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Original Article

Higher platelet counts are associated with metabolic syndrome independent of fatty liver diagnosis

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Abstract

Background: Platelet count (PC) and fatty liver are both associated with metabolic syndrome (MS), obesity, and type 2 diabetes. While PC increases in obesity and type 2 diabetes, the severity of hepatic fibrosis caused by fatty liver reduces PC. We aimed to investigate the correlation of PC and MS in patients with and without fatty liver.

Methods: We enrolled consecutive patients who received health check-ups at Taipei Veterans General Hospital from 2002 to 2009. Ultrasonography was used to diagnose fatty liver, and MS was diagnosed according to the criteria defined by the International Diabetes Federation Task Force on Epidemiology and Prevention.

Results: Among the 29,797 patients, MS was present in 28.74%. Higher PC was correlated with MS using multivariate analysis, while fatty liver had the strongest association with MS. After dividing the patients by the presence or absence of fatty liver, higher PC was still associated with MS in both groups. The patients were further stratified by age and gender, and MS was correlated with PC among all age groups in women and in men under 60 years of age; however, the association between PC and MS did not reach statistical difference in men older than 60 years.

Conclusion: There is a significant correlation between PC and MS, and the correlation exists independent of gender, age, and fatty liver. PC may act as a surrogate marker for MS, and physicians should be concerned with the presence of MS among patients with high PC.

Keywords: body mass index; fatty liver disease; metabolic syndrome; platelet count; sonography

1. Introduction

Metabolic syndrome (MS) has several risk factors, including central obesity, dyslipidemia, raised blood pressure, and fasting glucose for cardiovascular disease and Type 2 diabetes mellitus.[1,2] Fatty liver disease used to be considered an incidental pathological finding in Type 2 diabetes and

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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obesity; however, it is found to be strongly related with features of MS and even considered to be included in the definition of MS.[3,4]

Higher PC is associated with cardiovascular disease and vascular complications as a result of its role in inflammation and thrombosis; also, platelet activation is observed in people with diabetes, hypertriglyceridemia, and insulin resistance.[5–9] Diabetes, hypertriglyceridemia, and insulin resistance are strongly associated with MS, and previous studies have found that PC is also elevated in patients with MS after adjustment for age, gender, ethnicity, and total cholesterol.[10,11] On the contrary, decreased PC is observed when significant hepatic fibrosis develops in patients with fatty liver, especially in conditions of nonalcoholic steatohepatitis, which is another disease that is highly associated with MS.[12,13]

Although MS, PC, and fatty liver are closely related, the association between PC among patients with MS with or without fatty liver has not been clarified by comprehensive analyses. The present study therefore aimed to investigate the correlation of PC and MS in patients with and without fatty liver from a large-scale cohort in Taiwan.

2. Methods

2.1. Study population

From the years 2002 to 2009, a total of 34,346 consecutive patients received health check-ups in the Healthcare Center at the Taipei Veterans General Hospital.[14–16] After excluding patients with hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and HBV/HCV dual infections, 29,797 patients were enrolled for the final analysis (Fig. 1). All of them received complete clinical evaluations, laboratory examinations, and abdominal sonography. Body mass index (BMI) was defined as body weight in kilograms divided by the square of body height in meters.

Three of the following five abnormal findings are required for a diagnosis of MS according to the joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention[1]: elevated waist circumference (WC, men ≥90 cm or women ≥80 cm), triglyceride (TG) ≥150 mg/dL, low high-density lipoprotein (HDL)−cholesterol (men <40 mg/dL or women <50 mg/dL), systolic blood pressure (BP) ≥130 mm Hg and/or diastolic BP ≥85 mm Hg, and fasting glucose ≥100 mg/dL. Ultrasonography was performed to diagnose fatty liver according to the practice guideline proposed by the American Gastroenterological Association.[17]

This study followed the standards of the Declaration of Helsinki and was approved by the Institutional Review Board of Taipei Veterans General Hospital. As the dataset used in this study consisted of de-identified data from a retrospective cohort, the requirement for written informed consent was waived.

2.2. Biochemical, hematology, and serological markers

Venous blood samples were collected after an overnight fast. Serum HBV surface antigen (HBsAg) was tested by a radioimmunoassay (Abbott Laboratories, North Chicago, IL, USA), and antibodies to HCV were tested using a second-generation enzyme immunoassay (Abbott Laboratories). Serum biochemistry were measured with a Roche/Hitachi Modular Analytics System (Roche Diagnostics GmbH, Mannheim, Germany). Hematological analysis was performed using a Beckman Coulter LH 780 Hematology Blood Analyzer (Beckman Coulter, Miami, FL, USA).

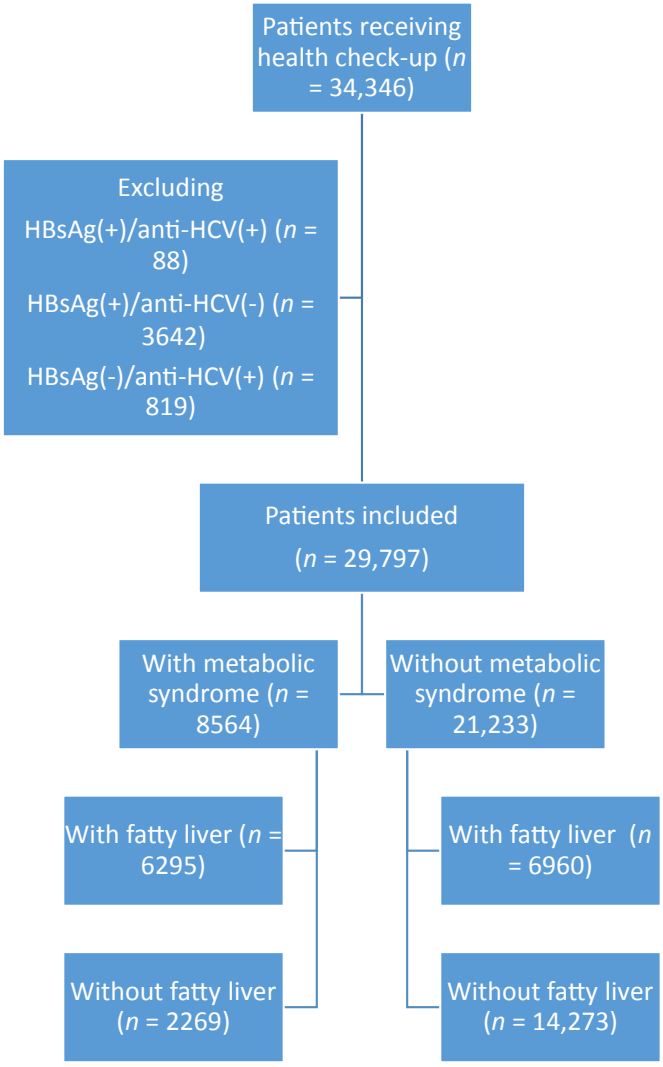

Fig. 1. Flow chart of patients in the study.

2.3. Statistical analysis

The study cohort was first stratified by gender, and patients with fatty liver were selected for further analysis. PC was stratified by age to show association with MS in both men and women. Pearson χ^2 and Student t test analyses were performed to compare categorical and continuous variables with two samples, respectively. Variables with statistical significance ($p < 0.05$) or approximate significance ($p < 0.1$) in univariate analysis were further included in multivariate analysis using a logistic regression model with the forward stepwise selection procedure. A p value < 0.05 was considered

Table 1
Factors associated with male patients with and without metabolic syndrome.

	All (N = 16,098)	Metabolic syndrome (n = 6525)	Nonmetabolic syndrome (n = 9573)	p
BMI, kg/m^2 [a]	24.64 ± 3.38	26.1 ± 3.12	23.64 ± 3.19	<0.001
Age, (y) [a]	53.0 ± 13.7	55.1 ± 12.6	51.5 ± 14.2	<0.001
WC, cm [a]	87.5 ± 9.2	91.8 ± 8.1	84.5 ± 8.7	<0.001
SBP, mm Hg [a]	126.8 ± 17.1	133.6 ± 16.7	122.1 ± 15.9	<0.001
DBP, mm Hg [a]	79.6 ± 14.4	83.8 ± 16.3	76.6 ± 12.1	<0.001
Fasting glucose, mg/dL [a]	97.6 ± 26.8	108.9 ± 35.4	90.0 ± 14.6	<0.001
Cholesterol, mg/dL [a]	198.1 ± 36.3	201.2 ± 37.3	196.0 ± 35.4	<0.001
HDL, mg/dL [a]	47.9 ± 12.1	41.6 ± 9.7	52.2 ± 11.7	<0.001
LDL, mg/dL [a]	126.9 ± 32.2	128.0 ± 32.8	126.2 ± 31.7	0.001
TG, mg/dL [a]	150.1 ± 98.6	205.7 ± 117.6	112.2 ± 58.3	<0.001
AST, U/L [a]	24.1 ± 13.3	25.9 ± 17.3	22.8 ± 9.4	<0.001
ALT, U/L [a]	30.9 ± 24.2	36.1 ± 29.9	27.3 ± 18.6	<0.001
GGT, U/L [a]	29.8 ± 43.2	36.3 ± 55.4	25.4 ± 31.6	<0.001
Platelets, 1000/mm^3 [a]	241.1 ± 57.5	242.9 ± 59.9	239.9 ± 55.8	0.001
Fatty liver (Yes/no) (%)	8710/7388 (54.1/45.9)	4760/1765 (73.0/27.0)	3950/5623 (41.3/58.7)	<0.001

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DBP = diastolic blood pressure; GGT = γ-glutamyltransferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure; TG = triglyceride; WC = waist circumference.
[a] Data expressed as mean ± standard deviation.

to be statistically significant. All statistical analyses were performed with SPSS for Windows version 17.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. Patient characteristics stratified by gender and MS

The demographic data of male patients are summarized in Table 1. The mean age of the male population was 53.0 years, and 6525 (40.53%) had MS. Male patients with MS were older and had higher BMIs, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltranspeptidase (GGT), fatty liver prevalence, and PC.

The demographic data of female patients are summarized in Table 2. The mean age of the female population was 51.3 years, and 2039 (14.88%) had MS. Similarly, female patients with MS were older and had higher BMI, ALT, AST, GGT, and PC. They also had a significantly higher rate of fatty liver compared with those without MS (75.3% vs. 25.8%, $p < 0.001$).

3.2. Factors associated with MS by multivariate analysis

Using multivariate analysis, the presence of fatty liver diagnosed by ultrasonography had the strongest association with MS in both men and women, with odds ratios of 2.205 (95% confidence interval 2.0–2.4) and 3.275 (95% confidence

Table 2
Factors associated with female patients with and without metabolic syndrome.

	All (N = 13,699)	Metabolic syndrome (n = 2039)	Nonmetabolic syndrome (n = 11,660)	p
BMI, kg/m^2 [a]	22.85 ± 3.57	26.65 ± 3.84	22.19 ± 3.07	<0.001
Age, (y) [a]	51.3 ± 12.6	60.0 ± 11.1	49.8 ± 12.3	<0.001
WC, cm [a]	79.5 ± 9.8	90.5 ± 9.3	77.5 ± 8.5	<0.001
SBP, mm Hg [a]	121.3 ± 19.8	138.9 ± 18.4	118.2 ± 18.4	<0.001
DBP, mm Hg [a]	75.2 ± 13.7	83.4 ± 20.9	73.7 ± 11.4	<0.001
Fasting glucose, mg/dL [a]	93.0 ± 21.9	115.3 ± 34.4	89.2 ± 15.9	<0.001
Cholesterol, mg/dL [a]	200.5 ± 37.8	209.0 ± 39.9	199.0 ± 37.2	<0.001
HDL, mg/dL [a]	60.5 ± 15.2	47.1 ± 10.2	62.8 ± 14.8	<0.001
LDL, mg/dL [a]	123.4 ± 33.6	132.2 ± 34.7	121.9 ± 33.1	<0.001
TG, mg/dL [a]	107.3 ± 66.8	187.4 ± 88.0	93.3 ± 50.7	<0.001
AST, U/L [a]	21.8 ± 13.0	26.4 ± 20.6	21.0 ± 10.9	<0.001
ALT, U/L [a]	22.5 ± 18.5	31.8 ± 26.0	20.9 ± 16.3	<0.001
GGT, U/L [a]	18.8 ± 26.3	27.5 ± 31.9	17.3 ± 24.9	<0.001
Platelet, 1000/mm^3 [a]	260.1 ± 62.0	262.2 ± 66.2	259.7 ± 61.2	0.009
Fatty liver (yes/no) (%)	4545/9154 (33.2/66.8)	1535/504 (75.3/24.7)	3010/8650 (25.8/74.2)	<0.001

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DBP = diastolic blood pressure; GGT = γ-glutamyltransferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure; TG = triglyceride; WC = waist circumference.
[a] Data expressed as mean ± standard deviation.

Table 3
Factors associated with metabolic syndrome by multivariate analysis.

	Odds ratio	95% confidence level	*p*
All patients			
Female			
BMI, per kg/m^2	1.311	1.288–1.335	<0.001
Age, per year	1.065	1.059–1.071	<0.001
ALT, per U/L	1.007	1.004–1.009	<0.001
GGT, per U/L	1.004	1.002–1.005	<0.001
Platelets, per 1000/mm^3	1.001	1.001–1.002	0.002
Fatty liver	3.275	2.888–3.714	<0.001
Male			
BMI, per kg/m^2	1.242	1.225–1.259	<0.001
Age, per year	1.032	1.029–1.035	<0.001
ALT, per U/L	1.006	1.004–1.008	<0.001
GGT, per U/L	1.005	1.004–1.007	<0.001
Platelets, per 1000/mm^3	1.002	1.001–1.002	<0.001
Fatty liver	2.205	2.040–2.384	<0.001
Patients with fatty liver			
Female			
BMI, per kg/m^2	1.382	1.339–1.426	<0.001
Age, per year	1.080	1.070–1.089	<0.001
ALT, per U/L	1.010	1.005–1.015	<0.001
Platelets, per 1000/mm^3	1.002	1.000–1.003	0.028
Male			
BMI, per kg/m^2	1.351	1.320–1.383	<0.001
Age, per year	1.032	1.028–1.037	<0.001
ALT, per U/L	1.005	1.001–1.009	0.021
GGT, per U/L	1.005	1.003–1.007	<0.001
Platelets, per 1000/mm^3	1.002	1.001–1.003	0.002
Patients without fatty liver			
Female			
BMI, per kg/m^2	1.270	1.242–1.297	<0.001
Age, per year	1.054	1.046–1.061	<0.001
ALT, per U/L	1.006	1.003–1.009	<0.001
GGT, per U/L	1.005	1.002–1.007	0.001
Platelets, per 1000/mm^3	1.001	1.000–1.002	0.027
Male			
BMI, per kg/m^2	1.185	1.166–1.205	<0.001
Age, per year	1.031	1.027–1.036	<0.001
ALT, per U/L	1.007	1.005–1.009	<0.001
GGT, per U/L	1.005	1.004–1.007	<0.001
Platelets, per 1000/mm^3	1.002	1.001–1.003	<0.001

ALT = alanine aminotransferase; BMI = body mass index; GGT = γ-glutamyltransferase.

interval 2.9–3.7), respectively. Older age and higher BMI, ALT, and GGT were correlated as well (Table 3 and Fig. 2A). Stratifying patients by age revealed that those with fatty liver had a higher rate of MS in all age groups (Fig. 2B). Further analysis disclosed that a higher serum ALT level was associated with MS in people with fatty liver disease and the association existed in all age groups as well (Fig. 2C and 2D).

3.3. J curve phenomenon occurred between PC and MS

The prevalence of MS was further analyzed after the male and female population was separated into 10 quantiles based on PC from 1 (the lowest PC group) to 10 (the highest PC group) (Fig. 3A and 3B). The result showed a J curve phenomenon in both genders, and the phenomenon was more prominent in men. The prevalence of fatty liver was also evaluated after the male and female population was divided to 10 quantiles by PC (Fig. 3C and 3D). No J curve phenomenon was noted between fatty liver disease and PC.

3.4. PC was associated with MS irrespective of fatty liver and age

As fatty liver was the most important determinant of MS in this study, we divided patients by fatty liver disease to further assess the impact of PC on MS. As shown in Table 3, higher PC was still an independent risk factor associated with MS in both genders irrespective of the status of fatty liver.

The prevalence of MS in each age group among men and women is documented in Table 4. With further analysis, higher PC was correlated with MS among all age groups in women and in men under 60 years of age (Fig. 4). The association between PC and MS did not reach statistical significance in men older than 60 years.

4. Discussion

Our large study demonstrated that PC was higher in MS patients, and, more importantly, the association existed after adjusting for age, gender, and the status of fatty liver.

The prevalence of MS is nearly 35% in the United States, according to a recent analysis of the population from 2003 to 2012.[18] While the prevalence of MS was approximately 12% between 1999 and 2002 in Taiwan, it was much higher in the current study (28%), which may have been because of westernization of diet, greater awareness of the syndrome, or higher socioeconomic status of the patients.[19]

Nonalcoholic fatty liver disease (NAFLD) is strongly associated with MS, which is demonstrated by the fact that approximately 90% of the patients with fatty liver have more than one feature of MS, and 33% of them have three or more. NAFLD has also been seen as the hepatic expression of MS.[4] The association between NAFLD and MS exists in not only obese and type 2 diabetes mellitus patients but also nonobese and nondiabetic individuals.[20] In concordance with previous published results, our current study showed that the prevalence of MS increased with age (Fig. 2B), and that fatty liver was the strongest association factor with MS in both genders (Table 3). Of note, people with fatty liver disease who had active hepatic necroinflammation and elevated serum ALT levels were correlated with an even higher rate of MS, and the association existed among all age groups (Fig. 2C and 2D).

Regarding the pathogenic role of mean platelet volume (MPV) and PC in the development of MS, growing evidence suggests that MPV should be regarded as a new inflammation marker and associated with the risk of cardiovascular disease, Type 2 diabetes, and MS.[21] Information with respect to MPV might not have been available in the current study because the data were obtained from routine health check-ups; however, a recently published study demonstrated a close association between MPV and PC.[22] According to published literature, more and larger reactive platelets develop in the presence of conditions such as obesity and endothelial dysfunction under the influence of growth factors and cytokines.[23] Additionally,

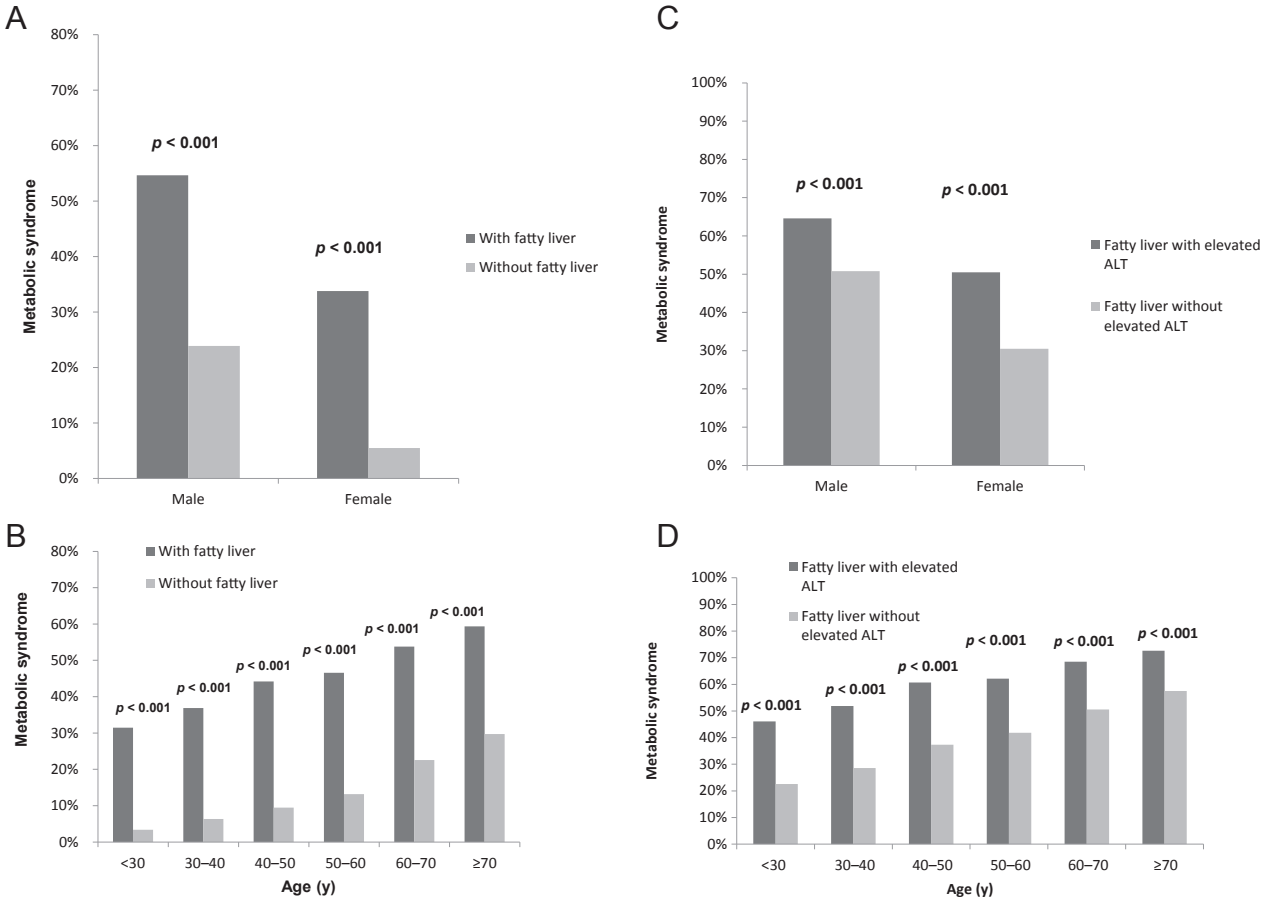

Fig. 2. Metabolic syndrome prevalence divided by (A) gender and fatty liver disease, (B) age and fatty liver disease, (C) gender and ALT among people with fatty liver (D) age and ALT among people with fatty liver. ALT = alanine aminotransferase.

platelets are associated with cardiovascular disease and vascular complications because of their role in inflammation and thrombosis. Stokes et al[5–8] mentioned that platelets deposited chemoattractants on the vessel wall and directly interact with leukocytes and the vessel wall through the mediation of factors, such as P-selectin, glycoprotein (GP)1a, GPIIb/IIIa, and CD40L.[5–8] Platelet activation has also been observed in people with Type 2 diabetes, hypertriglyceridemia, and insulin resistance through the decreased production of nitric oxide and increased oxidative stress.[9] Insulin resistance, obesity, and high triglyceride are the underlying factors for MS, and previous studies have found that PC is elevated in patients with MS after adjustment for age, gender, ethnicity, and total cholesterol.[10,11,24–26] The present study confirmed that PC was significantly associated with MS after adjustment for age, gender, and status of fatty liver (Table 3 and Fig. 4). Although other factors, such as age, BMI, and fatty liver, had higher odds ratios than PC had, multivariate analysis and stratified analysis confirmed that a higher PC was correlated with MS. It indicated that platelet activation might also play an important and independent role in MS. Further prospective studies are warranted to validate this phenomenon.

Different from our study results, a Korean study that enrolled 3827 patients showed that PC and MS were associated in women only.[27] The possible explanations for this discrepancy were different population composition and a larger sample size compared with our current study. Also, our study showed that the association between PC and MS was less significant for participants above 60 years of age, especially in men. Older patients of each ethnicity consistently have lower PC than young adults, and the phenomenon may be explained by a survival advantage to having lower PC or diminished hematopoietic stem-cell reserve.[28,29] Accordingly, the linkage between PC and MS in elderly patients might be weakened, but the hypothesis needs to be further elucidated.

The role of PC in patients with fatty liver is intriguing. Obesity is characterized by chronic inflammation and associated with an increased risk of fatty liver, and insulin resistance is a universal finding in the disease.[30,31] Meanwhile, PC is independently associated with insulin resistance, and the decrease in PC observed in obesity patients after bariatric surgery may reflect decreased hepatic inflammation.[32,33] In contrast, a linear decrease of PC with increasing histological severity of hepatic fibrosis in fatty liver is noticed, especially in conditions of nonalcoholic steatohepatitis. PC is included in several noninvasive scores, which reveal a negative correlation with fibrotic levels in patients with fatty liver diseases.[12,13] While MS is related to PC and fatty liver, the relationship between PC among patients with MS with or without fatty liver was not clarified. Based on this study, we found that PC

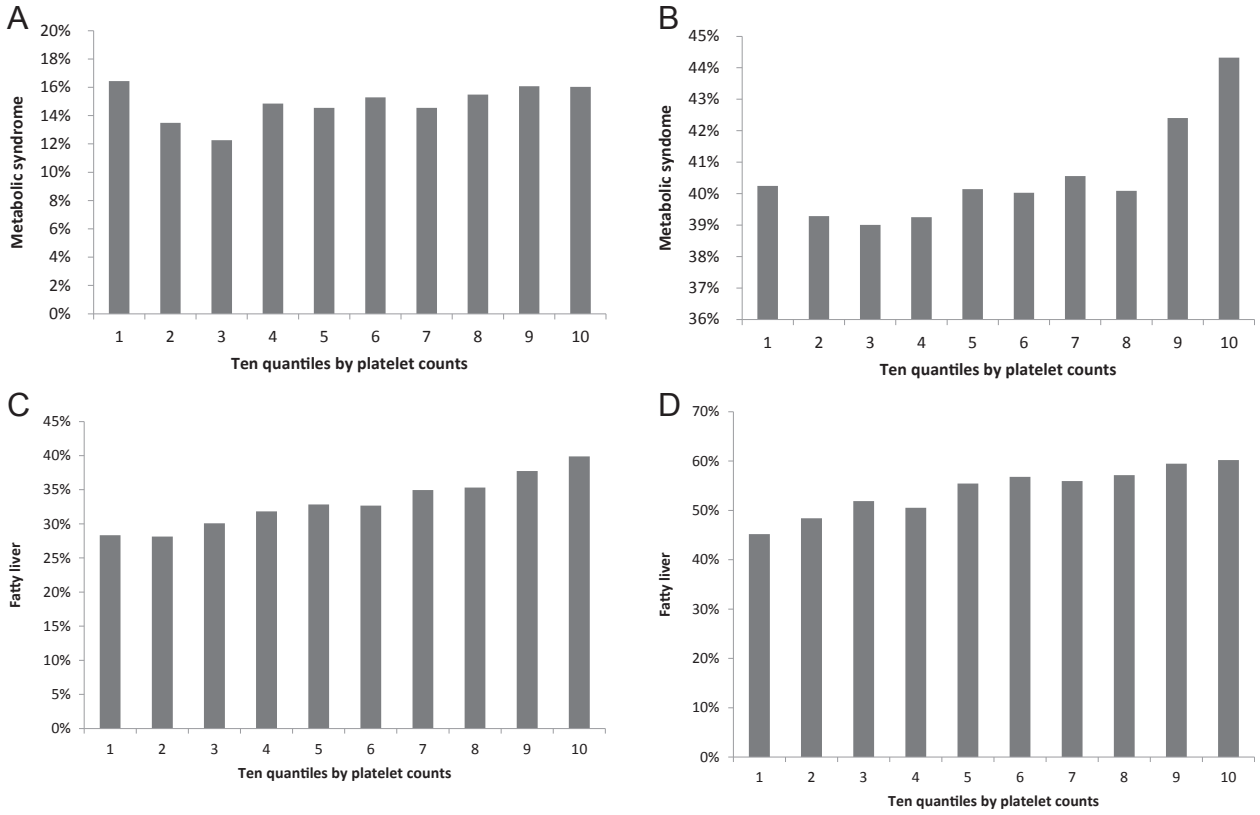

Fig. 3. Metabolic syndrome prevalence in different quantiles based on PC in (A) women and (B) men. Fatty liver prevalence in different quantiles by PC in (C) women and (D) men. PC = platelet count.

was positively related with MS after adjustment for BMI, age, and gender. After dividing patients by the status of fatty liver, PC was still correlated with MS (Table 3).

Our study demonstrated a J curve phenomenon between PC and MS, which is consistent with the concept that extreme values of PC are related to cardiovascular diseases.[34] However, the phenomenon did not apply to the relationship between PC and fatty liver. The exact mechanism is not fully elucidated. However, previous studies showed that the grade of steatosis might reduce with the progression of hepatic fibrosis and reduced PC in patients with fatty liver disease.[35] It may explain the lower PC being paired with increased fibrosis and reduced steatosis.

The strengths of this study were the large sample size and detailed biochemical data, which provide robust evidence to elucidate the correlation between PC and MS. However, several limitations need to be addressed. First, our study population had a high socioeconomic status, and could afford the expense of a physical check-up in a medical center. Whether the results of this study could represent the general population in Taiwan requires further studies to be validated. Second, alcohol consumption was not recorded and assessed. However, the prevalence of alcoholism was reported to be 1.5% in Taiwanese communities; therefore, it might have little influence on the result.[36] Third, PC can be influenced by other factors, including infection, medication, and hematological diseases. Given that the patients received physical check-ups in the hospital, the incidence of acute infection should be minimal. The incidence of drug-induced thrombocytopenia was also low, at about one or two cases per 100,000 per year. Primary hematological diseases account for <5% of patients with elevated PC.[37,38] These factors might have had only a little impact on the current study. Fourth, whether patients had diabetes mellitus, hypertension, or dyslipidemia was unknown

Table 4
Metabolic syndrome prevalence in different age groups.

Male						
Age (y)	<30	30–40	40–50	50–60	60–70	≥70
People with metabolic syndrome (%)	106 (15.6)	561 (28.9)	1418 (39.5)	2265 (43.1)	1246 (48.7)	929 (45.0)
People without metabolic syndrome (%)	547 (84.4)	1382 (71.1)	2175 (60.5)	2991 (56.9)	1314 (51.3)	1137 (55.0)
Female						
Age (y)	<30	30–40	40–50	50–60	60–70	≥70
People with metabolic syndrome (%)	16 (2.3)	49 (2.8)	235 (7.3)	727 (15.2)	599 (27.6)	413 (37.5)
People without metabolic syndrome (%)	673 (97.7)	1719 (97.2)	2968 (92.7)	4043 (84.8)	1568 (72.4)	689 (62.5)

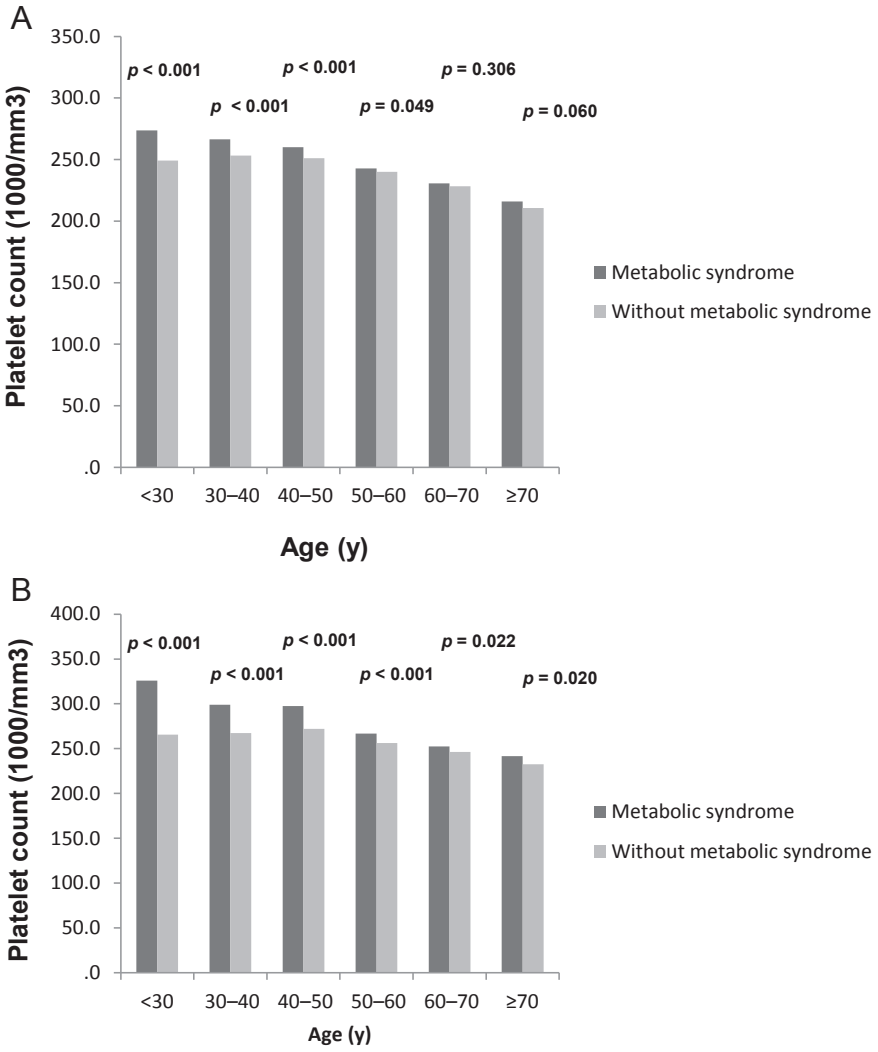

Fig. 4. Platelet count in different age groups stratified by metabolic syndrome in (A) men and (B) women.

and whether they took medication to control these diseases was not documented, either. Fifth, the gold standard for the diagnosis of fatty liver is liver biopsy. However, the invasiveness of that procedure means that it is not feasible for the general population. The lack of biopsy results also prevented us from further analyzing the influence of fibrosis severity. In the present study, the diagnosis of fatty liver was made by ultrasonography and defined by at least two of three abnormal findings: diffusely increased echogenic liver greater than kidney or spleen, vascular blurring, and deep attenuation of ultrasound signal with a sensitivity of 89% and specificity of 93%.[39,40]

In conclusion, the present study indicated a significant correlation between PC and MS, and the association existed independent of gender, age, and status of fatty liver. PC may act as a surrogate marker for MS, and physicians should be concerned with the presence of MS among patients with high PC.

Acknowledgments

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