Association between plasma complement factor H concentration and clinical outcomes in patients with sepsis

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Research

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Abstract

Background The complement system is important for defending against pathogens; however, excessive complement activation is associated with a poor prognosis and organ dysfunction in sepsis. Complement factor H (CFH) acts to prevent excessive complement activation and damage to the self through the regulation of the complement alternative pathway.

This study aimed to investigate the association between plasma CFH levels on admission to the ICU and 90-day mortality and organ dysfunction, in patients with sepsis.

Methods This is a single-center prospective observational study conducted from July 2016 to March 2019. Logistic regression analysis and correlation analysis were performed to assess the relationship between the plasma CFH on admission to the ICU and 90-day mortality, and organ dysfunction.

Results This analysis included 62 patients. The plasma CFH levels were significantly lower in 90 day non survivors than those in survivors (70.0 μg/ml [interquartile range (IQR) 51.2 - 97.6] vs 104.8 μg/ml [IQR 66.8 - 124.2] , P=0.006) . The plasma CFH levels were associated with 90 day mortality (OR 0.977 95% CI 0.957 – 0.994, p = 0.01). Correlation analysis showed that the plasma CFH levels were negatively correlated with the Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score and Simplified Acute Physiology Score 2 (SAPS 2) (r= -0.35, P=0.005; r=-0.28, P=0.026; r=-0.30, P=0.019, respectively). Regarding the SOFA scores for each organ, those for the coagulation and neurological components were negatively correlated with the CFH concentration (r=-0.33, P=0.010; r=-0.25, P=0.046, respectively).

Conclusion Lower plasma levels of CFH were associated with sepsis severity and mortality and were correlated with the coagulation and neurological components of the SOFA score in patients with sepsis on admission to the ICU.

Introduction

Sepsis is a leading cause of morbidity and mortality among critically ill patients and a major global medical problem. Its mortality rate has been estimated to exceed 30% [1, 2]. Recently, sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [3].The complement system is an essential component of the innate immune system [4 -6]. Activation of the complement system occurs through three pathways: the classical pathway, the lectin pathway, and the alternative pathway [5, 6]. Complement factor H (CFH) is the major negative regulator of the alternative pathway [7]. CFH acts to prevent excessive complement activation and damage to the self through the repression of the complement alternative pathway [8, 9]. Abnormalities in CFH causing the dysregulation of the alternative pathway have been involved in the pathogenesis of atypical hemolytic uremic syndrome (aHUS), which is a type of thrombotic microangiopathy[10, 11].

The rapid activation of the complement system plays an important role in defending against pathogens; however, the excessive complement activation in sepsis has been reported that to produce the detrimental effects; including neutrophil dysfunction [12,13], coagulopathy [14], and organ failure, leading to a poor outcome [15]. However, it is unclear whether CFH is associated with severity, mortality and organ dysfunction in patients with sepsis. The objective of this study was to assess the association of CFH with 90 - day mortality, sepsis severity and organ dysfunction, including coagulopathy, in patients with sepsis upon admission to the ICU.

Materials And Methods

Study design and population

We conducted a single-center prospective observational study from July 2016 to March 2019 in the surgical and medical intensive Care Unit (ICU) of Shiga University of Medical Science, Japan. Subjects were sepsis patients admitted to that ICU. Sepsis was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock [3]. The exclusion criterion was age of < 18 years. The patients were followed for 90days. Written informed consent to participate in this study was obtained from the patients or their relatives. The protocols for this study were approved by the Scientific-Ethical Committees of Shiga University of Medical Science (protocol ID R2015-220), and adhered to the Declaration of Helsinki principles.

Measurements and outcome

The following data were collected: age, sex, platelet count, PT activity, activated partial thromboplastin time (APTT), fibrinogen level, white blood cell count, C-reactive protein (CRP) level, lactate level, Acute Physiology and Chronic Health Evaluation (APACHE) II score [16], Sequential Organ Failure Assessment (SOFA) score [17], Simplified Acute Physiology Score (SAPS) II [18], and 90-day mortality. The main prognostic outcome was 90-day mortality. The correlations of CFH with each SOFA score and the correlations of CFH with the coagulation test results were investigated.

Blood collection

Blood samples were collected within 24 hours of admission to the ICU. The blood platelet count and white blood cell count were assessed using samples collected in EDTA tubes, and CRP was measured in samples collected in vacuum blood collection tubes with coagulation accelerators and serum separators. Coagulation tests including PT activity, APTT, and fibrinogen were performed with samples collected in sodium citrate tubes. Lactate was measured with blood gas analysis. These blood sample measurements were performed in the hospital’s central laboratory.

Plasma CFH measurement

The plasma CFH level was measured with a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Hycult Biotech, Pennsylvania, USA) in accordance with the manufacturer’s instructions. Blood

samples were collected in vacutainers containing EDTA. The samples were then centrifuged at 3000 rpm for 10 minutes at room temperature. Immediately after centrifugation, the plasma was collected and stored at -80°C until measurement.

Statistical analysis

Data are presented as either frequencies and percentages for categorical variables or medians and interquartile ranges (IQRs) for continuous variables. The chi-squared test or Fisher's exact test was used for the comparison of categorical variables, while the Mann-Whitney U test was used for the comparison of continuous variables. Univariate and multivariate analyses were performed using logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was carried out to evaluate the predictive accuracy. Spearman's test was used for correlation analysis. All tests were two tailed, and p values less than 0.05 indicated statistical significance. Data were analyzed using SPSS software, version 25 (IBM Corp., Armonk, NY, USA).

Results

Study patients

A total of 109 patients met the inclusion criteria. Written informed consent was obtained from 62 of those patients, and those patients were included in the analysis. The characteristics of the patients included in this study are shown in Table 1. The median age was 75 [interquartile range (IQR) 68 – 80] years, and the SOFA score, SAPS 2, and APACHE II score, which are indicators of severity, were 9 [IQR 7 – 12], 55 [41-63] and 23 [16 – 28], respectively. Eighteen patients (29.0%) died within 90 days. In the comparison of 90-day survivors and nonsurvivors, age and all severity scores were significantly higher in 90-day nonsurvivors. Inflammatory markers such as the WBC count and levels of CRP and lactate were not different between the two groups on admission to the ICU; however, the plasma level of fibrinogen was significantly lower in the nonsurvivors than in the survivors. The other coagulation markers did not differ between the two groups.

Table 1 Patient characteristics

Patient characteristics	Total, N = 62	90-day survivors, N = 44	90-day nonsurvivors, N = 18	p value
Age, years	75 (68 - 80)	72 (67 - 77)	77 (72 - 82)	0.022
Male sex, n (%)	42 (67)	29 (66)	13 (72)	0.629
APACHE-II score	23 (16 - 28)	18 (14 - 27)	27 (22 - 34)	0.003
SOFA score	9 (7 - 12)	9 (6 - 10)	12 (9 - 14)	0.001
SAPS 2 score	55 (41 - 63)	49 (35 - 57)	63 (55 - 68)	0.002
Platelet count, $\times 10^9$/l	154 (103 - 231)	158 (119 - 269)	121 (68 - 195)	0.166
PT activity, %	63 (53 - 76)	61 (53 - 73)	64 (53 - 87)	0.375
APTT, seconds	39 (33 - 48)	39 (33 - 45)	41 (32 - 52)	0.633
Fibrinogen, g/l	378 (274 - 524)	417 (308 - 540)	320 (172 - 421)	0.026
White blood cell count, / µl	14.7 (9.3 - 19.9)	14.2 (9.9 - 19.5)	15.3 (8.5 - 19.9)	0.816
CRP, mg/dl	8.6 (5.4 - 18.7)	9.5 (6.1 - 20.4)	7.6 (5.0 - 17.8)	0.174
Lactate, mg/dl	18.0 (12.0 - 37.0)	17.0 (12.5 - 33.5)	22.5 (11.0 - 52.0)	0.433

APACHE-II Acute Physiology and Chronic Health Evaluation, SOFA Sequential Organ Failure Assessment, SAPS 2 Simplified Acute Physiology Score, CRP C-reactive protein

Plasma levels of complement factor H and 90 day mortality

Overall, the median plasma CFH level was 94.1 µg/ml [IQR 61.6 - 120.0], and the CFH level was significantly lower in nonsurvivors than in survivors, with values of 70.0 µg/ml [IQR 51.2 - 97.6] and 104.8 µg/ml [IQR 66.8 - 124.2], respectively (P=0.006) (Figure 1). In univariate logistic regression analysis, age, SOFA score and CFH level were associated with 90-day mortality (OR 1.097, 95% CI 1.016 - 1.185, p = 0.02, OR 1.415 95% CI 1.140 – 1.755, p = 0.02, OR 0.977 95% CI 0.957 – 0.994, p = 0.01). A multivariable logistic regression analysis with age and SOFA score as confounders showed that the plasma CFH levels were not independently associated with 90-day mortality (Table 2). To assess the diagnostic accuracy of CFH for the prediction of 90-day mortality, receiver operating characteristic analysis was performed and showed that the CFH level had significant predictive value, with an area under the curve (AUC) of 0.724 (95% CI, 0.587 – 0.862) (Fig. 2).

Table 2 Univariable and multivariable logistic regression analysis for 90-day mortality

	Univariable analysis			Multivariable analysis		
	OR	95% Confidence interval	P value	aOR	95% Confidence interval	P value
Age, years	1.097	1.016 – 1.185	0.02	1.124	1.005 – 1.256	0.04
SOFA score	1.415	1.140 – 1.755	0.02	1.432	1.099 – 1.865	0.01
CFH (µg/ml)	0.977	0.957 – 0.994	0.01	0.986	0.965 – 1.008	0.205

CFH Complement factor H, OR odds ratio, aOR adjusted odds ratio

Correlation analysis between CFH and severity scores and coagulation factors

Correlation analysis showed that the plasma CFH levels were negatively correlated with the severity scores, namely, the APACHE II score, the SOFA score and the SAPS 2 (r= -0.35, P=0.005; r=-0.28, P=0.026; r=-0.30, P=0.019, respectively) (Figure 3). In the individual SOFA scores for each organ, the scores for the coagulation and neurological components were negatively correlated with the CFH level (r=-0.33, P=0.010;

r=-0.25, P=0.046, respectively) (Figure 4). Plasma CFH levels were positively correlated with the fibrinogen level and PT activity (r=0.31, P=0.015; r=0.32, P=0.012, respectively) and negatively correlated with the APTT (r=-0.35, P=0.007) (Figure 5).

Discussion

In this study, plasma levels of CFH on admission to the ICU were related to severity and mortality in patients with sepsis. The CFH level was correlated with the coagulation and neurological components of the SOFA score and with the fibrinogen level, PT activity and APTT. To our knowledge, this is the first report showing an association between the CFH level and the prognosis of and organ damage in sepsis in a clinical setting.

Our study showed that the plasma levels of CFH were lower in the 90-day nonsurviving group than in the surviving group and were negatively correlated with severity score. Previous studies have reported organ damage due to excessive complement activation in sepsis[19 - 22]. Among the complement components, C3a, C4a, C5a and membrane attack complex (MAC) have been reported to be associated with coagulopathy, organ dysfunction and prognosis [23 - 27]. These complement components and terminal complement complexes are regulated by CFH [7, 8]. Taken together, the decreased plasma CFH concentrations may have resulted in dysregulated complement activation, leading to a worse prognosis.

Concerning coagulation abnormalities, our study showed that lower plasma concentrations of CFH were associated with lower PT activity, lower fibrinogen levels, prolonged APTT and the coagulation components of the SOFA score. Recently, immunothrombosis and immunohemostasis processes involving the innate immune system have been identified as helping prevent the dissemination of and tissue invasion by pathogens [28, 29]; however, excessive activation leads to the development of disseminated intravascular coagulation (DIC), which is characterized by systemic coagulation activation and organ dysfunction due to disordered microcirculation [30]. These coagulation systems have been reported to interact with the complement system, [31 - 34], and excessive complement activation has been reported to be associated with sepsis-associated DIC and a poor prognosis [27, 35, 36]. Mutations of CFH or CFH autoantibodies are causes of aHUS, which is known to cause thrombocytopenia and coagulation disorders [10,11,37, 38]. In this context, the association of lower plasma concentrations of CFH with lower PT activity, lower fibrinogen levels, prolonged APTT and the coagulation components of the SOFA score shown in this study may suggest abnormal coagulation due to excessive complement activation.

This study found a correlation between the plasma CFH concentration and the neurological components of the SOFA score. Patients with sepsis are known to have complications involving the central nervous system, such as sepsis-associated encephalopathy and sepsis-associated delirium [39,40]. Central nervous system complications are also common in aHUS, which is caused by abnormalities in CFH [41 - 44]. It has been reported that complement activation, including C3 and C5a, is associated with central nervous system dysfunction in sepsis [45 - 47]. C5a is reported to play an important role in the blood-

brain barrier (BBB) breakdown in septic encephalopathy [48]. These previous reports support our finding that a lower plasma CFH concentration is correlated with neurological dysfunction.

The results of the present study have several potential implications for future research. Patients with low CFH levels may have a worse prognosis of sepsis. In clinical practice, it is difficult to distinguish among the C3 species related to the outcome because circulating C3 exists in different sizes [25]. It is also difficult to detect C5a due to its low plasma concentration [13]. CFH is one of the most abundant complement components in human blood [7]; therefore, CFH may represent a potential candidate biomarker for excessive complement activation. The pharmacological enhancement of CFH and the administration of CFH may be therapeutic options for patients with sepsis who present with organ dysfunction or coagulopathy due to excessive complement activation.

A major limitation of this study was the small sample size and the single-center nature of the study. We did not measure any complement components other than CFH. Therefore, it was not possible to determine whether the low levels of CFH actually led to excessive complement activation. The CFH level was correlated with the severity scores; therefore, CFH is not a prognostic factor for 90-day mortality independent of these severity scores. It took three or four hours from the collection of the sample from the arterial line to centrifugation and storage at -80°C, and it is possible that the CFH concentration had changed by the time of measurement. However, all measurements were performed under the same conditions with regard to the time from blood sample collection to measurement, and we believe that the results of the study are reliable.

Conclusion

Lower plasma levels of CFH were associated with increased severity and mortality in patients with sepsis on admission to the ICU and were correlated with central nervous system dysfunction and coagulopathy. Further large-sample studies are needed.

Abbreviations

CFH: Complement factor H; ICU: intensive care unit; IQR: interquartile range; APACHE II: Acute Physiology and Chronic Health Disease Classification System II; SOFA: Sequential Organ Failure Assessment; SAPS 2: Simplified Acute Physiology Score 2; aHUS: atypical hemolytic uremic syndrome; ROC: receiver operating characteristic; AUC: area under the curve; MAC: membrane attack complex; DIC: disseminated intravascular coagulation; BBB: blood-brain barrier

Declarations

Acknowledgments

None

Founding

None

Authors' contributions

JS, KF and YE designed the study. The data collection and evaluation were conducted by JS, KF, YT, and YE. TT and TS supported the study design, data collection, and evaluation. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics declarations

Ethics approval and consent to participate

The study protocol was approved by our local research ethics committee (protocol ID R2015-220), and informed consent was obtained from all participants.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

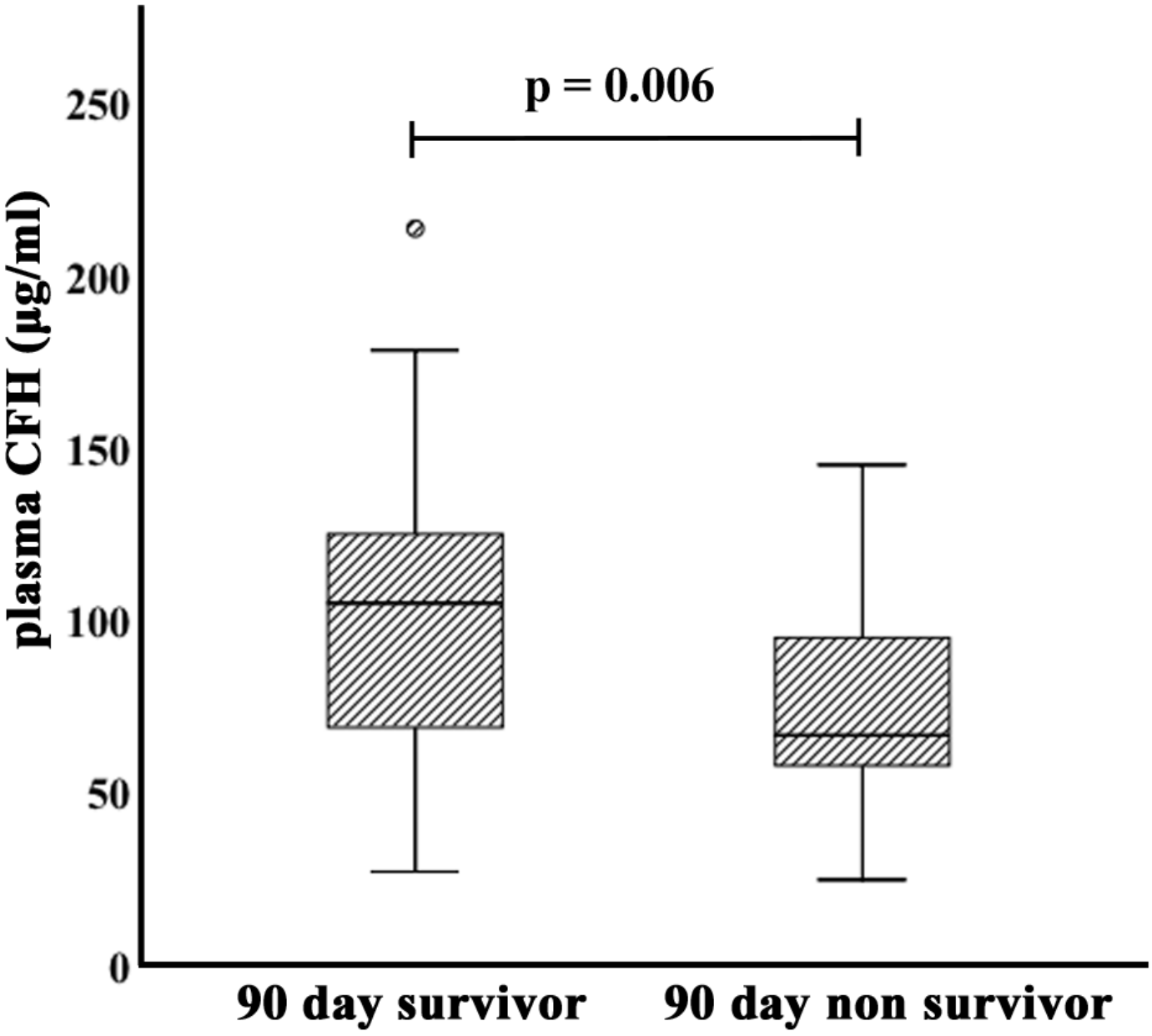

Figure 1

Plasma levels of CFH and 90-day mortality Plasma CFH levels were significantly lower in nonsurvivors than in survivors.

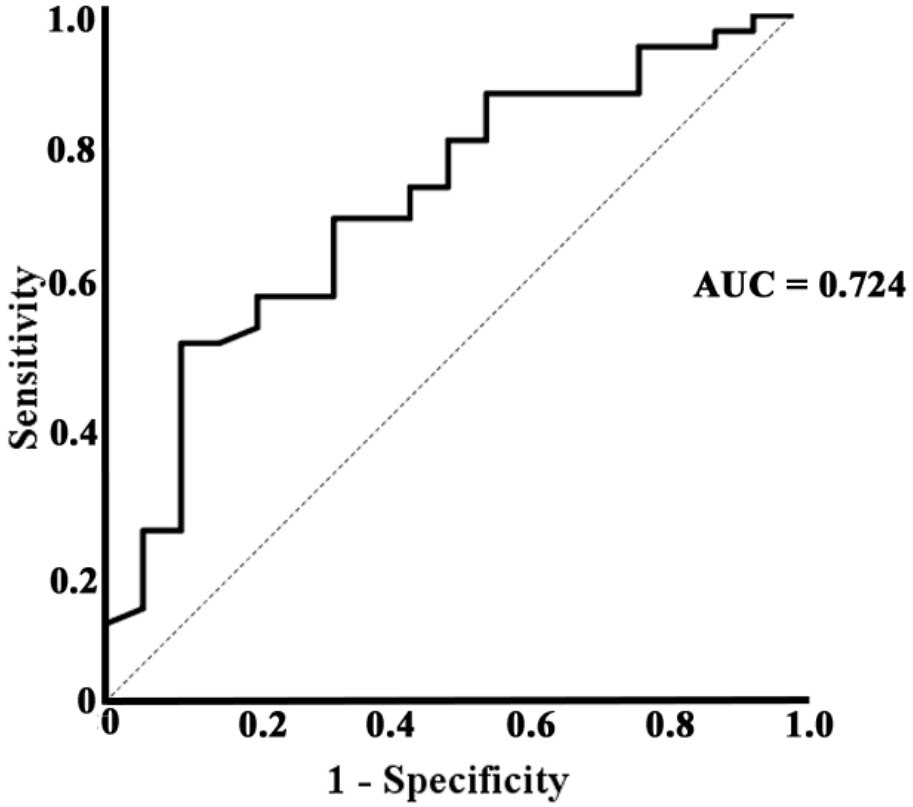

Figure 2

ROC curve for CFH as a predictor of 90-day mortality The receiver operating characteristic curve analysis assessing the diagnostic accuracy of CFH for the prediction of 90-day mortality showed that it had significant predictive value.

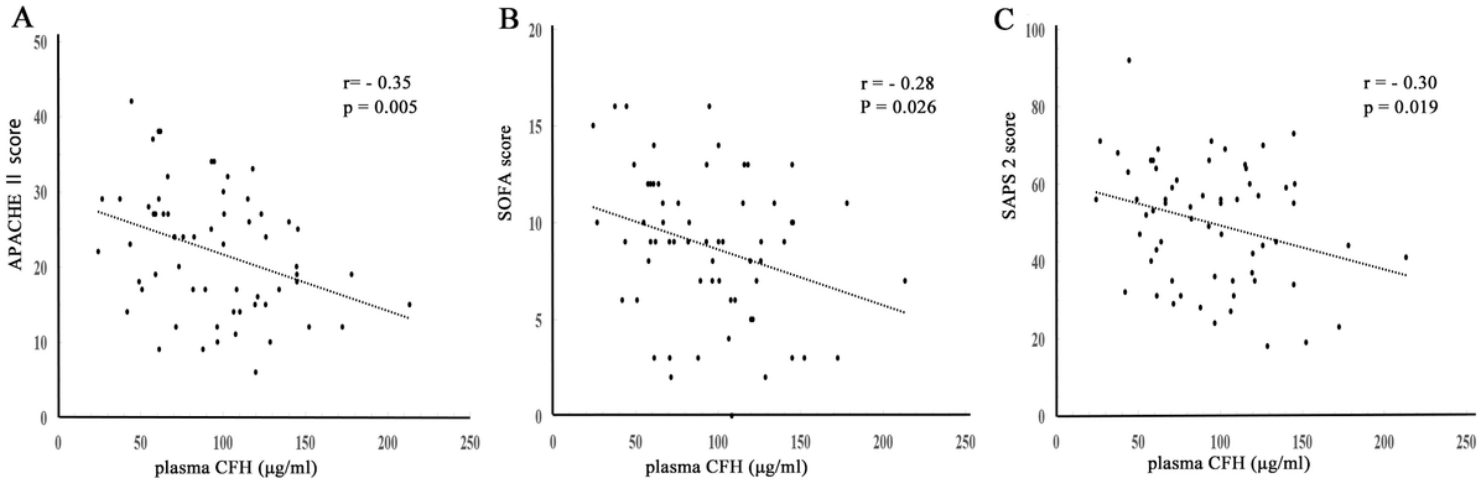

Figure 3

Correlation analysis between CFH and severity scores Correlation analysis showed that the plasma CFH levels were negatively correlated with the severity scores, namely, the APACHE II score, SOFA score, and SAPS 2.

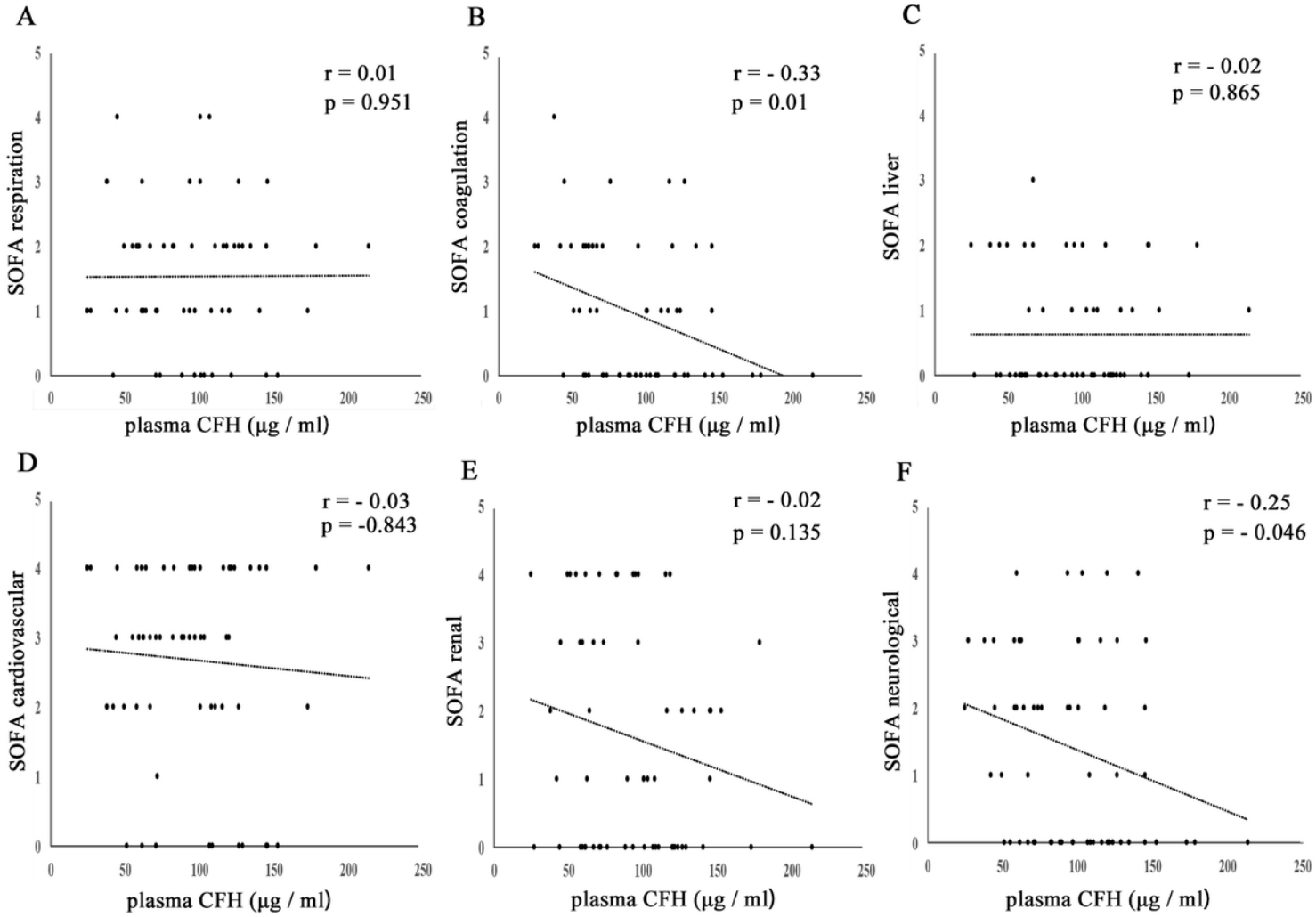

Figure 4

Correlation analysis between CFH and the SOFA score for each organ The coagulation and neurological components of the SOFA score were negatively correlated with the CFH level.

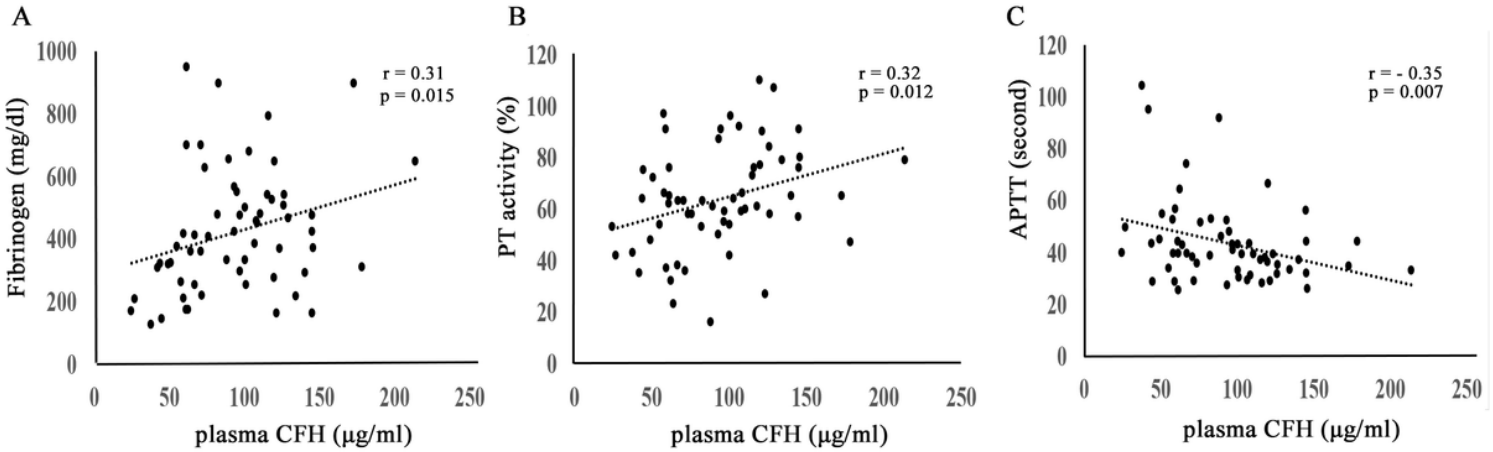

Figure 5

Correlation analysis between CFH and coagulation test results The CFH level was positively correlated with the fibrinogen level and PT activity and negatively correlated with the APTT.