Clinical Investigation

Predictive Value of Plasma Fibrinogen Levels

in Patients Admitted for Acute Coronary Syndrome

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In recent years, researchers have investigated the relationship between biological markers of inflammation and prognosis in patients who experience acute coronary syndromes; however, the association between plasma fibrinogen and coronary heart disease is still not clear. We studied the prognostic value of fibrinogen, an acute-phase protein that is directly involved in thrombotic processes, by measuring plasma fibrinogen levels serially in 136 patients who had acute coronary syndromes, 142 patients who had stable coronary heart disease, and 82 healthy control participants.

Plasma fibrinogen levels were significantly higher in the patients with acute coronary syndromes (302 ± 90 mg/dL) than in the patients with stable coronary heart disease (274 ± 61 mg/dL) and the control group (243 ± 55 mg/dL) (both P <0.05). We also found significantly higher plasma fibrinogen levels in patients who developed clinical events than in those who did not, at 30 days and 2 years (P <0.05). Cox regression analysis showed that high C-reactive protein values and plasma fibrinogen levels ≥350 mg/dL were predictors of poor long-term prognosis. The adjusted odds ratio (95% confidence interval) for patients who had higher levels of plasma fibrinogen was 5.207.

Plasma fibrinogen level can be used as an independent predictor of major adverse cardiac events during short- and long-term follow-up (P <0.01). The association is independent of other classical risk factors, such as age and sex. ***(Tex Heart Inst J 2010;37(2):178-83)***

Key words: *Acute-phase proteins; biological markers/blood; cardiovascular diseases/blood/etiology; coronary disease/complications/physiopathology; fibrinogen/analysis/classification; logistic models; multivariate analysis; predictive value of tests; prognosis; risk factors; survival analysis*

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Over the past 30 years, coronary heart disease (CHD) has been a leading cause of death in developed countries. Among all types of CHD, patients with acute coronary syndrome (ACS) constitute a major proportion of persons who require admission to cardiac units for urgent care (including invasive treatment, and aggregate anticoagulant and antiplaque drug therapy).[1] To determine prognoses and appropriate treatments, physicians need to evaluate patients' risk of ACS within a short time of admission, which requires awareness of certain risk predictors. The association between inflammation and atherosclerosis has been confirmed, and studies have shown that the plasma level of acute-phase reactants such as C-reactive protein (CRP) and fibrinogen are significantly increased in most patients with ACS.[2,3] We sought to determine the relationship between plasma levels of fibrinogen and the occurrence of major adverse cardiac events (MACEs) at 30 days and 2 years—including death, recurrent ischemia, or reocclusion of the infarct-related artery—among patients who were admitted to the hospital with suspected ACS.

Patients and Methods

Patients

We performed a retrospective study of 278 patients who were confirmed via coronary angiography to have CHD (defined as the presence of ≥50% stenosis of any of the main coronary arteries, according to the American College of Cardiology/American Heart Association lesion classification) and who received percutaneous coronary intervention treatment; and 82 healthy control participants. All were referred from 2005 through 2007. Patients who had experienced unstable angina pectoris, ST-elevation myocardial infarction, or non-ST-elevation myocardial infarction were considered to have ACS. Of the 278 patients who had CHD, 136 patients were diagnosed with ACS and 142 with stable angina pectoris.

We excluded individuals who had a history of recent surgery, trauma, peripheral arteriopathy, hepatic insufficiency (prothrombin ratio, <50%), renal insufficiency (creatinine, >1.5 mg/dL), malignancy, febrile disorders, or acute or chronic inflam-

matory disease at the time of study enrollment; persons who had autoimmune diseases with or without immunosuppressive therapy, or a prior myocardial infarction and ACS; and anyone who was undergoing anticoagulant treatment.

A follow-up period of 2 years was enabled by telephone interviews and reviews of clinical histories. Follow-up was obtained for 100% of the ACS patients at 30 days and in 84% at 2 years; 22 patients were lost to long-term follow-up. The MACEs involved death or reocclusion of an infarct-related artery. The study was approved by the Ethics Committee of the Zhejiang University School of Medicine, and each study participant provided informed written consent.

Laboratory Investigation of Blood Samples

Blood samples for fibrinogen and other biochemical analyses were taken before any treatment was initiated. All analyses were performed in our hospital laboratory. Plasma fibrinogen levels were determined via the Clauss method[4] and use of a BBL™ semiautomated fibrometer (BD Diagnostic Systems; Sparks, Maryland). Other biochemical measurements were determined by standard laboratory methods.

Statistical Analysis

All laboratory data were collected from the patients' records. Data were expressed as mean ± SD. Continuous variables among the 3 groups were compared via 1-way analysis of variance for parametric data and the Kruskal-Wallis test for nonparametric data. Frequency variables were compared by means of the χ^2 test. Also, predictive factors were sought by stepwise logistic regression analysis of variables that were considered to be relevant from a clinical point of view. The variables in the study were age, sex, CRP level, white blood cell (WBC) count, plasma fibrinogen level, diabetes mellitus, dyslipidemia, arterial hypertension, and smoking. Plasma fibrinogen level and WBC count were dichotomized into binary predictors. The cutoff points were 1.0×10^9/L for WBC count and ≥350 mg/dL for plasma fibrinogen level. A Kaplan-Meier analysis (log-rank test) was performed in order to analyze the relationship between survival time and plasma fibrinogen level by comparing survival rates without combined cardiac events in the high- and low-fibrinogen-level groups. To study the effects of other variables, we performed a multivariate Cox regression analysis, including those variables that had a *P* value of less than 0.05 upon stepwise logistic analysis. Confidence intervals (CIs) corresponded to the 95% level. Differences were considered to be significant when the *P* value was less than 0.05. The data conformed to each test by which they were analyzed. All statistical analysis was performed with use of SPSS version 16.0 software (SPSS, Inc.; Chicago, Ill) on a Windows XP platform.

Results

Table I shows the relevant baseline data on the study population. No significant differences were observed in terms of age, sex, or creatinine level between the ACS, stable-CHD, and control groups. Of all 360 study participants, 110 had arterial hypertension (30.5%), 32 had diabetes mellitus (9%), and 66 had dyslipidemia (18%). Incidences of arterial hypertension, diabetes mellitus, and dyslipidemia were similar among the 3 groups.

Comparison of Plasma Fibrinogen Levels between the Groups

The plasma fibrinogen levels of the 3 groups were compared (Table I). The mean levels upon hospital admission were 302 ± 90 mg/dL in the ACS group, 274 ± 61 mg/dL in the stable-CHD group, and 243 ± 55 mg/dL in the control group. There were significant differences between the ACS group and the other 2 groups in plasma fibrinogen level (both $P < 0.05$). Significant differences were also found between the ACS group and each of the other 2 groups in WBC counts and CRP values.

Plasma Fibrinogen Levels and the Development of Clinical Events

Table II shows the plasma fibrinogen levels of ACS patients who developed clinical events during the 1st

TABLE I. Clinical Characteristics of the ACS, Stable-CHD, and Control Groups

Variable	ACS (n=136)	Stable CHD (n=142)	Control (n=82)
Age, yr	56 ±12	54 ± 10	51 ± 15
Men	80 (59)	96 (67)	46 (58)
Smokers	70 (51)	86 (60)	36 (44)
Plasma fibrinogen, mg/dL	302 ± 90	274 ± 61*	243 ± 55*
WBC count, $\times 10^9$/L	10.04 ± 5.03	5.06 ± 2.78*	4.98 ± 2.04*
CRP, mg/dL	3.91 ± 3.67	0.64 ± 0.45*	0.58 ± 0.37*
Diabetes mellitus	10 (7)	14 (10)	8 (10)
Arterial hypertension	42 (31)	46 (32)	22 (28)
Dyslipidemia	20 (15)	28 (19)	18 (23)

ACS = acute coronary syndrome; CHD = coronary heart disease; CRP = C-reactive protein; WBC = white blood cell

Data are expressed as mean ± SD or as number (percentage) of patients.

*$P < 0.05$ in comparison with ACS group, via the Kruskal-Wallis test.

TABLE II. Plasma Fibrinogen Values in the Acute Coronary Syndrome Group upon Hospital Admission According to Clinical Events and the Time of Follow-Up

	First 30 Days			2 Years		
	No. (%)	**Avg.** (mg/dL)	***P* Value**	**No.** (%)	**Avg.** (mg/dL)	***P* Value**
Cardiac death						
Yes	7 (5)	402 ± 101	<0.05	25 (18)	370 ± 122	<0.05
No	129 (95)	296 ± 83		111 (82)	286 ± 68	
Reocclusion of IRA						
Yes	5 (4)	378 ± 94	<0.05	22 (16)	342 ± 114	<0.05
No	131 (96)	299 ± 82		114 (84)	294 ± 70	
Combined						
Yes	12 (9)	392 ± 96	<0.05	33 (24)	361 ± 116	<0.05
No	124 (91)	292 ± 85		103 (76)	282 ± 69	

Combined = cardiac death and IRA; IRA = infarct-related artery

Data are expressed as mean ± SD or as number (percentage) of patients. Statistical analysis was by the Kruskal-Wallis test. $P < 0.05$ is considered statistically significant.

month and by the 2nd year. During a follow-up period of 2 years, 33 patients (24%) with combined MACEs (reocclusion of infarct-related artery, and death) were recorded. Among these patients, 7 deaths (5%) and 5 cases of reocclusion (4%) were reported in the first 30 days; in comparison, 25 deaths (18%) and 22 cases of reocclusion (16%) were reported upon long-term (2-year) follow-up. Our study showed that ACS patients who developed clinical events had significantly higher fibrinogen levels than those who did not ($P < 0.05$), and that the difference was more apparent between patients who developed clinical events during the first 30 days and those who did not.

Comparison of Clinical Characteristics According to Plasma-Fibrinogen-Level Subgroups

Table III shows the clinical characteristics among patients who had higher levels of plasma fibrinogen (≥350 mg/dL), and those who had lower levels (<350 mg/dL) at baseline. A significantly higher percentage of patients with ACS (25%) were in the higher-level plasma fibrinogen category than were patients in the stable-CHD group (3%) and the control group (2%) (both $P < 0.05$). In addition, patients who had higher fibrinogen levels generally had a higher WBC count ($11.9 \pm 7.96 \times 10^9$/L) and CRP value (6.9 ± 4.76 mg/dL) than did patients who had lower fibrinogen levels (WBC count, $6.3 \pm 4.17 \times 10^9$/L; CRP value, 1.23 ± 0.82 mg/dL; both $P < 0.05$). No significant differences were found with respect to age, sex, and other cardiovascular risk factors.

Thirty-Day Clinical Outcomes and Independent Predictors of Combined Endpoints

In a logistic regression analysis, CRP was a significant risk factor that had predictive value, with an odds ratio of 107.333 (95% CI, 1.485–140.779; $P = 0.0007$) (Table IV). In addition, high WBC count ($\geq 1.0 \times 10^9$/L) and high plasma fibrinogen level (≥350 mg/dL) were associated with poor short-term prognosis, with respective odds ratios of 34.000 (95% CI, 4.108–281.404; $P = 0.0011$) and 9.999 (95% CI, 2.752–36.332; $P = 0.0005$). Other variables, such as age, sex, smoking, and a history of diabetes mellitus or arterial hypertension or dyslipidemia, were not significant in this logistic regression analysis.

TABLE III. Clinical Characteristics of Patients According to Plasma Fibrinogen Levels

	Plasma Fibrinogen Level		
Variable	**≥350 mg/dL** (n=40)	**<350 mg/dL** (n=320)	***P* Value**
Age, yr	57 ± 11	50.5 ± 8	0.6
Men	28 (70)	194 (61)	0.7
Smokers	18 (45)	174 (54)	0.4
Diabetes mellitus	6 (15)	26 (8)	0.1
Arterial hypertension	12 (30)	98 (31)	0.8
Dyslipidemia	8 (20)	58 (18)	0.6
CRP, mg/dL	6.9 ± 4.76	1.23 ± 0.82	0.001
WBC count, $\times 10^9$/L	11.9 ± 7.96	6.3 ± 4.17	0.002
ACS group (n=136)	34 (25)	102 (75)	0.01
Stable-CHD group (n=142)	4 (3)	138 (97)	0.01
Control group (n=82)	2 (2)	80 (98)	0.01

ACS = acute coronary syndrome; CHD = coronary heart disease; CRP = C-reactive protein; WBC = white blood cell

Data are expressed as mean ± SD or as number (percentage) of patients.

Statistical analysis was by the Kruskal-Wallis test or the χ^2 test. $P < 0.05$ is considered statistically significant.

TABLE IV. Clinical Characteristics and Occurrence of 30-Day Combined Major Adverse Cardiac Events

Characteristic	Odds Ratio	95% Confidence Interval	*P* Value
Smoker	0.798	0.236–2.699	0.1200
Sex	1.083	0.296–3.964	0.9037
Age	1.504	0.614–3.682	0.3714
DM	1.709	0.438–6.669	0.4406
Dyslipidemia	2.101	0.480–7.837	0.4512
AHT	3.676	0.797–10.526	0.3454
Plasma fibrinogen, ≥350 mg/dL	9.999	2.752–36.332	0.0005
WBC count, >1.0 $\times 10^9$/L	34.000	4.108–281.404	0.0011
CRP, mg/dL	107.333	1.485–140.779	0.0007

AHT = arterial hypertension; CRP = C-reactive protein; DM = diabetes mellitus; WBC = white blood cell

Statistical analysis was performed by logistic multivariate regression analysis. *P* <0.05 is considered statistically significant.

Two-Year Clinical Outcomes and Independent Predictors of Combined Endpoints

In a logistic regression analysis, a fibrinogen level ≥350 mg/dL represented an odds ratio of 9.308 (95% CI, 2.142–38.321; *P*=0.0013) (Table V). The CRP value maintained its significance in predicting combined MACEs, with an odds ratio of 101.237 (95% CI, 1.065–146.474; *P*=0.0009). In addition, WBC count of more than 1.0 $\times 10^9$/L was a significant risk factor to have predictive value, with an odds ratio of 32.02 (95% CI, 3.452–292.819; *P*=0.0017). Age, sex, and other risk factors were not significant in this logistic regression analysis.

Comparison of Clinical Outcomes on the Basis of Plasma Fibrinogen Level

As seen in Figure 1, a survival analysis (Kaplan-Meier, log-rank by level) showed that patients who had higher levels of fibrinogen had a much worse prognosis than did patients who had lower fibrinogen levels. The increasing progression in the occurrence of MACEs from the lower to higher fibrinogen level is in accord with the results shown in Tables I through V. Figure 1 also shows a significantly higher MACE-free survival rate in patients with lower levels of fibrinogen (*P*=0.001).

Multivariate Analysis of 2-Year Independent Predictors of Combined Endpoints

In the aforementioned logistic stepwise regression analysis, we evaluated the individual contribution of various risk factors that could have been relevant to the prognosis of patients in the study. Next, in order to determine the predictive value of variables that had a *P* value of less than 0.05 upon logistic stepwise regression analysis (WBC count, CRP value, and plasma fibrinogen level), we performed a multivariate Cox regression analysis. As Table VI shows, CRP and fibrinogen maintained their significance in predicting MACEs.

Discussion

Although previous studies have reported a strong correlation between plasma fibrinogen concentration and car-

TABLE V. Clinical Characteristics and Occurrence of Long-Term (2-Year) Major Adverse Cardiac Events

Characteristic	Odds Ratio	95% Confidence Interval	*P* Value
Smoker	0.852	0.228–2.634	0.1327
Sex	1.305	0.311–3.851	0.8433
Age	1.704	0.814–3.641	0.3724
DM	1.431	0.349–6.257	0.6452
Dyslipidemia	1.821	0.440–8.233	0.5710
AHT	3.444	0.712–13.204	0.4500
Plasma fibrinogen, ≥350 mg/dL	9.308	2.142–38.321	0.0013
WBC count, >1.0 $\times 10^9$/L	32.02	3.452–292.819	0.0017
CRP, mg/dL	101.237	1.065–146.474	0.0009

AHT = arterial hypertension; CRP = C-reactive protein; DM = diabetes mellitus; WBC = white blood cell

Statistical analysis was performed by logistic multivariate regression analysis. *P* <0.05 is considered statistically significant.

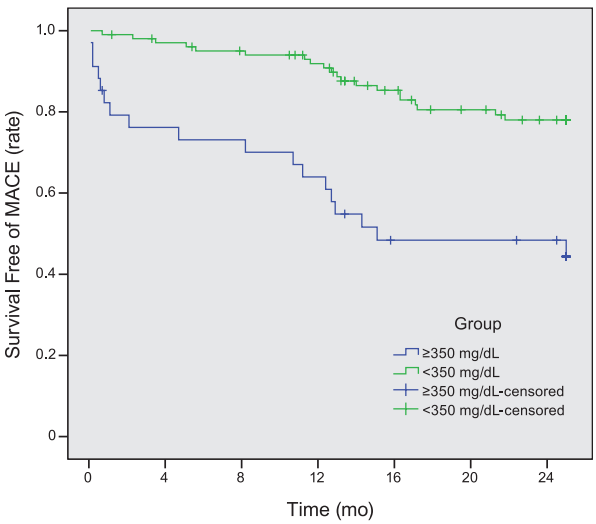

Fig. 1 *Fibrinogen level and combined major adverse cardiac events (MACEs) at follow-up. Statistical analysis was performed by Kaplan-Meier analysis (log-rank test).*

TABLE VI. Multivariate Analysis of Statistically Significant Clinical Variables and Occurrence of Long-Term (2-Year) Major Adverse Cardiac Events

Variable	Odds Ratio	95% Confidence Interval	*P* Value
CRP, mg/dL	1.388	1.215–144.277	0.001
WBC count, >1.0 $\times 10^9$/L	2.652	3.753–299.003	0.301
Plasma fibrinogen, ≥350 mg/dL	5.207	2.323–39.214	0.007

CRP = C-reactive protein; WBC = white blood cell

Statistical analysis was performed by Cox multivariate regression analysis. $P < 0.05$ is considered statistically significant.

diovascular disease risk,[5,6] little attention has been paid to the prognostic importance of plasma fibrinogen level in ACS patients. In our study, we found that an elevated baseline fibrinogen level predicts an increased risk of long-term (2-year) MACEs and a worse prognosis in patients who are admitted for the treatment of ACS.

Several epidemiologic studies have confirmed that fibrinogen is a cardiovascular risk factor. In a 2005 meta-analysis of 31 studies with a total of 7,087 CHD cases (in a Western and North American population), a 1-g/L increase in baseline fibrinogen level rendered an age- and sex-adjusted hazard ratio of 2.42 for CHD (95% CI, 2.24–2.6) and a hazard ratio for CHD of approximately 1.8 after further adjustment for measured values of several established vascular risk factors.[7] One study from India showed that individuals with fibrinogen levels above 300 mg/dL have an odds ratio of 4.4 (95% CI, 2.4–19) for CHD, which further confirms an association between fibrinogen and CHD.[8]

Numerous investigations have confirmed the close relationship between inflammation and ACS.[9,10] In the development of ACS, impaired vascular walls attract inflammatory cells, such as monocytes and T-lymphocytes.[11,12] The interaction between leukocytes and endothelial cells promotes the release of various cytokines (for example, interleukin-6), which stimulate hepatic synthesis of acute-phase reactive proteins, including CRP and fibrinogen.[13] The results of our study were in accord with this hypothesis, showing that the plasma fibrinogen level was significantly higher in ACS patients than in stable-CHD patients or healthy control participants. However, further studies are needed to investigate the expression level of other acute-phase reactive proteins—such as factor VIII and von Willebrand factor—in ACS.

Because CRP has long been recognized as a marker that reliably predicts the occurrence of clinical events in ACS patients[14,15] (which was further confirmed in our study), plasma fibrinogen may also portend the severity of ACS events. Moreover, because fibrinogen is genetically regulated and directly involved in multiple mechanisms that mediate atherothrombotic processes,[16] it becomes an effective predictor of clinical events. For example, fibrinogen can promote endothelial-cell migration[17] and extracellular accumulation of low-density lipoproteins.[18] Fibrinogen can promote platelet aggregation by interacting with GPIIb/IIIa receptors on the platelet membrane.[19] In addition, an elevated level of plasma fibrinogen increases blood viscosity, which causes impaired microcirculatory flow, endothelial shear-stress damage, and predisposition to thrombosis.[20] Therefore, an increased level of plasma fibrinogen—participating in thrombosis after rupture of vulnerable plaque—might exacerbate the development of ACS. In accordance with previous studies,[21,22] our study showed that patients with ACS who developed clinical events typically had significantly higher fibrinogen levels than did patients who did not experience clinical events. We also demonstrated an association between elevated fibrinogen concentration upon hospital admission and a higher incidence of 2-year MACEs.

Moreover, we observed that WBC count was positively related to ACS. White blood cell count is a long-recognized marker of inflammation, and a high WBC count typically indicates a substantial inflammatory response. Previous studies have shown that elevation of WBC count in acute myocardial infarction is associated with adverse outcomes.[23] Our study confirmed a relationship between WBC count and 2-year MACE. We also found higher WBC counts in patients with ACS than in the stable-CHD and control groups, which might indicate a more intense inflammatory response in ACS than in stable CHD, as reflected by CRP value and fibrinogen level.

Conclusion

We found that elevated levels of CRP, WBCs, and plasma fibrinogen are associated with a worse long-term prognosis in patients who have ACS. However, our study is limited by its number of study subjects and by its retrospective nature. Further multicenter clinical and epidemiologic investigations with large populations are needed in order to verify our conclusions.

Acknowledgments

We thank Dr. Tieer Gan of our Department of Pathophysiology for her assistance in data processing and our medical college students for their assiduous data collection.

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