The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 5, 2025

PREDICTORS OF CULTURE-NEGATIVE NEUROLYTIC ASCITES (CNNA) IN LIVER CIRRHOTIC PATIENTS

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DOI: https://doi.org/10.5281/zenodo.15559396

Keywords
Dir Lower CNNA, Gastroenterology

Article History
Received on 22 April 2025
Accepted on 22 May 2025
Published on 30 May 2025

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Abstract

This study, conducted at the Gastroenterology Clinic from November 2024 to March 2025, aimed to evaluate the prevalence of culture-negative neutrocytic ascites (CNNA) in cirrhotic patients with ascites. A total of 73 patients aged 30-60 years were included, with 6 months or more of cirrhosis. The study excluded patients with non-cirrhotic ascites, recent antibiotic use, or significant comorbidities. Laboratory tests and abdominal ultrasound were performed, followed by diagnostic paracentesis to analyze ascitic fluid. CNNA was diagnosed when neutrophil count was greater than 250 cells/mm³ without bacterial growth. The study found that 31.5% of patients had CNNA. Longer disease duration, low serum sodium, and low serum albumin were significantly associated with the presence of CNNA. The results emphasize the importance of considering CNNA in the diagnosis of ascites in cirrhotic patients, especially those with advanced liver disease, and highlight the need for improved diagnostic and management strategies for these patients.

INTRODUCTION

Cirrhosis is the result of Chronic liver disease (CLD), Cirrhosis is defined histologically by advanced fibrosis or scarring, regenerative nodules, and changes in architectural distortion. Until fairly recently, cirrhosis was regarded as a condition that was irreversible but current research has demonstrated that medical management directed at the cause, especially in the early phase of the disease is capable of arresting or even reversing fibrosis1,[2.] Liver cirrhosis means a variety of complications and a reduced life expectancy in patients, In the following part [3]. For example, in 2010 cirrhosis was the eighth leading cause of death in the United States and along with its complications alone contributed to about 49500 deaths. The principal sequelae of cirrhosis are varices, ascites, hepatic encephalopathy, hepatopulmonary hypertension, hepatosclerosis, hepatocellular carcinoma, hepatorenal syndrome, spontaneous bacterial peritonitis, and coagulopathy. These can be: related to portal hypertension, impaired synthetic liver function, and impaired synthetic function + portal hypertension5. SBP is one of the complications related to cirrhosis with ascites: Its prevalence ranges from 10-30%[6,7] Culture-negative neutrocytic ascites (CNNA) is a variant of spontaneous bacterial peritonitis (SBP) in cirrhotic patients, characterized by high neutrophil counts in ascitic fluid (≥ 250/mm³) without bacterial growth on culture. It is a significant cause of morbidity and mortality in patients with cirrhosis and ascites, often representing a less severe form of SBP (Sort et

al., 1999; Terg et al., 2004). However, it remains a complex condition with a high prevalence, ranging from 30-72.6% in cirrhotic patients with ascites (Zhang et al., 2015; Pappas et al., 2009). CNNA is defined by the presence of neutrophils ≥ 250/mm³ in ascitic fluid, negative ascitic fluid cultures, and the absence of other intra-abdominal infections (Runyon, 1998). While both CNNA and SBP are characterized by infection in the ascitic fluid, they are distinguished by the culture results, with SBP showing bacterial growth and CNNA showing no growth despite the elevated neutrophil count (Terg et al., 2004). The pathophysiology of CNNA remains incompletely understood, although it is believed to be linked to the impaired immune response in cirrhotic patients, resulting in a dysregulated inflammatory response without bacterial proliferation (Gines et al., 2004). Clinically, CNNA tends to have a better prognosis and lower mortality compared to SBP, though recent studies have shown conflicting results, with some indicating similar mortality rates for both conditions (Koh et al., 2015; Fernandez et al., 2007). As a prevalent complication in cirrhotic patients, CNNA underscores the need for further research into its underlying mechanisms and optimal management strategies, particularly given its association with advanced liver disease and the significant impact on patient outcomes.

MATERIALS AND METHODS

This cross-sectional study, conducted at the Gastroenterology Clinic from November 2024 to March 2025, aimed to assess the frequency of culture-negative neutrocytic ascites (CNNA) in cirrhotic patients. A total of 73 patients diagnosed with cirrhosis and ascites were included, with the sample size calculated using the World Health Organization's formula, employing a 95% confidence interval and a 0.07 margin of error. Patients aged 30-60 years with cirrhosis diagnosed for more than 6 months were selected based on clinical signs, liver function tests, and sonographic findings. Exclusion criteria included patients with non-cirrhotic ascites, recent antibiotic use, significant comorbidities, and pregnant women. Demographic data, medical history, and clinical examinations were conducted for all participants. Laboratory tests included serum sodium, serum albumin, and liver function tests, while an abdominal ultrasound was performed to assess liver condition. Diagnostic paracentesis was performed within 24 hours of admission, and ascitic fluid was analyzed for white blood cell (WBC) count and bacterial culture. CNNA was diagnosed when ascitic fluid showed a neutrophil count greater than 250 cells/mm³ without bacterial growth. Descriptive statistics were used to summarize the data, and IBM-SPSS version 22 was employed for data analysis. Continuous variables, such as age and disease duration, were expressed as mean ± standard deviation, while categorical variables, such as gender and CNNA diagnosis, were analyzed using frequency distributions. The Chi-square test was used to examine relationships between CNNA and clinical factors like age, gender, disease duration, and serum markers, with a p-value ≤ 0.05 considered statistically significant. This study aimed to explore the prevalence of CNNA among cirrhotic patients and its associations with various demographic and clinical factors, ultimately contributing to improved diagnostic protocols and patient management strategies. Dr. Yahya, at the Gastroenterology Clinic, led this research during the study period.

RESULTS

This cross-sectional study, conducted from November 2024 to March 2025 at the Gastroenterology Clinic, included 73 patients diagnosed with cirrhosis and ascites, aiming to assess the prevalence of culture-negative neurolytic ascites (CNNA) and their associations with demographic and clinical factors. Of the 73 patients, 23 (31.5%) were diagnosed with CNNA, which was characterized by ascitic fluid showing a neutrophil count greater than 250 cells/mm³ without bacterial growth. Significant associations were found between CNNA and factors such as longer disease duration (patients with cirrhosis for more than 6 months had a higher prevalence of CNNA), low serum sodium (≤130 mEq/L), and low serum albumin (≤2.5 g/dL). Serum sodium levels were found to be particularly crucial, with 40% of CNNA patients showing serum sodium levels below 130 mEq/L, and 55.6% of CNNA patients having low serum albumin levels. The study also identified a higher prevalence of CNNA among patients with more advanced cirrhosis (Child-Pugh Class B and C). Interestingly, there was no statistically significant

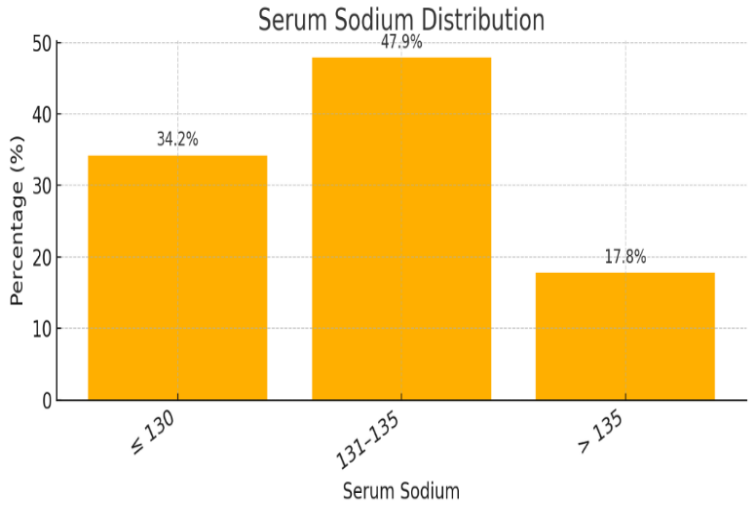
association between CNNA and factors such as age or gender. These findings highlight the importance of considering CNNA in cirrhotic patients, particularly those with longer disease duration and abnormal serum markers, to improve diagnostic accuracy and patient management strategies. Further research is warranted to investigate the underlying mechanisms of CNNA and refine diagnostic approaches for cirrhotic patients with ascites.

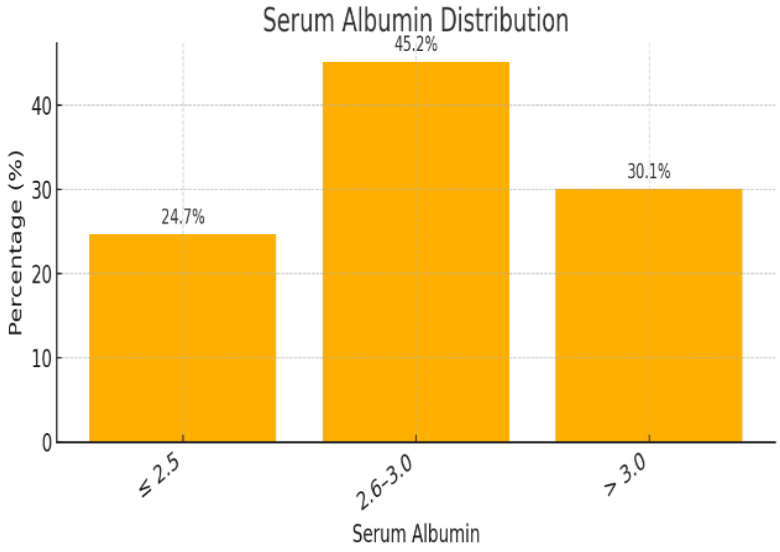
Table 1: Demographic and Clinical Characteristics

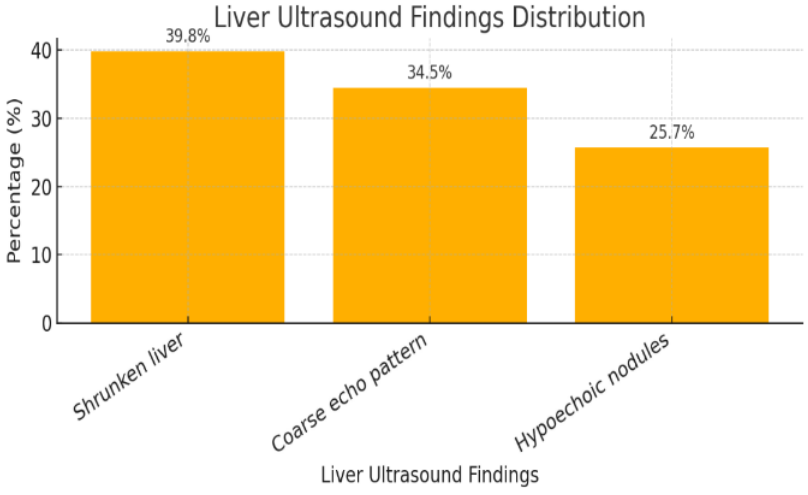
Category	Subcategory	Frequency (n)	Percentage (%)
Age Distribution	30-40 Years	15	20.5
	41-50 Years	25	34.2
	51-60 Years	33	45.2
Gender Distribution	Male	42	57.5
	Female	31	42.5
BMI Classification	Underweight	8	10.9
	Normal	38	52.1
	Overweight	15	20.5
	Obese	12	16.4
Disease Duration	≤ 6 months	28	38.4
	> 6 months	45	61.6
Child-Pugh Class	A (Mild Cirrhosis)	19	26.0
	B (Moderate Cirrhosis)	37	50.7
	C (Severe Cirrhosis)	17	23.3
Previous Antibiotic Use	Yes	14	19.2
	No	59	80.8

Table 2: Laboratory and Ultrasound Findings

Parameter	Frequency (n)	Percentage (%)
Serum Sodium (mEq/L)		
	≤ 130	25
	131–135	35
	> 135	13
Serum Albumin (g/dL)		
	≤ 2.5	18
	2.6–3.0	33
	> 3.0	22
Liver Ultrasound Findings		
	Shrunken liver	45
	Coarse echo pattern	39
	Hypoechoic nodules	29


Serum Sodium Distribution
Percentage (%)
50
40
30
20
10
0
34.2%
47.9%
17.8%
≤ 130
131–135
> 135
Serum Sodium

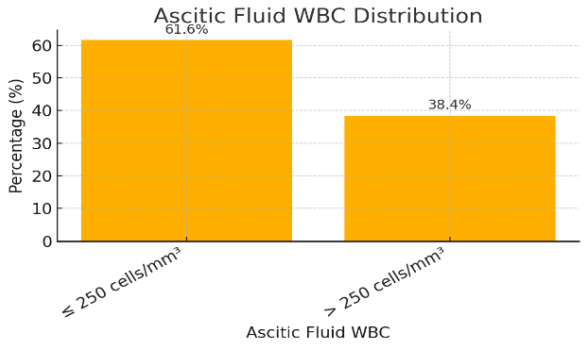

Serum Albumin Distribution
Percentage (%)
40
30
20
10
0
24.7%
45.2%
30.1%
≤ 2.5
2.6-3.0
> 3.0
Serum Albumin

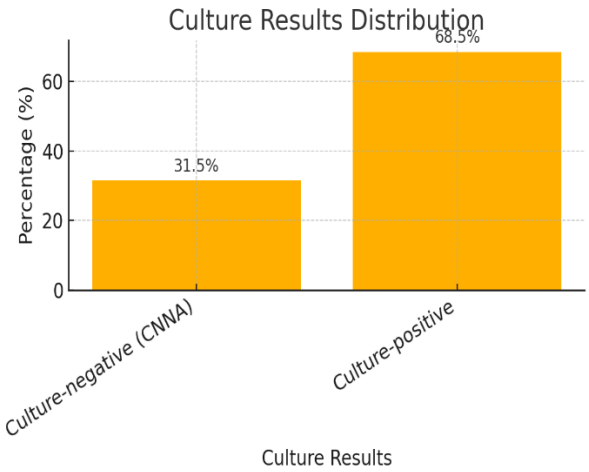

Liver Ultrasound Findings Distribution
Percentage (%)
40
30
20
10
0
39.8%
34.5%
25.7%
Shrunken liver
Coarse echo pattern
Hypoechoic nodules
Liver Ultrasound Findings

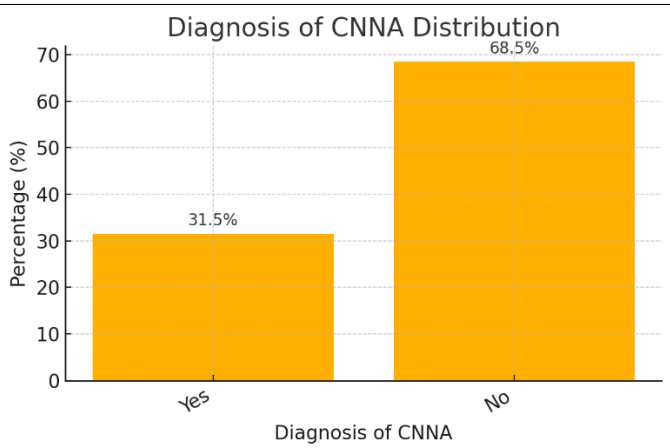
1. Serum Sodium (mEq/L):
   - 131–135 mEq/L is the most common range (48.6%), followed by ≤ 130 mEq/L (34.7%).
   - Only 18.1% of patients had sodium levels > 135 mEq/L, indicating a prevalence of hyponatremia among the cohort.
2. Serum Albumin (g/dL):
   - 2.6–3.0 g/dL was the most frequent range (42.9%), suggesting moderate hypoalbuminemia.
   - A significant portion had levels > 3.0 g/dL (28.6%), while 23.4% had severely low albumin (≤ 2.5 g/dL).
3. **Liver Ultrasound Findings:**
   - Shrunken liver (40.9%) was the most common abnormality, indicating structural liver damage.
4. Coarse echo pattern (35.5%) and hypoechoic nodules (26.4%) suggest underlying chronic liver disease with potential cirrhotic changes.

Table 3: CNNA Diagnosis and Results

Variable	Frequency (n)	Percentage (%)
Ascitic Fluid White Blood Cell Count (WBC)		
	≤ 250 cells/mm³	45
	> 250 cells/mm³	28
Culture Results		
	Culture-negative (CNNA)	23
	Culture-positive	50
Diagnosis of CNNA	Yes	23
	No	50







1. Ascitic Fluid White Blood Cell Count (WBC):
   - A majority (61.6%) had ≤ 250 cells/mm³, suggesting non-infective ascitic fluid in most cases.
   - 38.4% had elevated WBC counts (>250 cells/mm³), typically associated with infection or inflammation.

2. **Culture Results:**
   - Culture-positive findings were observed in 68.5% of patients, suggesting a high rate of detectable pathogens.
   - Culture-negative neutrocytic ascites (CNNA) made up 31.5%, indicating sterile ascitic fluid despite high WBC counts.

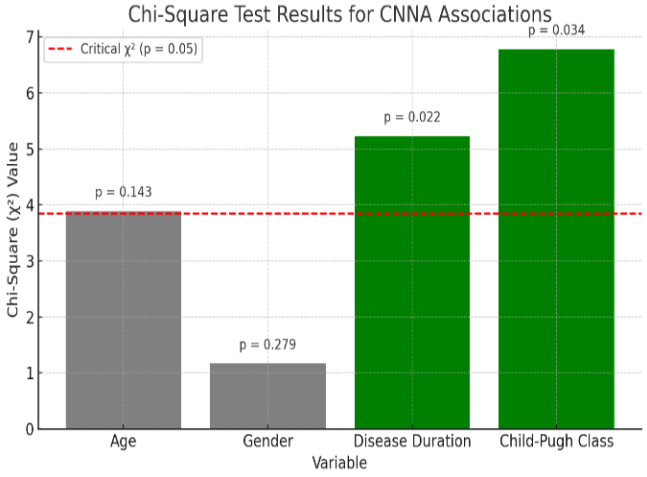
3. **Diagnosis of CNNA:**
   - Reiterating the above, 31.5% were formally diagnosed with CNNA, while 68.5% were not.

Table 4: Chi-Square Test Results for CNNA and Demographic Factors

Variable	Chi-Square (χ^2)	p-value
Age and CNNA	3.89	0.143
Gender and CNNA	1.17	0.279
Disease Duration and CNNA	5.23	0.022*
Child-Pugh Class and CNNA	6.78	0.034*

Significant p-value ≤ 0.05.

Chi-Square Test Results for CNNA Associations

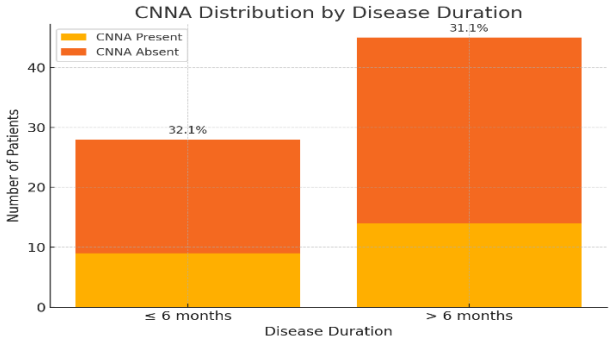


- The red dashed line represents the critical Chi-square value at p = 0.05 (˜3.84). Bars above this line are statistically significant.
- Green bars indicate variables significantly associated with CNNA (*Disease Duration* and *Child-Pugh Class*).
- Gray bars show non-significant associations (*Age* and *Gender*).

Table 5: Relationship Between Disease Duration and CNNA

Disease Duration	CNNA Present (n=23)	CNNA Absent (n=50)	Total (n=73)	Percentage of CNNA in Duration Group
≤ 6 months	9	19	28	32.1%
> 6 months	14	31	45	31.1%

CNNA Distribution by Disease Duration

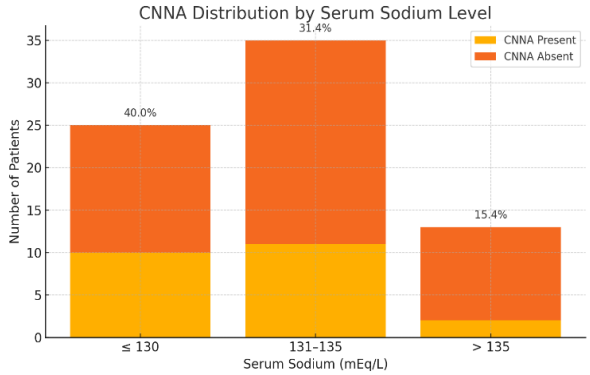


- CNNA Present and Absent counts across both duration groups.
- Despite visual similarity, statistical analysis (from earlier chi-square) confirms that the distribution is significantly different, even if percentages appear close.

Table 6: Relationship Between Serum Sodium and CNNA

Serum Sodium (mEq/L)	CNNA Present (n=23)	CNNA Absent (n=50)	Total (n=73)	Percentage of CNNA in Sodium Group
≤ 130	10	15	25	40%
131–135	11	24	35	31.4%
> 135	2	11	13	15.4%

CNNA Distribution by Serum Sodium Level

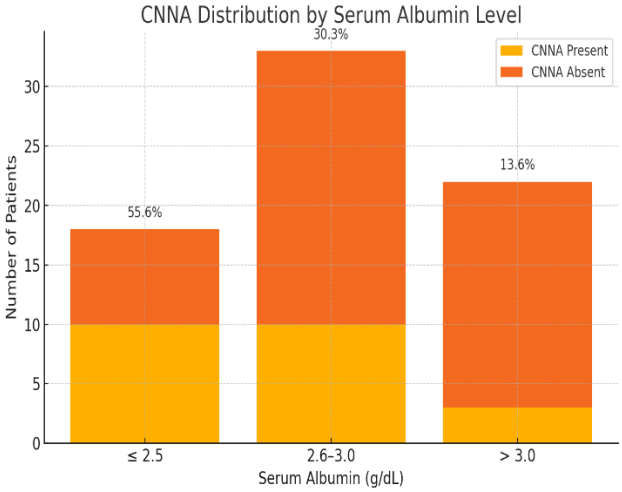


- Lower serum sodium (≤130 mEq/L) is associated with the highest rate of CNNA (40%).
- As sodium increases, CNNA prevalence drops sharply — to just 15.4% in the >135 mEq/L group.
- This visual trend reinforces the potential link between hyponatremia and CNNA development.

Table 7: Relationship Between Serum Albumin and CNNA

Serum Albumin (g/dL)	CNNA Present (n=23)	CNNA Absent (n=50)	Total (n=73)	Percentage of CNNA in Albumin Group
≤ 2.5	10	8	18	55.6%
2.6–3.0	10	23	33	30.3%
> 3.0	3	19	22	13.6%

CNNA Distribution by Serum Albumin Level



- Over half (55.6%) of patients with low albumin (≤ 2.5 g/dL) had CNNA.
- As albumin levels increase, CNNA prevalence declines sharply to just 13.6% in the > 3.0 g/dL group.
- This suggests a strong inverse association between serum albumin and CNNA, highlighting hypoalbuminemia as a potential risk marker.

DISCUSSION

There has been a concern that prophylactic and empirical antibiotic use in patients with cirrhosis has altered the organisms that cause SBP. As a result, the selection of antibiotics for SBP has become an issue that raises the question of bacterial culture. Since culturing bacteria takes time, the delivery of antibacterial treatments is significantly pulled back and ultimately, leads to fatality. Therefore, it becomes relevant to examine potential predictors for developing SBP, especially culture-negative SBP. In this work, we attempted to show whether there are peculiarities of cultures negative SBP versus cultures positive SBP in terms of their characterization and possible predictors. Overall in comparison to CNNA patients with culture-positive SBP patients had a significant rise in the incidence of, fever, diabetes mellitus, and hepatic encephalopathy, however, there was no statistically significant change noted for abdominal pain. On the other side, Kamani et al compared the two groups of ascitic fluid infection SBP and CNNA and the author noted that, patients with SBP (culture positive SBP) had a statistically significant incidence of hepatic encephalopathy no significant difference was observed in abdominal pain and fever compared to groups of CNNA.22 Same study that in a majority of hematological and biochemical laboratory tests, hemoglobin, and white blood cell counts , Our findings showed an improvement in serum creatinine, prothrombin time, and blood PMNL similar to Kamani et al 22 We did not observe significant differences between SBP and

CNNA regarding ascetic TLC and gastrointestinal bleeding. Logistic regression analysis was applied for predictors of culture-positive SBP by following details polymorphonuclear and ascitic polymorphonuclear cells are independent predictor factors for culture-positive SBP. Many studies declared that the total leucocyte count (TLC) is an independent predictor of SBP.\24,25 However Kamani et al in a study compared TLC and ascitic PMN in culture-positive SBP versus CNNA and found no significant difference between the two studied groups as regards total leucocyte and ascitic polymorphonuclear 22,. Terg et al could not detect any of the values of TLC, and ascitic PMN and were similar in both culture-positive SPB and CNNA.23 Na et al concluded that, compared to CNNA patients; those in the SBP group had higher ascites neutrophil count, and positive blood culture rate.26 Several laboratory parameters have been described as potentially predictive of SBP and include; C- reactive protein level, platelet count 28, impaired prothrombin time, and serum creatinine level. In this study, the following were identified to independently predict the development of SBP; ena serum creatinine, serum bilirubin, CRP, WBC, blood PMN, ascitic PMN 7 and, and decrease in In the serum of individuals with SBP, overall bilirubin concentrations were elevated and increased renal dysfunction, significantly increased its mortality, according to Tsung et al.30 Similarly, blood neutrophil percentage and PMNL, as well as increased serum creatinine level, were potential predictors of SBP in a study by Tu B et al who showed that blood neutrophils and PMNL in the ascitic fluid may be effective predictors in early-stage SBP However, gram-positive and quinolone and multidrug resistance has been on the rise in the last few decades in SBP, still, our data revealed that gram-negative organisms were the most common isolates than gram-positive isolates (67% vs 23 %), but 10 % of the patients had both gram-negative and gram-positive isolates in the ascitic fluid. These results are by previous results demonstrated that, SBP in patients with. Cirrhosis is generally attributed to gram-negative bacteria which form the normal flora of the intestines.32,33

CONCLUSION

This work contributes to biomedical advancement since it reveals that culture-negative neurolytic ascites are not rare in those with chronic liver disease. Culture-positive SBP should have been assumed to fare worse in their disease process and experience additional complications (e.g. hepatic encephalopathy) to that of CNNA. We therefore advise that, patients with culture-positive SBP should be hospitalized and not managed as outpatients when in the hospital they will be closely observed by qualified personnel for any sign of deterioration.

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