ORIGINAL RESEARCH—CLINICAL

The Prognostic Significance of the Platelet Count in Alcoholic Hepatitis

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BACKGROUND AND AIMS: Thrombocytopenia is present in up to 76% of patients with chronic liver disease, and lower platelet counts (PCs) are associated with greater severity of portal hypertension. In this study, we assess the relationship of PC in patients with a clinical diagnosis of severe alcoholic hepatitis (SAH) with clinical severity and response to corticosteroid (CS) therapy. **METHODS:** Clinical characteristics, treatment, and hospital outcomes for patients admitted with SAH were analyzed from an electronic health record system. Patients were categorized based on admission PC (k/uL) into 5 categories: <50, 50–99, 100–149, 150–199, and ≥200. Frequency of complications (acute kidney injury, ascites, and hepatic encephalopathy), length of stay, and admission to an intensive care unit were analyzed across PC categories. Characteristics of patients who did and did not receive at least 4 days of CS therapy were compared. **RESULTS:** Among 159 patients, 15 (9.4%) were in the PC < 50 category, 42 (26.4%) in PC 50-99, 51 (32%) in PC 100–149, 23 (14.5%) in PC 150–199, and 28 (17.6%) in PC ≥ 200. A higher admission PC was associated with greater white blood cell count, absolute neutrophil count, and total bilirubin ($P < .05$). Patients with higher PC on admission were more likely to receive steroids. PC was inversely associated with Lille score at treatment day 4 ($P < .05$). **CONCLUSION:** A higher PC in SAH was associated with a greater inflammatory response and total bilirubin. Patients with a higher PC were more likely to receive CS and have a favorable treatment response.

Keywords: Alcoholic Hepatitis; Platelet Count; Corticosteroids; Interleukin-6

Introduction

Alcoholic hepatitis (AH) develops in up to 35% of patients with heavy, sustained alcohol use [1] and is a cause of substantial morbidity and mortality. It accounts for approximately 18.4% of alcohol-associated liver disease hospitalizations in the United States (US) [2] and was estimated in 2010 to be responsible for 1% of all US hospital admissions.[3] Frequent emergency department visits, inpatient admissions, and high mortality further contribute to health-care-related costs, with total expenditure exceeding an estimated $1.5 billion for insured patients in the US in 2013.[3] This estimate grossly underestimates the current economic and social burden of AH which has been steadily increasing annually and rose dramatically during the COVID-19 pandemic.[4]

AH presents with a wide clinical spectrum of disease severity, ranging from asymptomatic cases to severe liver failure with jaundice, fever, malaise, and tender hepatomegaly.[5] Patients with mild disease have a favorable outcome. Although prolonged abstinence can lead to marked improvement in liver function among those with severe AH (SAH), severe disease is associated with 1- and 6-month mortality approaching 30% and 40%–70%, respectively.[3]

Prognostic models for AH that are employed for therapeutic decisions include the total serum bilirubin level (TBili) and international normalized ratio (INR). Severity is mostly commonly defined by the Maddrey discriminant function (DF) and more recently by the Model for End-Stage Liver Disease (MELD). The mainstay of treatment is corticosteroids (CS), and in select cases, they significantly reduce short-term mortality but also carry the risk of adverse events such as infection, sepsis, and gastrointestinal bleeding.[6]

Thrombocytopenia (TCP) is the most common laboratory abnormality in patients with chronic liver disease and is present in up to 76% of patients.[7] Multiple pathophysiologic processes lead to TCP in the cirrhotic patient, the most important of which are reduced platelet production due to impaired hepatic thrombopoietin (TPO) production and splenic sequestration due to portal hypertension. In patients with AH, the platelet count (PC) can also be affected by the acute effects

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Abbreviations used in this paper: AH, alcoholic hepatitis; ANC, absolute neutrophil count; CP, Child-Turcotte-Pugh; CS, corticosteroid; DF, Maddrey discriminant function; HD, hospital day; IL-6, interleukin-6; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; NST, no specific treatment; PC, platelet count; SAH, severe alcoholic hepatitis; SI, splenic index; TBili, total serum bilirubin level; TCP, thrombocytopenia; TD, treatment day; TPO, thrombopoietin; US, United States; WBC, White Blood Cell.

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of alcohol with direct impairment of megakaryopoiesis, platelet toxicity, and accelerated platelet apoptosis.[7]

A low PC is an important prognostic marker in patients with chronic liver disease. There is an inverse relationship between PC and severity of fibrosis, portal hypertension, and prognosis. Adding the PC to the albumin-bilirubin grade is more accurate than the Child-Turcotte-Pugh (CP) score in predicting survival of patients with hepatocellular carcinoma undergoing resection.[8] A low PC is also an independent risk factor for varices and may be used to predict the presence of varices with a high bleeding risk.[9] To date, there is only limited information on the PC in patients presenting with AH. In this study, we assess the spectrum of platelet counts in patients hospitalized with a clinical diagnosis of SAH and correlate its level with clinical severity and response to CS therapy.

Methods

Subjects

A single-center, retrospective cohort study was conducted on patients with a discharge diagnosis of alcoholic liver disease (International Classification of Diseases, 9th or 10th revision, clinical modification codes K70.10, K70.11, K70.40, K70.41, 571.5, 572.52, 572.8, 789.59) who were admitted from January 2016 to June 2020. Data were extracted from an electronic health record system (EPIC) using Clinical Looking Glass, (Emerging Health Information Technology, Yonkers, NY). EPIC is a computerized patient database that contains comprehensive data, including patient demographics, hospitalizations, discharge diagnoses (International Classification of Diseases codes), laboratory and imaging results, histopathology, endoscopic and surgical procedures, and medications. Clinical Looking Glass is a proprietary software program that permits exploration of the database contained within EPIC.

Eligible patients satisfied SAH criteria including age $\geq$18 years, documentation of ongoing heavy alcohol consumption, onset of jaundice within prior 8 weeks, $<$60 days of abstinent before onset of jaundice, serum total bilirubin $\geq$3.0 mg/dL, aspartate aminotransferase $\geq$50, aspartate aminotransferase/alanine aminotransferase $\geq$1.5, and both values $<$400 IU/L for enrollment into a clinical trial.[10] Exclusion criteria included liver transplantation or other underlying liver disease, absence of documentation of ongoing heavy alcohol consumption, hepatocellular carcinoma or other active malignancies, biliary obstruction, clinically significant upper gastrointestinal bleeding, HIV infection, pre-existing hemodialysis, kidney transplantation, kidney injury with serum creatinine $>$2.5 mg/dL, sepsis, other serious medical conditions that would significantly alter the

Table 1. Admission Platelet Categories and Clinical Characteristics

Characteristic mean (SD)	PC $<$ 50 (N = 15)	PC 50–99 (N = 42)	PC 100–149 (N = 51)	PC 150–199 (N = 23)	PC $\geq$ 200 (N = 28)	*P* value
Age (y)	51.3 (8.3)	51.8 (10.9)	52.1 (10.8)	48.6 (.9)	45.5 (10.9)	.0656
Male (%)	80.0% (12)	69.0% (29)	56.9% (29)	65.2% (15)	64.3% (18)	.3086
PC (k/uL)	38.5 (8.9)	74.4 (12.3)	122.8 (14.4)	171.6 (18.2)	283.4 (77.2)	-
Hgb (k/uL)	11.8 (2.5)	10.2 (3.4)	10.5 (3.4)	10.1 (4.7)	10.4 (7.0)	.1666
WBC (k/uL)	5.3 (2.6)	6.7 (3.4)	8.2 (3.4)	11.7 (4.7)	17 (7.0)	**<.0001**
ANC (k/uL)	3.8 (2.5)	4.7 (3.2)	5.9 (3.2)	9.0 (4.6)	13.6 (6.7)	**<.0001**
Na (mEq/L)	135.7 (5.0)	135.5 (5.2)	134.8 (4.8)	132.7 (6.0)	133 (4.2)	.0919
BUN (mg/dL)	9.2 (4.2)	11.9 (11.1)	12.1 (6.8)	12.4 (10.2)	13.2 (7.3)	.7085
Cr (mg/dL)	0.75 (0.28)	0.86 (0.43)	0.83 (0.41)	0.87 (0.35)	0.90 (0.53)	.8227
Alb (g/dL)	3.2 (0.62)	2.9 (0.71)	2.9 (0.57)	2.8 (0.44)	2.9 (0.63)	.4380
TBili (mg/dL)	7.6 (6.5)	7.9 (5.0)	9.2 (6.9)	10.9 (6.3)	13.8 (9.3)	**.0054**
ALT (U/L)	44.8 (13.2)	45.6 (34.5)	60.7 (40.7)	56.6 (51.1)	59.8 (30.8)	.2553
AST (U/L)	166.3 (68.4)	151.4 (88.4)	185.9 (96.5)	174.4 (104.3)	201.2 (92.3)	.2207
PT (s)	18.8 (6.9)	17.4 (3.7)	16.4 (3.9)	17.3 (6.8)	17.9 (5.2)	.4723
INR	1.8 (0.64)	1.7 (0.37)	1.6 (0.41)	1.7 (0.59)	1.7 (0.55)	.6188
DF	38.7 (36.5)	30.9 (22.4)	29.4 (21.9)	35.5 (34.7)	41.1 (30.0)	.3591
MELD	19.5 (5.0)	20.2 (4.5)	19.6 (4.6)	20.9 (5.5)	22.3 (6.6)	.2312
MELD-Na	20.5 (5.9)	21.8 (4.8)	21.6 (4.8)	23.9 (5.7)	24.6 (6.4)	**.0446**
Child-Pugh	9.5 (2.2)	9.9 (2.2)	10 (1.8)	9.7 (1.6)	10.2 (1.9)	.8370
AKI/HRS	6.7% (1)	16.7% (7)	11.8% (6)	13% (3)	17.9% (5)	.51
Ascites, mild	53.3% (8)	61.9% (26)	64.7% (33)	70% (16)	60.7% (17)	.74
Ascites, moderate/large	6.7% (1)	23.8% (10)	29.4% (15)	4.3% (1)	14.3% (4)	.25
HE, mild	13.3% (2)	14.3% (6)	11.8% (6)	8.7% (2)	21.4% (6)	.38
HE, overt	20.0% (3)	14.3% (6)	11.8% (6)	0.0% (0)	10.7% (3)	.17

Values represented as mean (± SD) or % (count). Significant difference between baseline characteristic and PC, category on ANOVA, and chi-squared (for continuous and categorical variables, respectively) ($<$.05) are represented by *P* values in bold. AKI/HRS, acute kidney injury or hepatorenal syndrome; Alb, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; Cr, creatinine; HE, hepatic encephalopathy; Hgb, hemoglobin; PT, prothrombin time; SD, standard deviation.

hospital course, active substance abuse, patients who were transferred from outside facilities, and absence of laboratory criteria. Only the first index case was analyzed for those with more than 1 admission.

Admission PC Category and Clinical Characteristics

The study cohort was stratified into 5 admission PC categories (k/uL): <50, 50–99, 100–149, 150–199, and ≥200.[11] PC categories were based on standard clinical definitions of mild, moderate, and severe TCP. PCs within the normal range were divided into 2 categories to maintain a standardized PC distribution of 50 cells per microliter. Clinical characteristics of subjects were recorded, and DF, MELD, Na-MELD, and CP scores were calculated. Clinical characteristics between the various PC categories were then compared.

Clinical Characteristics Based on PC Category and HD4 Admission Status

Hospital status at day 4 after admission (HD4) was recorded as discharge before vs at HD4 or later. For those discharged before HD4, the reason for discharge was recorded as improvement, discharge against medical advice, or death. Clinical characteristics for patients based on PC category and hospital status at HD4 were compared.

Baseline Characteristics and Outcomes Based on PC Category and SAH Treatment

Administration of specific treatment for SAH (no specific treatment [NST], CS, granulocyte colony-stimulating factor, or pentoxifylline) during the first 4 hospital days was recorded. For patients receiving NST, baseline and HD4 laboratory test results were recorded, and DF, MELD, Na-MELD, and 4-day Lille (observation) scores were calculated.[12] Differences in changes in the parameters were compared between the various PC categories. For patients who received CS for at least 4 days, liver tests at the start (TD0) and at treatment day 4 (TD4) were recorded, and 4-day Lille (CS treatment) scores calculated.

Estimation of Spleen Size

Spleen size was assessed by calculating the splenic index (SI) on abdominal computed tomography or magnetic resonance imaging obtained during hospitalization.[13] Abdominal ultrasound was used to determine SI if cross-sectional imaging was not available. Analysis was performed controlling for height using the SI-to-height ratio. SI was analyzed by correlation with PC category at admission and gender.

Statistical Analysis

Comparison of PC category characteristics at admission was performed. Hospital outcomes were analyzed based on admission PC, PC category, and treatment provided. Demographic and clinical characteristics of the study cohort were tabulated as means and standard deviations or counts and percentages. The distribution of categorical variables was compared using Spearman's chi-squared test or Fisher's exact test. Continuous variables were compared using the analysis of variance. A linear regression model was used to examine the association between continuous day-4 Lille score and the continuous PC. A logistic regression model was used to examine day-4 Lille score and its association with the continuous PC. Statistical significance was set at P value <.05. All analyses were performed using SPSS (IBM).

Table 2. Patient Admission Characteristics, Without Specific Therapy, Stratified by LOS

Characteristic, mean (SD)	LOS < 4 (n = 19)	LOS ≥ 4 (n = 116)	P value
Age (y)	51.4 (11.6)	51.1 (10.2)	.916
Male	73.7% (14)	64.6% (75)	.432
PC (k/uL)	143.5 (60)	129.0 (81.82)	.377
Hgb (k/uL)	10.7 (1.9)	19.0 (2.36)	.551
WBC (k/uL)	7.1 (2.4)	9.0 (5.35)	**.006**
ANC (k/uL)	4.6 (1.9)	7.0 (4.861)	**<.0005**
Na (mEq/L)	135.0 (5)	135.0 (5.366)	.585
BUN (mg/dL)	11.0 (5)	12.0 (9.41)	.326
Cr (mg/dL)	0.83 (0.18)	1.00 (0.45)	.325
Alb (g/dL)	3.1 (0.6)	3.0 (0.643)	.115
TBili (mg/dL)	5.7 (2.2)	9.0 (6.9)	**<.0005**
ALT (U/L)	76.0 (51)	52.0 (36.28)	.069
AST (U/L)	188.0 (97)	170.0 (94.1)	.446
PT (s)	14.5 (2.3)	17.0 (4.95)	**<.0005**
INR	1.4 (0.2)	2.0 (0.472)	**<.0005**
DF	16.0 (18.11)	31.6 (26.26)	**<.0005**
MELD	16.0 (2)	20.0 (5.08)	**<.0005**
MELD-Na	18.2 (4)	22.0 (5.57)	**<.0005**
Child-Pugh	8.6 (1.5)	10.0 (1.96)	**<.0005**

T-test for unequal variance. Values presented as mean (SD). Significant values are presented in bold (P < .05).
Alb, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; Cr, creatinine; Hgb, hemoglobin; LOS, length of stay; PT, prothrombin time; SD, standard deviation.

Results

Subjects

Records of 906 patients with a diagnosis of alcoholic liver disease were evaluated. One hundred fifty-nine (17.5%) patients satisfied criteria for SAH after excluding 116 (12.8%) for liver transplantation or other underlying liver disease; 82 (9.1%) for absence of documentation of ongoing heavy alcohol consumption; 85 (9.4%) for hepatocellular carcinoma or other active malignancies; 31 (3.4%) for biliary obstruction; 75 (8.3%) for clinically significant upper gastrointestinal bleeding; 16 (1.8%) for HIV infection; 9 (1.0%) for preexisting hemodialysis, kidney transplantation, or kidney injury with serum creatinine >2.5 mg/dL; 69 (7.6%) for sepsis; 34 (3.8%) for other serious medical conditions that would significantly alter the hospital course; 3 (0.3%) for active substance abuse; 94 (10.4%) patients who were transferred from outside facilities, and 133 (14.7%) due to absence of laboratory criteria. All patients included in the study were admitted to the hospital with alcoholic liver disease as the major diagnosis and met criteria for SAH.

Table 3. Baseline and HD4 Assessment for Patients With LOS ≥4 Receiving NST

Characteristic, mean (SD)	PC < 50 (n = 9)		PC 50–99 (n = 30)		PC 100–149 (n = 28)		PC 150–199 (n = 10)		PC 200 (n = 25)		*P* value across PC category at HD0 (ANOVA)
	HD0	HD4	HD0	HD4	HD0	HD4	HD0	HD4	HD0	HD4	
Age (y)	50.6 (8.9)		50.6 (11.5)		53.7 (11.3)		53.7 (10.2)		41.2 (8)		
Male (%)	77.8 % (7)		73.3% (22)		57.1% (16)		50.0% (5)		52.0% (13)		-
PC (k/uL)	37.0 (9)	55.0 (28)	73.0 (12)	78.0 (20)	126.0 (14)	110.0 (38)*	179.0 (19)	141.0 (58)*	223.0 (114)	214.0 (177.5)	-
Hgb (k/uL)	12.7 (2.5)	11.4 (2.3)	10.2(2.6)	9.8 (2.1)	10.5 (2.1)	9.9 (1.5)	10.3 (2.7)	9.8 (2.5)	10.0 (1.6)	9.6 (3)	**.015**
WBC (k/uL)	5.2 (3.2)	5.0 (3.2)	6.6 (3.8)	5.8 (2.3)	8.5 (4)	8.3 (3.5)	11.3 (4.7)	10.2 (6.3)	15.0 (5.9)	13.9 (7.3)	**<.0005**
ANC (k/uL)	3.7 (3.1)	3.2 (2.7)*	4.6 (3.5)	3.8 (1.9)	6.4 (4)	5.7 (3.2)	9.0 (4.2)	8.0 (5.6)	12.0 (5.4)	10.7 (6.6)	**<.0005**
Na (mEq/L)	137.0 (3)	138.0 (3)	135.0 (5)	136.0 (4)	134.0 (6)	136.0 (5)*	131.0 (6)	133.0 (6)	133.0 (5.8)	135.2 (5.1)*	.053
BUN (mg/dL)	8.0 (3)	9.0 (4)	13.0 (13)	12.0 (6)	12.0 (6)	10.0 (4)	16.0 (14)	12.0 (10)	12.0 (5.9)	9.9 (5.9)	.612
Cr (mg/dL)	0.64 (0.17)	0.60 (0.15)	0.90 (0.46)	0.87 (0.4)	0.89 (0.49)	0.76 (0.27)	0.94 (0.41)	0.84 (0.45)	1.00 (0.46)	0.70 (0.28)*	.928
Alb (g/dL)	3.4 (0.5)	3.0 (0.5)*	2.9 (0.7)	2.7 (0.7)*	2.8 (0.5)	2.5 (0.3)*	3.0 (0.2)	2.8 (0.4)*	3.0 (0.72)	2.6 (0.65)*	.703
TBili (mg/dL)	5.7 (2.4)	4.6 (1.5)	6.4 (4.8)	7.5 (5.3)	7.8 (3.9)	8.8 (5.3)	8.3 (6.2)	8.2 (6.3)	13.0 (8.1)	14.1 (8.2)	**0.047**
ALT (U/L)	46.0 (15)	35.0 (14)*	49.0 (40)	40.0 (22)*	54.0 (38)	47.0 (33)*	67.0 (64)	57.0 (46)	55.0 (29.7)	44.0 (23.9)*	.783
AST (U/L)	156.0 (74)	105.0 (50)*	143.0 (94)	90.0 (46)*	177.0 (100)	124.0 (70)*	181.0 (121)	123.0 (75)*	197.0 (100)	134.0 (50.5)*	.258
PT (s)	16.6 (2.3)	17.8 (3.8)	17.0 (3.4)	17.7 (5.3)	15.5 (3.2)	18.3 (4.3)*	13.0 (4.7)	15.9 (3.8)	20.0 (7.2)	21.0 (6.5)	.171
INR	1.6 (0.2)	1.7 (0.4)	1.7 (0.4)	1.7 (0.5)	1.5 (0.3)	1.8 (0.4)*	1.4 (0.2)	1.5 (0.4)	2.0 (0.72)	2.0 (0.69)	.0965
DF	26.9 (6.3)	31.0 (13)	28.0 (16)	35.0 (30)	23.6 (13.9)	35.0 (19)	19.0 (12)	28.0 (27)	44.8 (29.6)	59.6 (33.4)	.594
MELD	18.0 (2)	19.0 (2)	20.0 (5)	19.0 (3)	20.0 (4)	20.0 (4)	20.0 (4)	18.0 (3)	24.0 (5.9)	24.0 (6.2)	.413
MELD-Na	19.0 (3)	18.0 (4)	21.7 (5.6)	17.1 (2.9)	21.0 (5)	18.0 (5)	22.7 (5.3)	16.7 (2.8)	29.0 (6.6)	27.0 (6.9)	.152

Values represented as mean (SD). Analysis performed through paired t-test within PC categories. Significant change from HD0 to HD4 ($P < .05$) represented with *. Statistically significant values on ANOVA are represented in bold.

Alb, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; Cr, creatinine; HD0, hospital day at admission; HD4, hospital day 4 after admission; Hgb, hemoglobin; PT, prothrombin time; SD, standard deviation.

Table 4. Admission Characteristics, Stratified by Therapy

Characteristic, mean (SD)	No specific therapy (n = 135)	Corticosteroids (n = 24)	*P* value
Age (y)	51.2 (12)	45.4 (10.32)	**.03**
Male (%)	65.9	58.3	.473
PC (k/uL)	131.0 (79.09)	173.0 (100)	.08
Hgb (k/uL)	10.5 (2.30)	10.5 (2)	.88
WBC (k/uL)	9.0 (5.09)	10.6 (8.2)	**.03**
ANC (k/uL)	7.6(4.63)	9.1 (7.7)	**.05**
Na (mEq/L)	135.0 (5.26)	134.0 (4)	.50
BUN (mg/dL)	12.0 (8.93)	11.0 (7)	.40
Cr (mg/dL)	0.88 (0.42)	0.72 (0.38)	.09
Alb (g/dL)	2.9 (0.64)	2.8 (0.5)	.20
TBili (mg/dL)	8.8 (6.56)	15.7 (7.5)	**<.0005**
ALT (U/L)	56.0 (39.37)	48.0 (30)	.31
AST (U/L)	172.0 (94.43)	194.0 (86)	.27
PT (s)	16.7 (4.78)	19.8 (5)	**.008**
INR	1.6 (0.46)	1.9 (0.5)	**.007**
DF	28.8 (27.82)	51.7 (27.16)	**.0006**
MELD	20.0 (4.96)	24.0 (5)	**.001**
MELD-Na	22.0 (5.52)	26.0 (5)	**.0006**
Child-Pugh	9.8 (1.96)	10.4 (1.7)	.14

T-test assuming unequal variance used for continuous variables. Significant values presented in bold.
Alb, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; Cr, creatinine; Hgb, hemoglobin; PT, prothrombin time; SD, standard deviation.

Admission PC Category and Clinical Characteristics

Fifteen patients (9.4%) were in PC <50 category, 42 (26.4%) in the 50–99, 51 (32.1%) in the 100–149, 23 (14.5%) in the 150–199, and 28 (17.6%) in the ≥200 category. Increasing PC category was associated with greater white blood cell count (WBC) ($P < .0001$), greater absolute neutrophil count (ANC) ($P < .0001$), greater TBili ($P = .0054$), and higher Na-MELD scores ($P = .0446$). Admission diagnoses are presented in Table 1. There was no significant association between PC category and admission diagnoses.

Clinical Characteristics Based on PC Category and HD4 Status

Nineteen patients were discharged prior to HD4 (10%). Sixteen patients were discharged due to improvement, and 3 patients left against medical advice. Baseline characteristics of patients discharged before vs ≥HD4 are presented in Table 2. Patients with length of stay <HD4 had lower WBC, ANC, TBili, prothrombin time, and INR levels and lower DF, MELD, Na-MELD, and CP scores.

Baseline Characteristics and Outcomes Based on PC Category and AH Treatment

One hundred and thirty-five patients received NST during the first 4 hospital days, 24 patients received CS, 2 granulocyte colony-stimulating factors, and 1 pentoxifylline. Baseline and HD4 assessments for patients who received NST are presented in Table 3. Increased WBC, ANC, and TBili correlated with increased PC category at HD0. PC increased from HD0 to HD4 in the PC <50 and 50–99 categories and decreased in the PC 100-149, 150–199, and ≥200 categories, but the changes were only significant in the PC 100-149 and 150–199 categories. ANC decreased from HD0 to HD4 in all PC categories but was only significant in the PC <50 category. Alanine aminotransferase and aspartate transaminase levels decreased in all categories. There were no significant changes in DF, MELD, or Na-MELD scores between HD0 and HD4.

Thirty-six patients received at least 4 days of CS treatment during their hospital stay. Baseline characteristics of patients who received CS vs NST are presented in Table 4. Patients with a higher PC on admission were more likely to receive CS (173 vs 131, $P = .08$). Patients who received CS were younger; had greater WBC, ANC, TBili, prothrombin time, and INR levels; and had greater DF, MELD, and Na-MELD scores (Table 4). Assessments for the patients treated with CS on TD0 and TD4 are presented in Table 5. A higher PC was significantly associated with a lower day-4 Lille score (Table 6).

Spleen Size Based on Platelet Category

SI recorded for 136 patients is presented in Table A1 stratified by PC category and gender. Imaging in the remaining 23 patients did not include the spleen. Among men (n = 88), the mean SI was 1.89 (standard deviation 1.21). Greater SI was correlated with a lower baseline PC

Table 5. Treatment Day 0 and Treatment Day 4 Characteristics in Patients Receiving CS for ≥4 days

	PC < 50 (n = 2)		PC 50–99 (n = 9)		PC 100–149 (n = 5)		PC 150–199 (n = 10)		PC ≥ 200 (n = 10)	
Characteristic, mean (SD)	TD0	TD4	TD0	TD4	TD0	TD4	TD0	TD4	TD0	TD4
Age (y)	62.0 (9.19)		51.0 (13)		49.8 (4)		42.0 (10)		46.7 (10)	
Male (%)	100.0		33.3		60.0		70		40.0	
PC (k/uL)	46.0 (0.71)	74.5 (14.85)	84.0 (13.82)	198.0* (24.13)	292.0 (48.5)	252.0 (87.9)	174.0 (13.81)	159.0 (39.42)	292.0 (48.5)	252.0 (87.9)
Hgb (k/uL)	10.0 (0.35)	10.1 (0.71)	9.0 (1.06)	9.9 (1.02)	10.0 (1.96)	10.0(25.53)	9.9(1.48)	9.2 (1.32)	10.0 (1.96)	10.0(25.53)
WBC (k/uL)	3.6 (1.41)	4.7 (0.64)	8.9 (3.87)	20.6 (6.33)	33.0 (46.1)	20.0 (6.38)	16.0 (6.81)	12.8 (6.62)	33.0 (46.1)	20.0 (6.38)
ANC (k/uL)	2.0 (0.85)	3.4 (0.78)	5.7 (2.41)	16.8 (5.66)	16.0 (8.45)	17.0 (5.7)	13.0 (6.47)	9.6 (6.53)	16.0 (8.45)	17.0 (5.7)
Na (mEq/L)	139.0 (1.41)	136.0 (2.83)	136.0 (3.16)	134.0 (6.10)	133.0 (2.69)	134.0 (2.9)	130.0 (6.29)	136.0 (4.52)	133.0 (2.69)	134.0 (2.9)
BUN (mg/dL)	6.0 (0.85)	12.0 (5.66)	10.0 (9.10)	18.0 (9.75)	7.0 (2.8)	15.0 (10)	15.0 (5.05)	15.0 (6.64)	7.0 (2.8)	15.0 (10)
Cr (mg/dL)	0.71 (0.01)	0.80 (0.16)	0.58 (0.18)	0.77 (0.11)	1.00 (0.16)	1.00 (0.45)	1.01 (0.51)	0.61 (0.15)*	1.00 (0.16)	1.00 (0.45)
Alb (g/dL)	2.6 (0.92)	2.4 (0.57)	8.1 (0.29)	2.6 (0.32)	2.0 (0.38)	3.0 (1)	2.8 (0.72)	2.5 (0.56)	2.0 (0.38)	3.0 (1)
T. Bili (mg/dL)	9.3 (8.56)	6.4 (6.93)	12.4 (5.01)	16.2 (6.21)	17.0 (9.4)	16.0 (9.96)	17.5 (6.75)	11.8 (7.76)*	17.0 (9.4)	16.0 (9.96)
ALT (U/L)	48.0 (2.83)	38.5 (0.71) *	42.0(27.05)	59.0 (27.44)	37.0 (13.66)	57.0 (19.2)*	46.0 (32.70)	49.0 (24.47)	37.0 (13.66)	57.0 (19.2)*
AST (U/L)	198.0 (9.90)	93.5(0.71)	142.0 (60.92)	121.0 (54.14)	138.0 (37.8)	164.0 (34.6)	161.0 (102.18)	121.0 (66.24)	138.0 (37.8)	164.0 (34.6)
PT (s)	18.2 (5.23)	21.4 (2.83)	22.3 (3.61)	20.8 (4.28)	21.0 (5.6)	20.0 (2.97)	22.0 (6.73)	19.0 (4.26)*	21.0 (5.6)	20.0 (2.97)
INR	1.9 (0.49)	2.0 (0.49)	2.2 (0.34)	2.1 (0.45)	2.0 (0.65)	2.0 (0.3)	2.1 (0.66)	1.8 (0.45)*	2.0 (0.65)	2.0 (0.3)
DF	37.8 (19.30)	49.2 (6.01)	56.0 (16.84)	57.0 (20.31)	56.5 (31.20)	50.1 (24.33)	48.9 (34.21)	37.6 (22.96)*	56.5 (31.20)	50.1 (24.33)
MELD*	22.0 (2.83)	23.0 (0.71)	26.0 (3.77)	24.0 (3.66)	22.0 (5.82)	24.0 (4.95)	22.0 (6.28)	22.0 (4.12)*	22.0 (5.82)	24.0 (4.95)
MELD-Na	20.3 (0.71)	19.0 (0.71)	29.0 (2.5)	26.0 (4.21)	30.0 (4.63)	25.0 (5.06)	25.0 (5.84)	21.0 (4.03)*	30.0 (4.63)	25.0 (5.06)

Values represented as mean (SD). Analysis performed through paired t-test within PC categories. Significant change from TD0 to TD4 ($P < .05$) represented with *.
Alb, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; Cr, creatinine; CS, corticosteroid; Hgb, hemoglobin; PT, prothrombin time; SD, standard deviation; TD, treatment day.

Table 6. Regression for Baseline PC and Day-4 Lille Score

Variable	Estimate	SE	*P* value
Intercept	0.630	0.107	1.255E-6
PC TD0	−0.001	0.001	**.020**

Significance observed through linear regression of Lille score with continuous PC. Increasing PC associated with a lower Lille score. Significant values are in bold.
SE, standard error.

($P = .016$) and PC category ($P = .01$). No correlation was present among women.

Discussion

The important findings in our study include a direct relationship between baseline PC with markers of inflammatory response (WBC, ANC) and greater disease severity (TBili, Na-MELD). As expected, there was an inverse relationship with the SI. Patients with a higher PC were more likely to receive CS. Importantly, a higher PC was associated with a favorable response to CS as indicated by a lower day-4 Lille score.

Only 2 studies to date have assessed the significance of the PC in patients with AH. In a study of 58 patients with a high clinical suspicion for the diagnosis who underwent liver biopsy for confirmation, PC was higher in the biopsy-confirmed group (178 × 109/L) than in those without AH (98.4 × 109/L) ($P = .0005$).[14] A PC of >147.5 × 109/L had a sensitivity of 56% and a specificity of 93% for detecting AH.[14] Although a subsequent study assessing cytokine levels in the diagnosis of AH also reported elevated PC in patients with biopsy-proven AH compared to that in those without confirmation, the predictive value of PC was significantly lower.[15] Neither study correlated inflammatory markers of PC with disease severity.

A possible relationship between a higher PC and severity of AH is a shared pathophysiologic mechanism involving the inflammatory cytokine interleukin-6 (IL-6). The inflammatory response in AH is intimately linked to IL-6 expression. In patients with AH, IL-6 levels correlate with WBC, ANC, and clinical severity.[16] In a study of 127 patients, the plasma IL-6 level was the most precise predictor of morality.[17,18] In most situations, the PC is determined by hepatic TPO production which, in turn, is regulated by the circulating PC mass. Multiple factors have the potential to suppress the PC in AH, including impaired TPO production, splenic sequestration, and alcohol-induced bone marrow suppression. However, a link that has not previously been explored is the potential for IL-6 to affect the PC. IL-6 expression in inflammatory states enhances hepatic TPO mRNA transcription,[19,20] and administration of IL-6 results in a corresponding increase in TPO plasma levels and platelet counts. As a result, IL-6 could be driving both clinical severity as well as thrombocytosis in patients with severe disease.

There are several important limitations of our study. First, biopsy for diagnostic confirmation was not available. In a trial in which liver biopsy was required for confirmation, 25% of patients with clinically suspected AH did not have histologic confirmation.[14] The duration of abstinence prior to hospitalization was also not available. Abstinence from alcohol in alcohol-dependent patients leads to bone marrow recovery and increased platelet counts in peripheral blood.[21] The average PC in patients with a lower baseline PC (<100) increased during the first 4 days of hospitalization with confirmed abstinence from alcohol. Although patients with greater portal hypertension as indicated by lower platelet counts and greater splenomegaly might have influenced the decision to administer CS, the presence and severity of ascites with the concern for the development of spontaneous bacterial peritonitis was similar in all groups. Finally, the small sample size per PC category and uneven distribution among PC categories are significant limitations.

Summary and Conclusion

Our study is the first to emphasize the relationship between admission PC with systemic inflammation and liver damage. Confirmation use of PC as a predictor for response to CS should be assessed further in future studies.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.07.022.

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

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Discussion of statistical endpoints and analyses are included in the manuscript.