Original Article

Bacterial Infections in Patients with Liver Cirrhosis: Prevalence, Predictors, and in-Hospital Mortality at a District Hospital in Ghana

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Abstract

Background
In patients with liver cirrhosis, bacterial infections are common with high in-hospital mortality. In Ghana, bacterial infections in liver cirrhosis patients and their impact on in-patient mortality are generally unknown. This study was conducted to define the prevalence, predictors, and treatment outcomes of cirrhotic patients with bacterial infections admitted to a district hospital in Ghana.

Methods
Patients with liver cirrhosis hospitalized from 1st January, 2018 to 24th April, 2020 were consecutively recruited. The demographic data and clinical presentations of the patients were collected using standardized questionnaire. Full blood count, liver function test, renal function test, ascitic fluid analysis and culture, urinalysis and culture, hepatitis B surface antigen, anti-hepatitis C antibodies and abdominal ultrasound scans of the abdomen were conducted for all patients.

Results
There were 110 (65.09%) males out of the 169 patients with a mean age of 47.10±12.88 years. The prevalence of infections was 42.01% (71/169). Out of 71 participants with infections, 59.15% (42/72) died. Fever, encephalopathy, high white cell count, Child-Pugh Class C and Blood urea nitrogen were independent predictors of bacterial infections

Conclusion
Bacterial infection among the participants admitted to district hospital with liver cirrhosis was common with high in-hospital mortality.

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Introduction

Cirrhosis of the liver is one of the commonest causes of morbidity and mortality globally, and bacterial infection is the leading cause of death among these patients.[1,2] In patients with liver cirrhosis, bacterial infection is present in 20 – 60% either at the time of admission or develop during hospitalization.[3]

In cirrhotic patients, the rate of bacterial infection is 4–5 fold greater than the general population.[4] In decompensated liver cirrhotic patients, infection caused by bacteria increases by 3.75-fold with the likelihood of mortality reaching 30% at one month and 63% at one year.[5,6] Spontaneous bacterial peritonitis (SBP), urinary tract infections (UTI), pneumonia, soft tissue infections and bacteremia are

the commonest infections encountered in patients with liver cirrhosis. Complications of liver cirrhosis such as hepatorenal syndrome, hepatic encephalopathy, gastroesophageal variceal bleeding, acute on chronic liver failure and hypervolemic hypernatremia can be precipitated by bacterial infections.[1]

Furthermore, infections lead to impaired quality of life, increased health care cost and multiple hospital admissions in cirrhotic patients.[1] Factors that have been identified to increase risk of bacterial infections in patients with liver cirrhosis include upper gastrointestinal bleeding, poor liver function test, low ascitic fluid protein, prior SBP and hospitalization.[7,8] Gram negative bacteria from intestines have been found to be the commonest cause of bacterial infections in cirrhotic patients but in hospitalized patients, gram positive organisms are increasingly becoming common.[1] Primary infections in patients with liver cirrhosis are caused mainly by enterobacteriaceae and non-enterococcal streptococci. Based on this, drugs that have been used widely in the prevention and treatment of infections in cirrhotic patients are b-lactams and quinolones.[7,9]

Increasing use of these drugs and invasive procedures for which cirrhotic patients are subjected to have made essential changes in the epidemiology of bacterial infections in liver cirrhosis. Non-classical organisms and multidrug resistant bacterial are presently being described in this population as the cause of primary and secondary infections.[7,10] Bacterial infections associated with liver cirrhosis develop because of dysfunction of immune system that happens increasingly during the disease. Liver cirrhosis have been found to cause small intestinal bacterial overgrowth, intestinal permeability, bacterial translocation, and suppression of immune system. These factors come together as a pathophysiological culprit leading to mechanism of bacterial infections seen in patients with cirrhosis of the liver.[11] Making diagnosis of infections in cirrhotic patients is difficult, because they tend to have low baseline white cell count because of hypersplenism, hepatic encephalopathy leading to hyperventilation, increased baseline heart rate due to hyperdynamic circulatory syndrome and blunted raise of body temperature. Therefore, in making a diagnosis of bacterial infection in cirrhotic patients, a high index of suspicion is needed to prevent needless complications and mortality.[1,10]

An infection should be suspected in the presence of the classic general and local symptoms (fever, chills, abdominal pain, or tenderness etc.) or of one of the following signs: new onset hepatic encephalopathy without obvious causes; worsening of renal function; increase of white blood cell (WBC) count; and deteriorating liver function tests.

Timely diagnosis of infection and early treatment once it has occurred and giving prophylactic antibiotics to prevent it in high-risk groups are measures that can decrease clinical effects in patients with liver cirrhosis. Bacterial infections in patients with liver cirrhosis in Ghana and their clinical characteristics are generally unknown. This study was therefore to determine the prevalence, predictors, and treatment outcomes of bacterial infections in patients admitted with liver cirrhosis to a district hospital in Ghana.

Methods

This was a prospective hospital-based study conducted at the medical wards of St. Dominic hospital (SDH), Akwatia, from 1st January 2018 to 30th April 2020. One hundred and sixty-nine (169) participants with cirrhosis of the liver admitted to medical wards during the study period were involved. SDH is a district hospital of Denkyembour district, Akwatia in the eastern region of Ghana and serves as the main referral center for the other surrounding districts. It was founded in 1960 and has 339 beds. It offers a wide range of medical and surgical services such as general surgery, ophthalmology, obstetrics and gynaecology, gastroenterology, neurology, general internal medicine, endoscopy etc. Liver cirrhosis was diagnosed and managed by resident gastroenterologist of SDH based on

the clinical characteristics, haematological and liver function test, and ultrasound scan of the abdomen with findings suggestive of liver cirrhosis.

Inclusion criteria

All adult patients above 18 years with newly diagnosed liver cirrhosis.
Patients who provided informed consent

Exclusion criteria

Patients with HIV or HIV co-infection
Hepatocellular carcinoma patients without underlying liver cirrhosis
Those who refused to give informed consent

Data collection and measurements

Patients who met the criteria above were consecutively recruited after the study was explained to their understanding. Those who consented to the study were administered written standardized questionnaire which included demographic data, patients' clinical features and alcohol use. Data on laboratory and imaging findings were obtained within a day of admission. Based on the ascites club classification, ascites was graded as mild (detectable on ultrasound), moderate (visible moderate symmetrical abdominal distension) and severe (marked abdominal distension). Grading of hepatic encephalopathy was based on Conn's grading system (graded from grade 0 to IV). [12]

Blood and urine test

Ten (10) milliliters of blood were taken for full blood count, renal function test and liver function test including prothrombin time/international normalized ratio (INR). Hepatitis B surface antigen (HBsAg) and anti-hepatitis C antibodies (anti-HCV Ab) test were done for all patients. Child –Pugh scoring (CPS) system and Model for End stage Liver Disease sodium (MELD-Na) were calculated for all patients and were used to assess the severity of liver cirrhosis.[13] Urinalysis was performed for all patients and the parameters that were looked for includes leucocytes, erythrocytes, protein, pus cell, nitrites, crystals, and casts. Those with positive leucocytes or nitrites had a follow up urine culture.

Ascitic fluid analysis

Twenty milliliters (20mls) of ascitic fluid were aspirated for biochemical analysis and culture. Biochemical analysis includes cell count and differentials, albumin, and protein. Ten milliliters (10mls) of ascitic fluid were inoculated into sterile blood culture bottle at the patient bed side and was immediately transported to laboratory. Initial reports of the culture test were obtained after 48 hours, followed by typical identification and biochemical tests.

Imaging studies

All patients had abdominal ultrasound scan done, and the following information were noted: liver surface nodularity, liver mass, size of the liver and spleen and presence of ascites. X-ray of the chest was conducted for all participants with clinical suspicion of pneumonia, mainly to look for areas of consolidation.

Diagnosis of bacterial infection

Diagnosis of SBP was based on positive ascitic fluid cultures with only one species of organism identified and/or neutrophils cell counts of >250/mm3 in the ascetic fluid regardless of the outcome of the ascitic fluid culture. UTI was diagnosed on account of positive urine leucocytes and nitrite and pus cell of > 10 and /or positive culture of > 105 colonies/ml with organism identified not more than 2 species and accompanying with one or more of the following clinical features: fever >37. 5°C, dysuria, chills, or suprapubic tenderness.

Pneumonia was diagnosed based on symptoms such as dyspnea, cough, fever or chills and a new radiographic pulmonary infiltrate for which a non-bacterial complication was unlikely according to the clinical circumstances.

Infective gastroenteritis was diagnosed based on symptoms of fever, chills, watery and mucoid stools, and stool routine examination positive for leukocytes and/or red blood cell. Bacteremia was diagnosed on account of positive blood cultures and clinical characteristics of infection but without any other known cause.

Diagnosis of cellulitis was based on clinical features of infection such as fever or chills and the affected skin appears swollen, red, warm, and tender.

Statistical analysis

Stata (v.13) statistical software was used to analyze the data obtained. All variables were run using descriptive statistics and data presented in suitable figures and tables. Proportion of bacterial infections was determined, and additional analysis was conducted to decide if there were any relationship between bacterial infection and the clinical or laboratory parameters. Level of association was determined using chi square. Multivariable logistic regression analysis was done to determine if any of the clinical and laboratory parameters were predictors of bacterial infection. P-value less than 0.05 was considered significant

Ethical Approval

This study was approved by institutional ethical committee of SDH and conformed to the Helsinki Declaration on Human experimentation Sixth Revision (October 2008).

The study was fully described to the understanding of the potential participants and those who agreed to be part of the study were asked to sign an informed consent form. For those with hepatic encephalopathy, next of kin consented for them.

Results

Demographic characteristics and treatment outcomes

One hundred and sixty–nine (169) patients were recruited for this study, consisting of 110 (65.09%) males. The mean age of the participants was 47.10 ±12.88 years. Out of 71 participants with infections, 59.15% (42/71) died whereas death occurred in 28.57% of those without infection. A statistical significance was observed between those admitted with infection and death with a p value of less than 0.005. Patients with infections had a longer hospital stay (11.88 ± 7.19) than those without infection (9.41±5.59), (p - 0.016) (Table 1).

Table 1. Demographic characteristics, length of stay, and treatment outcomes against infection

Demographic	Overall patient (n=169)	Infection present (n=71)	Infection absent (n=98)	P value
Mean Age of patients	47.10 ±12.88	48.30 ±12.29	45.88±13.46	0.233
Sex of patients				0.042
Female	59 (34.91%)	31 (43.66%)	28 (28.57%)	
Male	110 (65.09%)	40 (56.34%)	70 (71.43%)	
Length of stay	10.65 ± 6.39	11.88 ± 7.19	9.41±5.59	0.016
Outcome of admission				<0.005
Death	70(41.42%)	42 (59.15%)	28 (28.57%)	
Discharge	99 (58. 58%)	29 (40.85%)	70 (71.43%)	

Multiple regression analysis of Child-Pugh class and MELDNa score

Majority of patients who had infections were in CPS class C. Those who were in Class C were 16.6 times more likely to have an infection, compared to those in Class A. [COR=16.6 (95% CI=2.1-130.6), P =0.008] (Table 2).

Patients with higher MELDNa score had more infections compared to those with lower score. Those with MELDNa score more than 32 were 86.6 times more likely to have infections compared to those with score <18. (Suppl Table 1)

Table 2. Multiple regression analysis of Child-Pugh class

	OR	P-value	95% CI
Child-Pugh Score			
A	1		
B	4.80	0.149	0.57 – 40.47
C	16.57	0.008*	2.10 – 130.56

Aetiology of liver cirrhosis

Excessive alcohol consumption and chronic HBV were the major causes of liver cirrhosis, representing 67 (39.64%) and 63 (37.28%) of the patients respectively. Other aetiologies identified were HCV in 5 (2.96%), nonalcoholic fatty liver disease (NAFLD) in 5 (2.96%), schistosomiasis in 4 (2.37%), alcohol in combination with hepatitis B in 7 (4.14%), alcohol in combination with hepatitis C in 2 (1.18%), HCV in combination with HBV in 2 (1.18%), and alcohol in combination with HCV and HBV in 1 (0.60%). In 13 (7.69%) of the patients, causes of their liver cirrhosis were not identified.

Types and Bacteria Identified in Diagnosed Infections

Out of 71 patients diagnosed with infection, pneumonia accounted for 38.03% (27/71), followed by UTI in 23.94% (17/71), SBP in 14.08% (10/71), sepsis in 11.27% (8/71), cellulitis in 7.04% (5/71) and infective gastroenteritis in 5. 63% (4/71). Bacterial isolated from culture was 39.44% of the infectious episodes (considering the type of infection) with majority being gram negative organisms mainly E. coli and K. pneumonia. Only few gram-positive organisms were isolated as shown in Figure 1. There was no death recorded among 4 patients diagnosed with gastroenteritis and all of them were discharged early from hospital. For patients with sepsis, majority of them died and their death occurred within a short period on admission (Suppl Table 2 and 3). In terms of admission outcome, there were no difference between culture negative and positive infection. (Suppl Table 4)

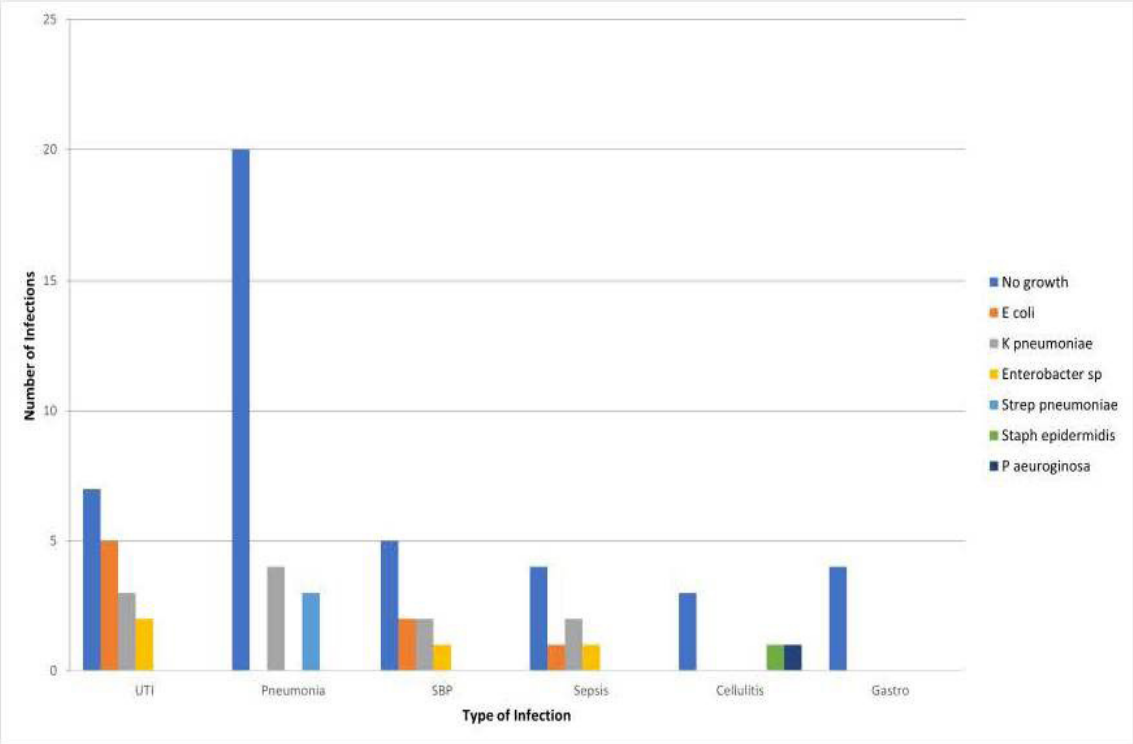

Figure 1. Types and Bacteria Identified in Diagnosed Infections

Association of sociodemographic and clinical features with bacterial infections

Univariate and multivariable logistic regression analysis were performed to determine the association of sociodemographic and clinical characteristics with bacterial infection. The features significantly associated with bacterial infections were male sex, fever, chills, jaundice, pedal oedema, and hepatic encephalopathy. Fever and hepatic encephalopathy were independent predictors of infection. (Table 3)

Table 3. Association of demographic and clinical features with bacterial infections

Variables	Crude OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Age, yrs	1.01	0.99 – 1.04	0.233	1.02	0.99 – 1.05	0.232
Sex (Male)	0.52	0.27 – 0.98	**0.043***	0.56	0.27 – 1.22	0.154
Ascites present	1.18	0.95 – 1.47	0.141	0.82	0.26 – 2.61	0.740
Fever	7.07	2.84 – 17.55	**<0.005***	5.45	1.40 – 21.21	**0.014***
Chills	6.84	2.17 – 21.48	**0.001***	1.74	0.32 – 9.47	0.522
Jaundice	2.22	1.19 – 4.14	**0.012***	1.36	0.65 – 2.87	0.418
Pedal oedema	2.00	1.07 – 3.74	**0.031***	1.94	0.85 – 4.44	0.114
Abdominal pain	0.58	0.31 – 1.12	0.104	0.47	0.20 – 1.06	0.068
Weight loss	1.59	0.74 – 3.45	0.237	1.74	0.69 – 4.41	0.240
Hematemesis	1.07	0.44 – 2.60	0.878	1.35	0.48 – 3.82	0.572
Encephalopathy	2.83	1.46 – 5.52	**0.002***	2.11	0.98 – 4.59	**0.004***

* P < 0.05 – Statistically significant

Association of laboratory parameters with bacterial infections

In the univariate and multivariable logistic regression analysis, laboratory parameters significantly associated with bacterial infections were high bilirubin, mainly conjugated bilirubin, low serum albumin, high international normalize ratio (INR), low sodium, high creatinine and BUN, CPS and MELDNa (Table 3, 4). White blood cell and BUN were the only independent predictors of infection (Table 4).

Table 4. Univariate and Multiple Logistic Regression Analysis (Laboratory data)

Variables	Crude OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Age, yrs	1.01	0.99 – 1.04	0.233	1.04	0.99 – 1.09	0.136
Hb (g/dl)	0.83	0.73 – 0.94	**0.002***	0.97	0.75 – 1.27	0.850
WBC (umol/l)	1.00	0.99 – 1.01	0.668	1.17	1.02 – 1.34	**0.028***
PLT. (10^9/l)	1.00	0.99 – 1.01	0.528	1.00	0.99 – 1.01	0.425
T. Bil. (umol/l)	1.00	1.00 – 1.01	**0.028***	0.98	0.95 – 1.00	0.088
D. Bil. (umol/l)	1.00	1.00 – 1.01	**0.016***	1.03	0.99 – 1.08	0.112
T. Protein(g/l)	0.98	0.96 – 0.99	**0.026***	1.00	0.96 – 1.03	0.828
Albumin (g/l)	0.89	0.84 – 0.93	**<0.005***	0.91	0.82 – 1.01	0.064
ALT (U/L)	0.99	0.99 – 1.00	0.063	1.00	0.98 – 1.02	0.847
AST (U/L)	1.00	0.99 – 1.00	0.522	1.00	0.99 – 1.01	0.914
ALP (U/L)	1.00	0.99 – 1.00	0.932	1.00	0.99 – 1.00	0.922
GGT (U/L)	1.00	0.99 – 1.00	0.625	1.00	0.99 – 1.00	0.852
INR	2.44	1.64 – 3.62	**<0.005***	1.05	0.45 – 2.43	0.910
CPS	1.49	1.27 – 1.74	**<0.005***	1.08	0.71 – 1.65	0.709
MELDNa	1.16	1.10 – 1.23	**<0.005***	1.12	0.94 -1.35	0.205
Na (mmol/l)	0.91	0.86 – 0.96	**0.001***	1.04	0.95 – 1.14	0.391
K (mmol/l)	1.20	0.82 – 1.75	0.351	1.11	0.55 – 2.24	0.775
Cr (umol/l)	1.01	1.00 – 1.01	**0.002***	0.99	0.98 – 1.00	0.189
BUN (umol/l)	1.12	1.05 – 1.19	**<0.005***	1.16	1.02 – 1.31	**0.019***

Abbreviations: ALT- Alanine aminotransferase; ALP- Alkaline phosphatase; GGT- Gamma glutamyl transferase; AST-Aspartate aminotransferase; BUN – Blood urea nitrogen; WBC – white blood cell; CPS – Child-Pugh score; MELDNa – Model for End Stage Liver Disease Sodium; Na – Sodium, K – Potassium, Cr – Creatinine, Hb – Haemoglobin, T. Bil – Total bilirubin; D. Bil – Direct bilirubin; PLT– Platelet; INR – International Normalized Ratio; *P < 0.05 – Statistically significant

Discussion

Due to increase of intestinal bacterial overgrowth and bacterial translocation in patient with liver cirrhosis, they are at increased risk of developing bacterial infection.[1,7] Bacterial infections deteriorate the haemodynamic status of patients with liver cirrhosis and cause decompensation as a result of vasodilation from inflammatory process. The prevalence of bacterial infections in cirrhotic patients varies in different studies and ranges between 20% and 60% at the time of admission or during hospitalization.[3] The prevalence of infection from this study was 42.01%, which is comparable to prevalence of 47.06% reported by a study conducted in Brazil.[14] A lower prevalence of 25.0% and 38.15% had been reported by other studies. [16,15] The difference may be as a result of the demographic characteristics of the patients as well as the causes and severity of liver disease.

According to previous studies, SBP, UTI and pneumonia were the commonest bacterial infections in patients with liver cirrhosis followed by soft tissue and skin infections, bacteremia and others.(3) In this study, the commonest bacterial infections identified were pneumonia (38.03%), UTI (23.94%), and SBP (14.09%). This is similar to common infections [UTI (21.56%), pneumonia (20.91%) and SBP (18.91%)] reported by other studies.[15,17] The common infections are the same in patients with liver cirrhosis, but the proportions differ amongst the types of infection in various studies.

Several studies have reported a variety of clinical features and laboratory parameters associated with the presence of infections in patients with liver cirrhosis. Increase serum aspartate aminotransferase, high serum bilirubin, MELD, BUN, gastrointestinal bleeding, low platelet count, C-reactive protein, Child-Pugh stage C, low ascitic fluid protein, hepatic encephalopathy and abdominal pain have been identified as predictors of bacterial infections.[18,19]

The present study recognized fever, hepatic encephalopathy, high INR, creatinine, bilirubin, BUN, CPS and MELDNa and low haemoglobin, albumin and sodium as predictors of infections. However, fever, encephalopathy, high white cell count and BUN were independent predictors of the presence of infections. One of the recommendations for screening for infections in patients with liver cirrhosis is appearance of hepatic encephalopathy. This is because in patients with hepatic encephalopathy, infections have been identified as one of the main precipitants. Fever is one of the common symptoms of infection. In the current study, patient presenting with fever at the time of presentation was an independent predictor of infections. Poor liver function has been acknowledged as one of the clinical factors linked with an increased risk of developing infections. The CPS and MELDNa are the scoring tools used to determine the severity of liver cirrhosis. Bacterial infections have been found to be common in patients with severe liver cirrhosis and the higher the scoring system (CPS and MELDNa), the more severe the liver disease. In the present study Child-Pugh class C was an independent predictor of bacterial infections. Renal failure has been found to be a complication of bacterial infections in patients with cirrhosis.[20] This is confirmed in this study by the strong association between the infections and renal dysfunction (raised creatinine, BUN and low sodium) Therefore, these parameters could be useful when considering a prophylactic antibiotics treatment for liver cirrhosis patients.

Infections in patients with liver cirrhosis are culture positive in about 50–70% of cases. [21] In a significant proportion of patient, gram negative bacteria are common causes, however, the incidence of gram-positive bacteria has been increasing during the last decade as a result of advancement in the management of liver cirrhosis with the increased use of invasive procedures and continued use of antibiotics such as norfloxacin as a prophylaxis.[8,11]

In this study, microbiological cultures were positive for 39.44% with gram negative organisms being the commonest isolate and only 17.86% gram-positive organisms isolated. This is in contrast with 38% gram-positive bacteria isolated by one study. [19] Increased use of prophylactic antibiotics and invasive procedures performed for patients with liver cirrhosis have accounted for the rising contribution of gram-positive organisms. Not much invasive procedures are being done in the current study site due to lack of resources and expertise, and this may have accounted for the low gram-positive organisms isolated in this study.

Liver cirrhosis patients with bacterial infection as a complication have a higher risk of in-hospital mortality and a longer hospital stay.[5] In cirrhotic patients, infections have been found to increase death rate by 4-fold; within one month about 30% of patients with infection die and another 30% die by 1 year.[22] Bacterial infections progressing to septic shock and multiple organ failure in cirrhotic patients are linked with a shortterm mortality of patients beyond 75%.[7,18] One study reported 30% in-patient death rate among cirrhotic patients admitted with bacterial infection and one systematic review reported mortality rate of between 32.3-47.2%.[14,22] In the current study, mortality among patients with infections were as high as 60% with longer hospital stay compared with those without infections. The variations among mortality rates maybe as a result of differences according to the study population, type and severity of infections identified, causes and severity of liver disease.

This study is not without limitations. This data is from a single center and may not be representative of the general population, as this was a district, hospital-based study in Ghana. Information of previous antibiotics use were not collected, and this may affect the culture results.

Conclusion

In patients admitted at SDH with liver cirrhosis, bacterial infection was common with high in-hospital death. The common bacterial infections were pneumonia, UTI, and SBP. Fever, encephalopathy, high white cell count and BUN independently predicted the presence of infections. Measures to prevent and treat bacterial infections timely may lead to an improvement in patient's outcome and reduce in-hospital mortality. Similar studies should be conducted nationwide in multiple centers and regions to get a countrywide prevalence, common infections, and in-hospital mortality of patients with liver cirrhosis and bacterial infection. In addition, studies must be conducted to define the frequency of multidrug resistant bacteria in these patients which is rising globally

Authors' contributions

AD and AAN were involved in the project design, recruitment of patients, analysis of data and manuscript drafting. FAA, FOP, DAB, FD, and SAA, assisted the primary investigator in patient enlistment, analysis, and interpretation of the data, analytically revised the article and provided final endorsement of the article.

Conflict of interest

No conflict of interest was declared by the authors.

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