variables	cGVHD			
	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Age, years				
<40	1.00			
≥40	1.65 (0.94-2.90)	0.08		
Gender				
male	1.00			
female	1.08 (0.62- 1.85)	0.78		
Diagnosis				
Acute leukemia	1.00			
Other diseases	0.43 (0.20-0.89)	0.25		
MDS	1.07 (1.17- 6.59)	0.93		
Lymphoproliferative diseases	0.34 (0.0.09-1.24)	0.10		
Sex mismatch				
Standard risk	1.00			
High risk	2.04 (0.14-3.65)	0.01*	2.33 (1.14-4.79)	0.08
Disease status				
Standard risk	1.00			
High risk	1.79 (1.03-3.10)	0,038*	1.78 (0.93-3.44)	0.08
Conditioning regimen				
RIC	1.00			
MAC	0.22 (0.10-0.49)	<0,001**	0.34 (0.14-0.8)	0.01*
Time to transplant				
<12months	1.00			
≥12 months	0.45 (0.23-0.88)	0.021*		
Serum fibrinogen level				
≤350	1.00			
>350	2.01 (1.16- 3.47)	0.012*	1.003 (1-1.006)	0.037*
Neutrophil engraftment	1.01 (0.96-1.06)	0.58		
Platelet engraftment	1.01 (0.96-1.06)	0.53		
CD34+ Count	0.95 (0.83-1.09)	0.51		
Infection (yes/no)	1.89 (0.99-3.64)	0.054		

MAC= Myeloablative Conditioning; RIC= Reduced Intensity Conditioning; OR= Odds Ratio; CI= Confidence Interval; cGVHD= chronic Graft Versus Host Disease; MDS= Myelodysplastic Syndrome; *<0.05; **< 0.01

had increased cGVHD risk compared with those who were younger than 40 years (OR 1.03, 95% CI: 1-1.05; p= 0.021)].

The parameters of gender, presence of infection, relapse, and the number of totals infused CD34+ cells showed no significant effect on cGVHD (p> 0.05).

In univariate analysis, the development of acute GVHD was not significantly associated with elevated serum fibrinogen levels (OR 0.6, 95% CI: 0.26 - 1.35; p= 0.22).

DISCUSSION

To the best of our knowledge, this is the first study evaluating the predictive impact of pretransplant

plasma fibrinogen levels on cGVHD occurrence in patients undergoing allo- HSCT. Our results suggest that elevated plasma fibrinogen levels before allo-HSCT are associated with cGVHD development but not with poorer PFS and OS. Therefore, plasma fibrinogen levels may be useful as a predictive marker for cGVHD.

Previous reports in cancer patients indicated that plasma fibrinogen levels are of prognostic significance in several solid malignancies including endometrial and ovarian,[26,27] renal cell,[28] esophageal,[29] and hepatocellular[30] and non-small cell lung cancer,[31] and in hematologic malignancies such as AML[32,33] and DBBH.[34] These findings in solid tumors and hematologic tumors led us to explore the impact of elevated plasma fibrinogen levels on cGVHD development in patients undergoing allo-hsct.

A possible explanation is that fibrinogen is a wide spectrum of functions in inflammation.[17] Inflammatory processes have been reported to play an important role in the pathophysiology of cGVHD. The pathogenesis of cGVHD is a complex process that involves early inflammation and tissue injury, chronic inflammation and, aberrant tissue repair and fibrosis.[18,35]

In most cases, the proinflammatory functions of fibrin (ogen) and its derivative peptides are associated with their ability to bind to and activate a wide range of immune cells through distinct ligand-receptor interactions. These receptors are expressed on dendritic cells, monocytes, macrophages, neutrophils, and some B cells.[17,36-38] Fibrinogen signals either directly or indirectly through a number of receptors, adhesion molecules, and cell- surface proteins that are involved in inflammatory processes. Several chemokines and cytokines, such as IL6, IL8, TNF-α, macrophage inflammatory protein-1 (MIP-1) α and β, matrix metalloproteinase (MMP)[1,39,40] release after the induction of macrophage activation by fibrinogen. Classical IL-6 signaling results in phosphorylation of STAT3, which is critical for the generation of cGVHD.[20,21,41]

Macrophages are also a source of transforming growth factor (TGF) beta (TGFb), TNF a, IL-1b, platelet-derived growth factor (PDGFR), and matrix metalloproteinases, with an ensuing cascade of fibrosis.[35,41] TGF-B released via macrophage stimulation by fibrinogen, indisputably, is one of the key drivers of fibrosis and inflammation. Its role in cGVHD as a profibrotic cytokine is that can directly induce the differentiation of fibroblasts into collagen-secreting myofibroblasts. In clinical cGVHD lesions, macrophages are abundant and are found in close proximity to collagen-producing myofibroblasts.[42,44]

Another possible explanation is that 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 platelet aggregation and thrombin generation. Thrombin in turn leads to increased conversion of fibrinogen to fibrin. Peptides released as a part of fibrin formation can act as chemoattractants for leukocytes and thus independently modulate inflammatory responses.[17,35,45] Activated platelets also release growth factors such as platelet-derived growth factor (PDGFR), a potent chemoattractant for inflammatory cells, and transforming growth factor-B1(TGFB-1), which stimülates extracellular matrix synthesis by local fibroblasts. Consequently, any prolonged disturbance in the coagulation cascade can lead to fibrosis.[35,46]

In a study on autologous hematopoietic stem cell transplantation (ASCT), Ogura and Nakazato[47] showed that pretransplant hyperfibrinogenemia was associated with poor survival in patients with lymphoma who underwent ASCT (5-year OS: $p< 0.001$). On the other hand, they did not find any relationship between the pretransplant hyperfibrinogenemia and survival in multiple myeloma patients (5-year OS $p= 0.17$). But their study was based on a small-sized analysis (47 patients with malignant lymphoma and 57 patients with multiple myeloma). In addition, their study was related to autologous hematopoietic stem cell transplantation.

In another study involving acute myeloid leukemia (AML) patients who did not undergo allo-HSCT, Berger et al.[32] showed that high fibrinogen levels at diagnosis of AML were associated with adverse OS and DFS ($p= 0.0009$ and $p= 0.0076$). However, the patients consisted of newly diagnosed AML patients.

This study has a number of limitations. First, this study was a retrospective, single-center study. Additional prospective multicenter studies are required to confirm the real association between fibrinogen and post-transplant GVHD. Second, In our laboratory devices, serum fibrinogen levels were between 100-350 mg/dl. We determined the cut-off level for abnormality of fibrinogen levels as > 350 mg/dl. The cut off value for fibrinogen has varied in different studies. For example, While the cut-off fibrinogen value was 376 mg/dl in a study in lymphoma patients who underwent auto-HSCT,[47] the cut-off value was 410 mg/dl in a study involving newly diagnosed AML patients.[32]

Consequently, the results of this study suggest that there is a rationale for adequately powered prospective studies to confirm the predictive significance of fibrinogen levels as a biomarker for cGVHD development in allo-HSCT recipients. We propose that plasma fibrinogen levels may become a useful biomarker on the prediction of the development of cGVHD, particularly because of the low associated cost and easy accessibility.

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