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D-dimers and ferritin: Expanding the diagnostic panel for cirrhotic ascites evaluation

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ABSTRACT

Objective: This study aimed to explore the diagnostic role of D-dimers and ferritin in ascitic fluid. We analyzed ascitic and blood samples from twenty cirrhotic patients, using the Child-Pugh classification to assess liver cirrhosis severity. Methods: Blood tests evaluated platelets, albumin, INR, fibrinogen, CRP, ferritin, and D-dimers, while ascitic fluid analysis incorporated total protein, albumin, LDH, cholesterol, leukocytes, with a focus on D-dimers and ferritin.

Results: The results showed a significant positive correlation between ascitic D-dimers and ferritin concentrations and ascitic albumin, total protein, and cholesterol. A correlation was also observed between ascitic ferritin and LDH. These correlations suggest a potential relationship between D-dimers and ferritin levels, disease severity, and the local production of these markers.

Conclusion: This study proposes that evaluating D-dimers and ferritin in ascitic fluid might reveal underlying inflammation, even when other inflammatory laboratory markers are normal. Our findings suggest that ascitic D-dimers and ferritin levels could offer valuable insights into inflammatory processes in ascitic fluid, potentially enhancing diagnostic and prognostic approaches for patients with ascites from liver cirrhosis or other causes. Further studies with larger and more diverse cohorts are needed to validate and extend our findings.

Keywords: ascites, D- dimers, ferritin, inflammatory markers, hemostasis

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INTRODUCTION

Ascites is a common complication in patients with cirrhosis and portal hypertension [1]. Under normal circumstances, the peritoneal membrane produces and rapidly reabsorbs the physiological peritoneal fluid, facilitating the unobstructed movement of organs within the peritoneal cavity. Pathological processes, such as transudation from surrounding tissues (commonly due to liver cirrhosis) or local production (resulting from neoplasms, acute, or chronic inflammation), can disrupt this balance [2]. In clinical practice, exudates and transudates are differentiated by measuring the concentrations of certain biological parameters, including total protein and albumin, in both ascites and serum [3]. Despite the array of biochemical parameters currently available for testing, physicians still face challenges in predicting the likelihood of spontaneous bacterial peritonitis (SBP), portal vein thrombosis, and gastrointestinal bleeding [4]. Consequently, there is a need for additional diagnostic tools to complement existing methods. Following the first simultaneous study of D-dimers and ferritin in ascites and blood in cirrhotic patients, it has become evident that abnormal levels of D-dimers and ferritin in ascites (using blood reference ranges), even without clinical symptoms, could signal underlying processes in the ascitic fluid, such as inflammation and fibrinolysis. [5] Nonetheless, the connections between inflammation and hemostasis within ascitic fluid remained undetermined.

MATERIALS AND METHODS

This study was conducted in adherence to ethical guidelines and standards, receiving full approval from the relevant Ethical Committee prior to its commencement on 29.12.2021 We ensured that all procedures performed in this study complied with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Twenty blood and ascitic samples from patients with liver cirrhosis were collected and analyzed. The primary cause of liver cirrhosis in this study was an alcohol-induced disease, which affected 15 patients . Hepatitis C

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(HCV) was present in three patients, Hepatitis B (HBV) in one patient, and Wilson's disease in another. The average age of the patients was 60.10 ± 10 years. Among them, fifteen were male and five were female. The severity of liver cirrhosis was evaluated using the Child-Pugh classification system [Pugh RN]. In this group, 12 patients were classified as Child-Pugh class B, while 8 patients were categorized as Child-Pugh class C. In the blood samples, we measured platelet, albumin, International Normalized Ratio (INR), fibrinogen, C-reactive protein (CRP), ferritin, and D-dimers levels. In ascitic fluid, we analyzed standard laboratory parameters to differentiate between transudates and exudates, such as total protein, albumin, lactate dehydrogenase (LDH), cholesterol, and leukocytes. Additionally, we assessed D-dimers and ferritin levels in ascitic fluid, similar to the serum analysis.

Blood and ascitic fluid samples were collected on the same day and analyzed immediately upon arrival at the laboratory. Total protein and albumin levels were measured using colorimetric and immunoturbidimetric assays, respectively, whereas ferritin levels were determined using an immunoturbidimetric assay. These assays were performed using a Cobas Integra 400 Plus clinical chemistry analyzer. D-dimers levels in the plasma and ascites were measured using Siemens' Inovance D-Dimers reagent on a Sysmex CS 2000i automatic coagulometer. The Inovance D-Dimers assay is a particle-enhanced, immunoturbidimetric method for quantifying cross-linked fibrin degradation products (D-dimers) in coagulation analyzers. Ascitic samples outside the measurement range were diluted to fit the linear range of the method. Statistical analysis was conducted using SPSS version 19.0, with a p-value less than 0.05 deemed statistically significant.

RESULTS

Blood markers

Plasma D-dimers levels in patients with decompensated liver cirrhosis (Median: 4.2mg/L (1,4-23)) are approximately 10 times the upper limit of normal (ULN). Serum ferritin levels in these patients (Median: 232 µg/l (28-1368)) were around the ULN. Eleven out of the 20 patients had normal serum ferritin levels. All median and mean values are shown and compared with those in the literature in Table 1.

Plasma D-dimers levels had a positive correlation with INR, whereas no relationships existed with platelets, total protein, serum albumin, fibrinogen, CRP, and ferritin. A positive correlation was observed between the serum ferritin and fibrinogen levels. Additionally, platelet count was positively correlated with both CRP and fibrinogen levels. Total protein and albumin were negatively correlated with INR. Notably, significant negative correlations were found between the INR and fibrinogen levels. All of these correlations are shown in Table 2.

Ascites

The mean ascitic D-dimers level was 318±338 mg/L, with a median of 167 (56-1269) mg/L. The average ascitic ferritin level was 276±382 µg/l, which is nearly twice as high as the median value reported in other studies. The mean and median values for albumin, total protein, cholesterol, LDH, and leukocytes were consistent with those observed in the transudates. Table 3 presents and compares all median or mean values to those from different studies.

Ferritin and D-dimers levels in ascites were positively correlated with albumin, total protein, and cholesterol

Table 1. Blood biological markers from patients with liver cirrhosis and ascites - Median (M) and Mean(X).

	Median(M) /Mean (x)Values in the study	Median(M)/ Mean (X) Values in other studies	Reference Range
Albumin [g/L]	M= 31.25 (20- 41) x= 31.25±6.7	M=36 (31-40) [4] x=34.77±6.22 [2]	35-55
INR	M= 1.39 (1.1-2.3) x= 1.42±0.33	M=1.27 (1.11-1.44) [1] M=1.22 (1.12–1.36) [4]	0.9-1.2
Fibrinogen [g/L]	M= 3 (1.1, 6.9) x= 3.3±1.6	x= 1.823±0.65 [1]	2.0-4.0
Platelets [x10^9/L]	M= 148 (52-366) x= 165.7±94	M=75 (42-137) [1]	112 – 330
CRP mg/L	M= 23 (5-143) x= 30±32.4	M= 15.8 (14.6-23.7) [3] M= 5.67 (2.58- 9.87) [4]	< 6
D- Dimer [mg/L]	M= 4.2 (1.4-23) x= 6.1±5.3	M=1.59 (0.72-3.89) [1]	< 0.55
Ferritin [µg/l]	M=232 (28-1368) x= 350.8±332	M=103.4 (35.8–271.9) [4]	40.00- 280.00

Table 2. Correlations between biological markers in blood

	Platelets	Total Protein	Albumin	INR	Fibrinogen	CRP	Ferritin	D- Dimer
Platelets	—	No	No	No	0.515	0.481	No	No
Total Protein	No	—	No	0.516	No	No	No	No
Albumin	No	No	—	-0.657	0.571	No	No	No
INR	No	-0.516	-0.657	—	-0.691	No	No	0.558
Fibrinogen	0.515	No	0.571	-0.691	—	No	0.464	No
CRP	0.481	No	No	No	No	—	No	No
Ferritin	No	No	No	No	0.464	No	—	No
D- Dimer	No	No	No	0.558	No	No	No	

* The numbers in the cases represent the correlation index r

Table 3. Ascitic biological markers from patients with liver cirrhosis and ascites - Median (M) and Mean (x)

	Median (M)/Mean (X) Values in the study	Median/ Mean Values in other studies
Albumin g/L	M= 6.6 (1.5-25) X= 9.6±7.5	X= 15±8 [5]
Total Protein g/L	M= 13 (3.8-41) X= 17.9±11.5	X= 23.5±14.9 [7]
Cholesterol mmol/L	M=0.45 (0.1-2.3) X= 0.67±0.61	X=1,45 ± 0,69 [5]
LDH IU/L	M=62 (39-151) X=78±34.2	X=93.4±64.9[5]
Leucocytes [Leukocytes/µL]	M= 40 (5,190) X= 60±57	Normal range- <250
D- Dimer mg/L	M= 167 (56-1269) X= 318±338	X= 311.69 ±137.61 [6]
Ferritin µg/l	M=95 (15-1532) X=276±382	X=117.5±115.6[5]

levels, but they did not share a positive correlation (Table 4). There was no correlation between D-dimers and ferritin levels in ascites and leukocytes in ascites. Additionally, leukocytes in ascites showed no relationship with any of the other six biological markers included in the study.

Blood and ascitic biological markers together

We analyzed the correlations between different proteins in the blood and ascites (Table 5). A strong positive correlation was found between albumin in ascites and both serum albumin and plasma fibrinogen levels, whereas a negative correlation was observed with plasma INR. A significant positive association was identified between D-dimers in ascites and plasma fibrinogen levels. Additionally, ferritin in ascites was positively correlated with serum albumin and plasma fibrinogen levels. Total protein, cholesterol, and LDH levels in ascites were correlated with serum albumin levels. Cholesterol in ascites also exhibited a positive correlation with fibrinogen and a negative correlation with INR.

Table 6 presents the serum ascites- albumin gradient (SAAG) of all samples and the ratio between ascitic albumin and serum albumin (A/S albumin), the ratio between ascitic ferritin and serum ferritin (A/S ferritin) and the ratio between ascitic D-dimers and plasma D-dimers (A/P DD). The ascitic albumin/ serum albumin ratio (A/S albumin) was <1 for all samples.

The lowest A/P DD was 3.2 and the highest ratio was 291. The lowest A/S ferritin was 0.04 and the highest was 5.8. We compared the ratios: A/S ferritin, A/P DD and A/S albumin. The median A/P DD was 39(3-291). The mean is 71 ± 75. In all the samples, the ratio was >1. The

Table 4. Correlations between biological markers in ascites

	Albumin	D- Dimer	Ferritin	Leucocytes	Total Protein	LDH	Cholesterol
Albumin	—	0.559	0.801	No	0.887	0.700	0.955
D- Dimer	0.559	—	No	No	0.638	No	0.550
Ferritin	0.801	No	—	No	0.716	0.567	0.750
Leucocytes	No	No	No	—	No	No	No
Total Protein	0.887	0.638	0.716	No	—	0.644	0.868
LDH	0.700	No	0.567	No	0.567	—	0.662
Cholesterol	0.955	0.550	0.750	No	0.750	0.662	—

* The numbers in the cases represent the correlation index r

Table 5. Correlations between biological markers in blood and ascites

Ascites / Blood	Albumin	D- Dimer	Ferritin	Leucocytes	Total Protein	LDH	Cholesterol
Albumin	0.774	No	0.530	No	0.655	0.516	0.735
INR	-0.547	No	No	No	No	No	-0.579
Fibrinogen	0.632	0.507	0.503	No	No	No	0.712
Platelets	No	No	No	No	No	No	No
CRP	No	No	No	No	No	No	No
D- Dimer	No	No	No	No	No	No	No
Ferritin	No	No	No	No	No	No	No

* The numbers in the cases represent the correlation index r

Table 6. SAAG, Ascites-to-Serum Albumin Ratio, Ascites-to-Serum Ferritin Ratio, and Ascites-to-Serum D-Dimer Ratio categorized by patients

Sample №	SAAG [g/L]	Ascitic Albumin/ Serum Albumin Ratio	Ascitic Ferritin/ Serum Ferritin Ratio	Ascitic D- dimer/ Serum D-dimer Ratio
1.	19.6	0.46	0.39	68.5
2.	17	0.2	0.4	36.8
3.	15	0.6	2.1	181.4
4.	25.5	0.2	0.5	45.8
5.	23	0.3	0.3	19.9
6.	22.2	0.11	0.25	15
7.	16	0.6	2.8	201
8.	25.5	0.1	0.4	21.4
9.	23.7	0.2	0.3	18.3
10.	28	0.3	1.5	53.8
11.	15	0.6	5.8	291
12.	18	0.3	0.2	112.5
13.	22	0.4	1.3	117.5
14.	23	0.1	0.1	23.7
15.	35	0.2	0.04	37
16.	24.3	0.2	0.5	11.6
17.	21.6	0.22	3.8	35.6
18.	18.8	0.2	0.3	3.2
19.	21	0.3	0.4	40.6
20.	18.5	0.1	0.2	92.8

median of the A/S ferritin level was 0.41(0.04- 5.8) and the mean was 1.1±1.5.

In Samples № 3,7,10,11,13 and 17, we observed that the A/S ferritin was >1, which was only observed in these six patients. This corresponds to the higher A/P DD (at least two times higher than the rest) in all samples except in samples №10 and 17. The median of A/S albumin is 0.23(0.08-0.6) and the mean- 0.28±0.17.

We conducted a correlation analysis between the various ratios and discovered positive correlations between the following pairs: A/P DD with A/S albumin, A/S ferritin with A/S albumin, and A/P DD with A/S ferritin.

DISCUSSION

In all samples, the SAAG was >11, which points to portal hypertension as the cause of ascites and classifies the ascites in all samples as transudate. Elevated plasma D-dimers levels are common in patients with liver cirrhosis, particularly in those with decompensated disease [6]. Saraya et al [7] found significantly higher D-dimers levels in patients with liver cirrhosis complicated by ascites compared to healthy controls. This finding aligns with our observations and those of Agarwal et al. [8], who reported that 93% of cirrhotic patients with ascites had increased plasma D-dimers levels. Elevated D-dimers levels have also been detected in ascitic fluid, indicating that reabsorption of ascites into the systemic circulation contributes to a hyperfibrinolytic state in patients with advanced liver disease [8,9]. The substantial reduction in circulating D-dimers levels observed after ascites depletion further supported this hypothesis. The source of D-dimers in ascites remains unclear. A significant proportion of the proteins present in the effusions originate from the plasma. The concentration of these proteins in the ascitic fluid primarily depends on three factors: mem-

brane permeability, molecular size, and local production. The molecular size of D-dimers is 180 kilodaltons (kDa), which allows it to pass through the membrane as it is roughly twice the molecular weight of albumin (66.5 kDa). [10,11] This observation aligns with a clinical case reported by Johnson et al. in 1976, involving an infant with abdominal ascites, hepatosplenomegaly, and a combination of plasma clotting factor deficiencies. [12] The infant had severe plasma deficiencies for all investigated clotting factors, except for factor VIII, which was within the normal limits. Detectable levels of every examined clotting factor were also found in the infant's ascitic fluid. The authors suggest that the infant's coagulopathy resulted from a significant loss of clotting proteins from the plasma into the ascitic fluid. In our study, we did not identify a strong correlation between serum and ascitic D-dimers levels, implying the possibility of the in situ production of this biological marker. This finding is consistent with that reported by El Gohary et al. [13]. In all our patients, the levels of D-dimers in the ascitic fluid were higher than the serum levels, consistent with the findings of Romanelli et al. [14], Takatory et al. [15], and Agarwal et al. [8]. However, this observation contrasts with that of El. Gohary et al, who reported that this percentage was only 60%.

The notably high A/P DD (>1 in all samples), as shown in Table 6, suggests that there may be another origin for these biological markers. Consequently, we speculated that in-situ production may occur. This is in line with the 1981 study by Hoefs et al., which found a significant amount of fibrin monomers in all samples, indicating that intraperitoneal coagulation had occurred [16].

Few studies have explored the relationship between serum ferritin and ascitic ferritin levels. A study by Kountouras et al from 1993, asserts that ascitic ferritin is a more accurate indicator of malignant ascites than SAAG and can help differentiate ascites due to HCC or other metastatic conditions from nonmalignant ascites. [17] In our study, we did not find any relationship between these two biological markers.

In the study by Cemil SAVAŞ et al., 61 patients were included: 39 with cirrhotic ascites and 22 with malignant ascites [18]. Patients with malignant ascites had significantly higher median ferritin levels than those with cirrhotic ascites. The concentration of ferritin in ascites was high in 4 of 39 cirrhotic patients and in 18 of 22 patients with malignant disease.

The increased ferritin levels associated with malignant diseases can be attributed to various mechanisms. These include elevated ferritin synthesis related to inflammation, increased ferritin secretion by cancer cells, and hepatocellular necrosis caused by liver metastasis. In turn, elevated ferritin levels may affect the immune system by altering T- cell function.

The molecular weight of ferritin is relatively high at 474 kDa (approximately eight times greater than that of albumin). [19] As shown in Table 6, the A/S ferritin was <1 in 14 out of 20 samples (in most cases, corresponding to A/S albumin).

One of the limitations of this study was its small sample size, as it was conducted at a single institution and within a short timeframe. Additionally, the study was limited by the uniform etiology of cirrhosis in all patients.

CONCLUSIONS

In conclusion, this study explored the relationship between various biological markers of ascites, including D-dimers and ferritin levels. Our findings indicate that there may be a connection between these markers, the severity of liver disease, and in situ production of these proteins. Despite the limitations of a small sample size and uniform cirrhosis etiology, our results suggest that evaluating the ascitic levels of D-dimers and ferritin could provide valuable insights into the underlying inflammation in ascitic fluid, even in patients with normal levels of inflammatory laboratory markers. Further research with larger sample sizes and diverse etiologies is needed to confirm and expand upon these observations, potentially leading to improved diagnostic and prognostic tools for patients with ascites caused by liver cirrhosis or other conditions.

ABBREVIATIONS

A/S albumin- Ratio between ascitic albumin and serum albumin

A/S ferritin- Ratio between ascitic ferritin and serum ferritin

A/P DD- Ratio between ascitic D-dimers and plasma D-dimers

CRP- C-reactive protein

ULT- Upper Limit of Normal

HBV- Hepatitis B Virus

HBC- Hepatitis C Virus

INR- International normalized ratio

kDa- kilodalton

LDH- Lactate Dehydrogenase

SAAG- Serum Albumin- Ascites Gradient

SBP- Spontaneous bacterial peritonitis

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AUTHORS' CONTRIBUTION

PT- design and implementation of the study; Analysis of the results; Writing of the manuscript.

II- design and implementation of the study; Analysis of the results; Writing of the manuscript. DJ- Analysis, Final Approval

RN- Analysis, Final Approval

ZK- Analysis, design of the study, final Approval

CONFLICT OF INTEREST

None to declare.

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