https://doi.org/10.48047/AFJBS.6.15.2024.9868-9874

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Association Between Fibrosis Severity and Coagulation Disorders in Non-Cirrhotic Metabolic-Associated Fatty Liver Disease (MAFLD)

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Volume 6, Issue 15, Sep 2024

Received: 15 July 2024

Accepted: 25 Aug 2024

Published: 05 Sep 2024

doi: 10.48047/AFJBS.6.15.2024.9868-9874

Abstract

Background: The term Metabolic-Associated Fatty Liver Disease (MAFLD), introduced in 2020, replaces Non-Alcoholic Fatty Liver Disease (NAFLD) to better reflect liver fat buildup linked to metabolic disorders, including those with a history of alcohol use. MAFLD is often associated with coagulation issues due to liver dysfunction, which can disrupt the balance of blood clotting factors. This study aims to determine the association between MAFLD fibrosis severity and coagulation disorders.

Methods: This cross-sectional study at Dr. Wahidin Sudirohusodo Central General Hospital involved 140 subjects with MAFLD aged ≥ 18 years, with sequential sampling. coagulations factor examination through blood samples with patient consent. Mann Whitney test was used for statistical analysis.

Results: This study involved 140 subjects, with a mean age of 49.6 ± 9.7 years. Obesity was observed in 106 participants (75.7%), hypertension in 42 participants (30%), elevated triglycerides (>150 mg/dL) in 110 participants (78.6%), and diabetes in 41 participants (29.3%). MAFLD severity was categorized as F1 in 53 participants (37.9%) and F2 in 87 (62.1%). This study found that patients with significant fibrosis (F2) had an extended Prothrombin Time (PT), lower platelet count, and higher D-dimer levels compared to patients with mild fibrosis (F1) (all $P<0.05$). Specifically, PT was 21.8 seconds in F2 compared to 13.3 seconds in F1, platelet count was 185 x 10^3/µL in F2 compared to 221 x 10^3/µL in F1, and D-dimer level was 1.85 µg/mL in F2 compared to 1.5 µg/mL in F1.

Conclusion: This study highlights a relationship between the severity of MAFLD fibrosis and changes in coagulation profiles, emphasizing the impact on PT, platelet counts, and D-dimer levels.

Keywords: Metabolic-associated fatty liver disease (MAFLD), coagulation, fibrosis, prothrombin time, platelet, d-dimer

1. Introduction

The 2020 introduction of the term Metabolic-Associated Fatty Liver Disease (MAFLD) marked a change in the way that liver fat buildup and its connection to metabolic dysfunction were understood. The term Non-Alcoholic Fatty Liver Disease (NAFLD) has been replaced by MAFLD, which has distinct diagnostic criteria. In contrast to NAFLD, MAFLD just requires the presence of metabolic abnormalities and does not exclude people with a history of alcohol consumption or other chronic liver diseases.[1]

Coagulation disorders are commonly associated with liver diseases, including MAFLD. Hemostasis, the tightly regulated process of balancing procoagulant and anticoagulant factors, is frequently disrupted when liver function is compromised. The liver synthesizes most coagulation factors, including fibrinogen, thrombin, and factors V, VII, IX, and X. Additionally, post-translational modifications of these factors occur in hepatocytes. Liver damage can thus lead to qualitative and quantitative changes in coagulation factor production, increasing the risk of hemorrhagic diathesis. Conversely, liver dysfunction may also promote a procoagulant state due to elevated inflammatory mediators, altered synthesis of endogenous coagulation inhibitors and fibrinolytic factors, and decreased clearance of von Willebrand Factor (vWF). As a result, patients with liver pathology are susceptible to a “rebalanced” hemostasis, which may lead to either bleeding or thrombosis, depending on the underlying cause and severity of liver disease.[2]

MAFLD encompasses a broad spectrum of conditions, ranging from simple steatosis to advanced fibrosis or cirrhosis, even developing into carcinoma.[3] Studies have suggested that as MAFLD progresses, there is a tendency towards a procoagulant state, marked by increased fibrinogen, decreased Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT), elevated D-dimer levels, and altered platelet counts.[4] However, the exact relationship between MAFLD severity and coagulation disorders remains unclear.

This study seeks to explore the correlation between the severity of fibrosis in non-cirrhotic MAFLD and changes in coagulation profiles. By analyzing coagulation markers such as PT, aPTT, D-dimer, and platelet counts, this research aims to understand whether the progression of MAFLD causes a hypercoagulable state or predisposes patients to bleeding tendencies.

2. Methods

This study was an observational analytical cross-sectional study at the Gastro-entero hepatology Center of Dr. Wahidin Sudirohusodo Central General Hospital, Makassar, from November 2023 until the minimum sample size (140 patients) was reached. Subject recruitment method used in this study was consecutive sampling. The inclusion criteria for this study are: (1) subjects must meet the diagnostic criteria for MAFLD, (2) have a Fibroscan result of ≥ F1, as well as ultrasound findings, and (3) willing to participate and sign the informed consent form. The exclusion criteria include a history of diseases affecting the coagulation system and any history of medication use that may influence coagulation.

MAFLD is diagnosed based on the presence of hepatic steatosis (through imaging or biopsy) and at least one of the following: type 2 diabetes, overweight/obesity (BMI ≥23 kg/m^2), or metabolic dysregulation (e.g., elevated waist circumference, blood pressure, plasma triglycerides, or prediabetes). MAFLD severity is assessed via Fibroscan, with fibrosis staged from F0 (no fibrosis) to F4 (cirrhosis). Coagulation markers are monitored, including PT, aPTT, fibrinogen, D-dimer, and platelet counts, with respective thresholds for normal, elevated, and decreased levels.

The study also considers the impact of antiplatelet and anticoagulant medications on coagulation. Antiplatelet agents, such as aspirin and clopidogrel, inhibit platelet aggregation, while anticoagulants, like warfarin and direct factor Xa inhibitors, prevent clot formation. Coagulation disorders that affect the study outcomes include hypercoagulable states, like factor V Leiden mutation, and hypocoagulable conditions, such as von Willebrand disease. Statistical analysis was conducted using the Mann Whitney test to determine the relationship between MAFLD severity and coagulation parameters, with significance considered if $p < 0.05$.

3. Results

Baseline Characteristics

Table 1 provides an overview of the sample's baseline characteristics. The study included 140 subjects, with a mean age of 49.6 ± 9.7 years. Obesity was observed in 106 subjects (75.7%), hypertension in 42 subjects (30%), elevated triglycerides (>150 mg/dL) in 110 subjects (78.6%), and diabetes in 41 subjects (29.3%). MAFLD severity was categorized as F1 in 53 subjects (37.9%) and F2 in 87 (62.1%).

Table 1. Baseline characteristics

Variable	n (140)	%
Sex		
Male	76	54.3
Female	64	45.7
Age	49.6 ± 9.7 years	
Obesity		
Yes	106	75.7
No	34	24.3
Hypertension		
Yes	42	30
No	98	70
TG		
≥150	110	78.6
<150	30	21.4
DM		
Yes	41	29.3
No	99	70.7
MAFLD Degree		
F1	53	37.9
F2	87	62.1

TG: triglyceride, DM: diabetes mellitus, MAFLD: metabolic-associated fatty liver disease

Table 2 illustrates the relationship between MAFLD fibrosis severity and coagulation disorders. In this study, the mean PT in subjects with significant fibrosis (F2) is significantly higher than those with mild fibrosis (F1) ($P < 0.05$). Platelet counts were also significantly lower in F2 compared to F1 ($P < 0.05$). Additionally, D-dimer levels were significantly elevated in patients with F2 compared to F1 ($P < 0.05$).

Table 1. Relationship between MAFLD fibrosis severity and coagulation disorders

Variable	n	Median	Mean	SD	Min	Max	*p
PT							
F1 (Mild fibrosis)	53	11.7	13.3	10.7	7.2	20.3	**0.000**
F2 (Significant fibrosis)	87	21.6	21.8	2.7	15.3	28.3	
aPTT							
F1 (Mild fibrosis)	53	25.6	25	3.3	20.3	38.5	0.967
F2 (Significant fibrosis)	87	24.6	25	3.5	18.3	33.2	
Platelets							
F1 (Mild fibrosis)	53	213	221	63.2	132	388	**0.001**
F2 (Significant fibrosis)	87	155	185	60.2	123	380	
D-dimer							
F1 (Mild fibrosis)	53	1.6	1.5	0.72	0.3	3.3	**0.022**
F2 (Significant fibrosis)	87	1.8	1.85	0.7	0.5	3.7	
Fibrinogen							
F1 (Mild fibrosis)	53	312	288.1	96.4	121	454	0.260
F2 (Significant fibrosis)	87	376	311	89.2	111	453	

Mann Whitney Test
PT: Prothrombin Time; aPTT: Activated Partial Thromboplastin Time

4. Discussion

Coagulation disorders are common in patients with liver disease and are determined by the degree of liver damage. While overall hemostatic profiles are maintained in MAFLD, most studies report a tendency towards a procoagulant state in these patients.[5]

Adam et al., in a population-based cohort study involving 435 NAFLD patients, found that prolonged PT and significantly reduced platelet counts were associated with Nonalcoholic Fatty Liver Disease (NAFLD).[6] Similarly, Morcillo et al. identified a significant correlation between increased D-dimer levels and the severity of liver steatosis.[7] Dhanunjaya et al. highlighted the importance of assessing D-dimer levels to evaluate fibrinolysis status in liver disease, noting that plasma D-dimer levels rise significantly with increasing liver disease severity.[8]

This study found significant differences in platelet counts related to MAFLD severity, with lower counts (185 x 10^3/μL) in subjects with significant fibrosis compared to those with mild fibrosis (221 x 10^3/μL). The mechanisms underlying reduced platelet counts in MAFLD are multifactorial. Previous research suggests that lower platelet counts are not only negatively correlated with liver fibrosis but also associated with chronic viral hepatitis or alcoholic hepatitis. Additionally, peripheral platelet production, primarily regulated by thrombopoietin (a glycoprotein hormone mostly synthesized in the liver), may be disrupted by excessive lipid deposition and oxidative stress, affecting thrombopoietin synthesis.[9]

5. Conclusions

There is an association between degree of MAFLD fibrosis severity and coagulation disorders, specifically on the PT, Platelet count, and D-dimer.

6. Acknowledgments

This research was supported by the Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia

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