Nosocomial Bacterial and Fungal Chest Infections in Cirrhotic Patients

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Background and aim: For a long time, the connection between liver cirrhosis (LC) and infections had been studied extensively. Because of their weakened immune system, cirrhotic patients are more likely to contract infectious diseases. Cirrhotic patients are more likely to undergo invasive diagnostic or surgical procedures that can change the host's protective barrier, putting them at a higher risk of contracting an infection.

Patients and Methods: The study was conducted over one year duration between January and December 2019 at intensive care unit (ICU). It enrolled all patients with decompensated LC but patients with compensated LC or underlying chronic chest disease were excluded. Baseline evaluation with laboratory data was done in all patients. Blood and sputum cultures were achieved in patients with suspected NCI.

Results: 845 patients with LC were admitted to ICU but 345 of them were excluded so, 500 patients were enrolled in the analysis. NCI occurred in 100 (20%) patients. The most frequent isolated organisms were Klebsiella species (32%), Candida albicans (19%), Strept.pneumoniae (12%) and Staph.aureus (10%). All of these infections were in form of pneumoniae. Up to 65% of patients with NCI were died. Based on the current study the predictors of NCI were; old age spontaneous bacterial peritonitis and low serum albumin.

Conclusion: Patients with liver cirrhosis are liable to infections secondary to dysregulated immunity. NCI in cirrhotic patients has serious outcome. Hospitalized cirrhotic patients should be screened for NCI.

INTRODUCTION

In hospitalized cirrhotic patients, nosocomial chest infections (NCI) are a frequent complication. Any chest infection contracted by a patient in a hospital at least 48–72 hours after admission is considered to be NCI. In cirrhotic patients, infectious complications are the most common cause of death. Antibiotics should be started as soon as possible based on the culture results **[1]**.

The high risk of infection in patients with liver cirrhosis (LC) is caused by defects in natural defense mechanisms, such as acquired and progressive defects of the innate immune and reticuloendothelial systems, which are exacerbated by the presence of alcohol (alcohol consumption; alterations in the enteric flora; intrinsic cellular defects and the increasing use of invasive procedures) **[2]**.

The seriousness of the disease, pre-existing conditions, and the host's reaction to infection are leading factors in poor outcome of these patients. Infections are a common cause of morbidity and mortality in patients with chronic liver disease **[3]**.

NCI is considered a fatal complication in LC patients, but there are few studies in this area. As a result, we created this study to examine the pattern of nosocomial infection in cirrhotic patients, including the incidence, organisms, and potential predictors of NCIs.

PATIENTS AND METHODS

Study setting and design

A cross sectional hospital study was prospectively conducted at Intensive Care Unit (ICU) of the Tropical Medicine and Gastroenterology Department at , Al Rajhi Liver Hospital, Assiut University Hospitals, Assiut, Egypt over one year duration between January and December 2019.

Inclusion& exclusion criteria

All patients with LC who were admitted to ICU during the study period were enrolled. Patients with known chronic chest diseases as bronchial asthma or chronic obstructive lung disease, human immunodeficiency virus, history of organ transplantation with immunosuppression, and liver cirrhosis with Child A classification were excluded.

Patients

A total of 845 cirrhotic patients were admitted during the study period. 345 patients were excluded (250 patients had compensated LC (Child A)) and 95 patients had chronic chest disease). So a total 500 patients had met the inclusion criteria. Out of enrolled patients 100/500 (20%) patients developed nosocomial chest infection while 400/100 (80%) patients didn't develop (figure 1).

Methods

Careful history taking and clinical evaluation were done to all enrolled patients. The clinical evaluation was repeated after two days to detect any manifestations of NCIs as development of fever, cough, dyspnea, and/or expectoration. Baseline laboratory assessment included liver and kidney functions, coagulation profile, complete blood count, and random blood sugar were achieved.

Plain chest radiograph was done at baseline and later on in case of suspicious of NCIs. Chest sonar was required if there was suspicious of underlying chest disease (if present, patient was excluded). All patients were assessed by abdominal ultrasound at baseline.

A sputum sample was obtained from cases with suspected NCIs for culture and antimicrobial sensitivity. In most cases, the sputum sample was collected early in the morning before patient ate or drunk anything after rinsing the mouth with water. In case of very sick or unconscious patients, the sample was obtained by suction through nasotracheal catheter.

The following media were used for culture: chocolate agar (non-selective growth media), blood agar (isolation of streptococci), Macconky agar (isolation of gram negative bacilli), Mannitol salt agar (isolation of staph aureus), and Sabroud dextrose agar was used for isolation of fungi. Also, blood culture was performed in case of suspicious of NCIs on the same media of sputum culture. Any detected organism in the culture was defined under a microscope or by chemical tests. Sensitivity testing was performed to know the effective antimicrobial agents.

Statistical analysis

Data was analyzed those using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data was expressed in form of mean ± SD while nominal data was expressed in form of frequency (percentage). Chi^2-test was used to compare the nominal data of patients with NCI and those without NCI while continuous data of both groups were compared with Student t test. Precitors of NCI among hospitalized decompensated cirrhotic patients were determined by multivariate regression analysis. Level of confidence was kept at 95% and hence, P value was considered significant if <0.05.

RESULTS

Demographic and clinical data of enrolled patients (table 1):

It was noticed that patients with NCI had significantly higher mean age in comparison to those without NCI (63.68 ± 9.30 vs. 54.56 ± 10.34; *P*< 0.001). Also, majority (95%) of patients who developed NCI was 40 years old or more while majority of patients without NCI were < 40 years old.

Mean duration of liver cirrhosis was significantly higher among patients with NCI (7.89 ± 2.34 vs. 4.55 ± 1.20 years; *P*= 0.04). Frequency of hematemesis/ melena alone was significantly higher among those without NCI (200 (50%) vs. 25 (25%); *P*= 0.04) but patients with NCI had significantly higher frequency of hepatic encephalopathy (45 (45%) vs. 80 (20%); *P*= 0.03), spontaneous bacterial peritonitis (50 (50%) vs. 120 (30%); *P*= 0.01). Both groups

showed no significant diffrences as regard baseline clinical evaluation (*P*> 0.05).

Baseline laboratory data and abdominal ultrasound of enrolled patients (table 2):

Both groups of patients had insignificant differences as regard baseline laboratory data and abdominal ultrasound with exception of significantly lower serum albumin (23.06 ± 6.18 vs. 29.11 ± 2.22 mg/dl; *P*= 0.03) in patients who developed NCI.

Radiological findings and cultures among patients with NCI (table 3):

Out of studied patients with NCI; 40 (40), 35 (35%) and 65 (65%) patients had pleural effusion, bronchopneumonia, and pneumonia, respectively. Ninety five patients had no growth in blood culture. Enterococcus, Actinobacter species, E.coli and Staph.aureus were observed in 2 (2%), 1 (1%), 1 (1%) and 1 (1%) patient, respectively.

The most detected organisms in sputum culture were Klebsiella species (32%), Candida albicans (19%), Strept.pneumoniae (12%) and Staph.aureus, respectively. It was noticed that Pseudomonas species was observed in 9(9%) while 8 (8%) patients had MRSA

Hospital stay and outcome of enrolled patients (table 4):

Patients with NCI had significantly longer duration of hospital stay (11.34 ± 2.34 vs. 8.34 ± 1.13 days; *P*= 0.01). It was noticed that majority (65%) of patients with NCI were dead while majority (60%) of patients with no-NCI were alive.

Predictors of NCI among enrolled patients (table 5):

Based on the current study, predictors for NCI in patients with advanced LC were; old age (OR=2.33, 95%CI= 1.09-4.65, *p*< 0.001), spontaneous bacterial peritonitis (OR=2.11, 95%CI= 2.01-5.67, *p*< 0.001), and low serum albumin (OR=4.01, 95%CI= 3.1-10.11, *p*<0.001).

Table (1): Demographic and clinical data of enrolled patients.

	NCI (N= 100)	**No-NCI (n= 400)**	***P* value**
Age (years)	63.68 ± 9.30	54.56 ± 10.34	**< 0.001**
Age group			**< 0.001**
< 40 years	5 (5%)	300 (75%)	
≥ 40 years	95 (95%)	100 (25%)	
Sex			0.45
Male	63 (63%)	272 (68%)	
Female	37 (37%)	128 (32%)	
Duration of liver cirrhosis (years)	7.89 ± 2.34	4.55 ± 1.20	**0.04**
Hypertension	27 (27%)	126 (31.5%)	0.34
Diabetes mellitus	34 (34%)	116 (29%)	0.09
Ischaemic heart disease	5 (5%)	18 (4.5%)	0.12
Chronic kidney disease	7 (7%)	20 (5%)	0.30
Previous ICU's admission	22 (22%)	84 (21%)	0.22
Causes of admission			
Hematemesis/ melena	25 (25%)	200 (50%)	**0.04**
Hepatic encephalopathy	45 (45%)	80 (20%)	**0.03**
ACLF	10 (10%)	20 (5%)	0.33
SBP	50 (50%)	120 (30%)	**0.01**
Aetiology of liver cirrhosis			0.45
Hepatitis C virus	65 (65%)	250 (62.5%)	
Hepatitis B virus	15 (15%)	75 (18.8%)	
Both HCV/HBV	10 (10%)	50 (12.5%)	
Autoimmune liver disease	7 (7%)	15 (3.7%)	
Cryptogenic cirrhosis	3 (3%)	10 (2.5%)	
Foeter hepaticus	14 (14%)	60 (15%)	0.08
Lower limb edema	87 (87%)	312 (78%)	0.06
Ascites	75 (75%)	280 (70%)	0.07
Splenomegaly	50 (50%)	212 (53%)	0.11
Hepatomegaly	33 (33%)	120 (30%)	0.10

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. **NCI**: nosocomial chest infection; **SBP**: spontaneous bacterial peritonitis; **ACLF**: acute on top liver cell failure; **HBV**: hepatitis B virus; **HCV**: hepatitis C virus

Table (2): Baseline laboratory data and abdominal ultrasound in enrolled patients.

	NCI (N= 100)	No-NCI (n= 400)	*P* value
Hemoglobin (g/dl)	8.92 ± 1.74	9.56 ± 2.22	0.45
Leucocytes (x10^9/l)	6.4 ± 2.40	5.68 ± 2.22	0.22
Platelets (x10^9/l)	130.68 ± 71.79	129.45 ± 44.56	0.09
INR	1.65 ± 0.38	1.45 ± 0.25	0.10
Bilirubin (mg/dl)	4.56 ± 1.01	3.98 ± 1.11	0.19
Aspartate transaminase (u/l)	69.43 ± 18.97	70.45 ± 4.77	0.23
Alanine transaminase (u/l)	91.13 ± 6.18	98.34 ± 10.11	0.35
Albumin (mg/dl)	23.06 ± 6.18	29.11 ± 2.22	**0.03**
Creatinine (mg/dl)	102.45 ± 21.09	99.98 ±11.33	0.55
Urea (mg/dl)	23.33 ± 11.09	19.89 ± 10.33	0.56
Sodium (mmol/l)	119.34 ± 2.34	122.11 ± 2.33	0.43
Potassium (mmol)	3.89 ± 0.74	4.01 ± 0.46	0.10
Ascites			0.19
Absent	15 (15%)	100 (25%)	
Mild	17 (17%)	80 (20%)	
Moderate	42 (42%)	160 (40%)	
Massive	26 (26%)	60 (15%)	
Splenomegaly	68 (68%)	200 (50%)	0.22
Hepatomegaly	33 (33%)	150 (37.5%)	0.10
Portal vein thrombosis	2 (2%)	16 (4%)	0.11
Hepatic focal lesions	3 (3%)	21(5.3%)	0.15
Child-Pugh class			0.56
Class B	47 (47%)	198 (49.5%)	
Class C	53 (53%)	202 (51.5%)	
Child-Pugh score	9.66 ± 1.22	8.87 ± 1.34	0.09

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. **INR**: international randomized ratio; **NCI**: nosocomial chest infection

Table (3): Radiological findings and cultures among patients with NCI.

	N= 100
Chest radiology	
Pleural effusion	40 (40%)
Bronchopneumonia	35 (35%)
Pneumonia	65 (65%)
Blood culture	
No growth	95 (95%)
Enterococcus	2 (2%)
Actinobacter species	1 (1%)
E.coli	1 (1%)
Staph.aureus	1 (1%)
Sputum culture	
Klebsiella species	32 (32%)
Candida albicans	19 (19%)
Strept.pneumoniae	12 (12%)
Staph.aureus	10 (10%)
Pseudomonas	9 (9%)
MRSA	8 (8%)
Pneumococcus	5 (5%)
Enterococcus	2 (2%)
Shingomonas paucimobis fungi	2 (2%)
Proteus	1 (1%)

Data expressed as frequency (percentage). **NCI**: nosocomial chest infection

Table (4): Hospital stay and outcome among patients.

	NCI (N= 100)	No-NCI (n= 400)	*P* value
Hospital stay	11.34 ± 2.34	8.34 ± 1.13	0.01
Outcome			0.03
Alive	35 (35%)	240 (60%)	
Dead	65 (65%)	610 (40%)	

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. **NCI**: nosocomial chest infection

Table (5): Predictors of NCI among enrolled patients.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Old age (> 40 years)	2.11 (1.19-5.11)	< 0.001	2.33 (1.09-4.65)	< 0.001
Duration of liver disease	1.11 (0.11-2.11)	0.22		
Hematemesis	0.98 (0.30-0.99)	0.08		
Encephalopathy	2.10 (0.49-3.01)	0.14		
SBP	3.33 (1.09-7.77)	0.01	2.11 (2.01-5.67)	< 0.001
Low serum albumin	3.98 (2.39-9.77)	0.01	4.01 (3.11-10.11)	< 0.001

OR: odd's ratio; **CI**: confidence interval; **SBP**: spontaneous bacterial peritonitis

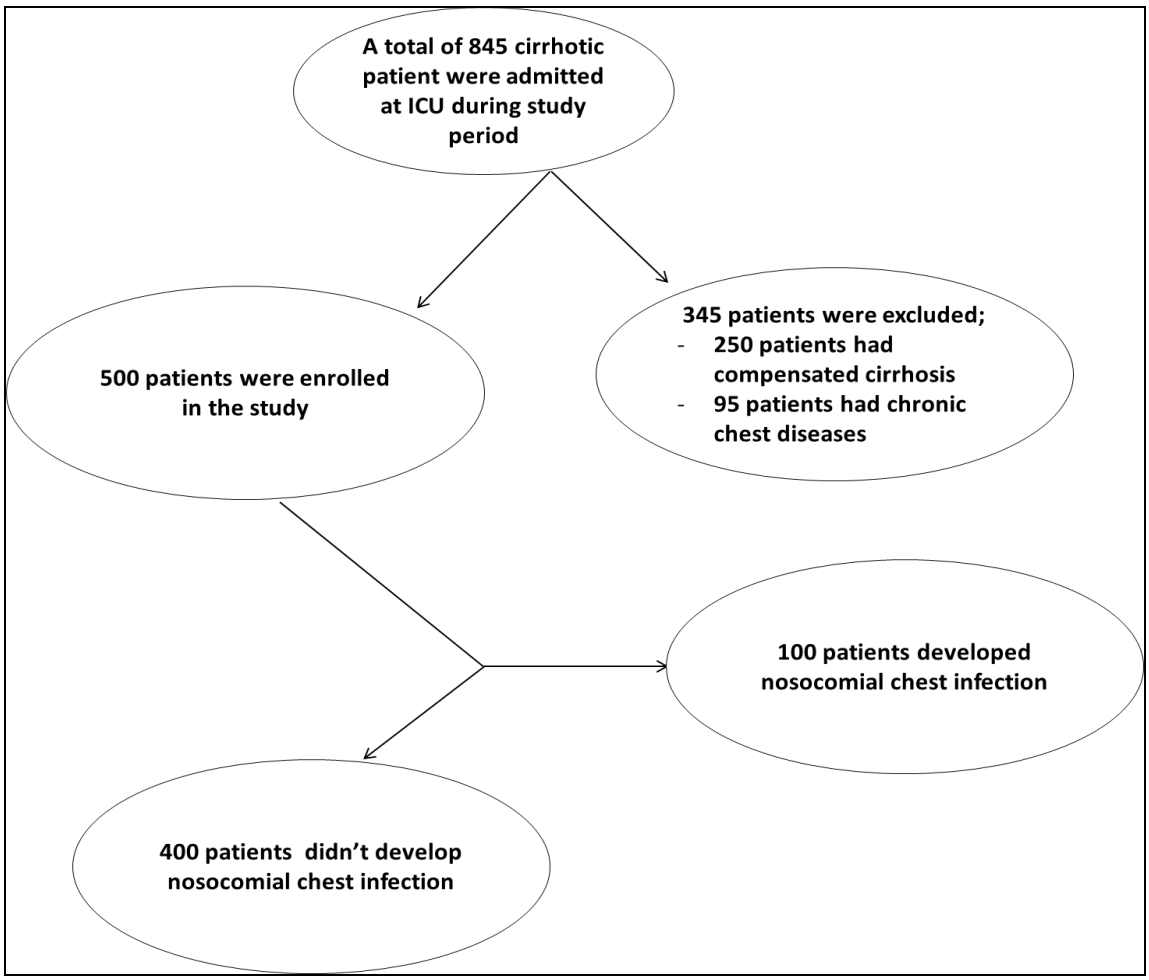

Figure (1): Flow chart of the current study.

DISCUSSION

Cirrhosis is one of the leading causes of death worldwide, especially in developing countries, with 1 year mortality rates ranging from 1% to 57% depending on stage **[4]**. Our study reported that incidence of NCI was 100/500 (20%). This incidence of NCI was fairly high. The fact that all of the patients in the current study had advanced liver disease may explain the high rate of NCI.

In a line with the current study, Fasolato et al [2009] registered that high incidence of NCI in patients with decompensated LC (24% of 337 patients included in the study). Following urinary infection, NCI was the second most common infection among patients with decompensated LC. Those patients who developed hospital acquired infection either NCI or UTI had high mortality rate up to 45% **[5]**.

Xu et al. [2018] registered that occurrence of NCI among decompensated cirrhosis was 6.5%. This was lower than many other studies that had previously been published. That may be due to the fact that the majority of their patients were in the early stages of liver disease **[4]**.

In the current research, the mortality rate in patients who developed NCI was (65% vs. 40%; P=0.03) as compared to those who did not develop NCI. Patients with NCI had a substantially higher mortality rate and length of stay in the hospital than those without NCI. According to previous research, infectious diseases was associated with a 4-fold increase in mortality in cirrhotic patients, with 30% dying within 30 days and another 30% dying within a year of infection **[6]**.

According to Hung et al, NCI occurred in 7.7% of enrolled patients and was associated with the highest risk of mortality among decompensated cirrhotic patients, which was around 3-fold higher than the mortality of cirrhotic patients without NCI, where 50% of patients with NCI died **[7]**.

Importantly, pneumonia had the highest 30-day mortality rate among all infection complications in an infectious disease study of 4576 cirrhotic patients, with a 2.95-fold rise in 30-day mortality. Cirrhosis harmed health outcomes and raised 28-day mortality by up to 11-fold in patients with care unit-acquired pneumonia **[8]**.

Based On the current study, predictors for NCI in patients with advanced LC were; old age (OR=2.33, 95%CI= 1.09-4.65, p< 0.001), hypertension (OR=1.45, 95%CI= 1.11-3.44, p<0.001), diabetes mellitus, (OR=2.50, 95% CI = 1.99-5.67, p<0.001), spontaneous bacterial peritonitis (OR=2.11, 95%CI= 2.01-5.67, p<0.001), and low serum albumin (OR=4.01, 95%CI= 3.1-10.11, p< 0.001).

According to our findings, age > 65 years, male sex, and the prevalence of chronic diseases such as cardiovascular disease and chronic lung disease were all predictors of mortality in a previous study of 520 patients **[9]**.

Klebsiella species (32%), Strept.pneumoniae (12%), and Staph aureus (10%) were the most commonly identified organisms in sputum culture, according to our findings. In certain cases (92%), no bacterial or fungal organisms could be found in blood cultures and only a few organisms could be detected (Enterococcus 2%, Actinobacter species 1%, E.coli 1% and Staph. aureus 1%).

Ekpanyapong and Reddy [2019] indicated that the most common pathogens for NCI were gram-negative bacilli and staphylococci, which were also linked to high mortality, supporting our findings **[10]**.

In contrast to our findings, Wu et al [2016] recorded that S. aureus was the most frequently isolated pathogen (27.4%) in cirrhotic patients with NCI. This was clarified by the fact that their research included a high number of diabetic patients. Metformin modified glucose flux through the airway epithelium to reduce hyperglycemia-induced bacterial development, and hyperglycemia encouraged respiratory S. aureus infection. Furthermore, diabetes is an immunosuppressive condition that increases the risk of methicillin-resistant S. aureus infection **[11]**.

Owing to the use of antibiotics to avoid infections, Candida spp. is the most common cause of fungal infections in patients with liver cirrhosis. Antibiotics favour an excessive growth of fungi. In our sample, sputum cultures of 100 patients showed Candida albicans in 19 patients (19%) and Shingomonas paucimobis fungi in two patients (2 %).

Candida spp. was found in 19 (10%) cases of 42 percent candidemia in a previous study of 185 patients with culture-positive infections. Just

47% of fungal infections were diagnosed and treated with antifungal agents while the remaining patients died. In patients with fungal infections, mortality rates were 58 percent and 29 percent at one month, respectively, as compared to those with bacterial infections **[12]**.

There were some drawbacks to our research. First of all, our study was a single center cohort. Our findings should be validated in larger sample studies due to the small number of patients. Second, immunosuppression was not included in our research, and organ transplantation was also not included.

As a consequence, exclusions can lead to statistical bias and erroneous conclusions. Finally, we did not conduct a long-term follow-up and survival study at various points after discharge. Nonetheless, our research was the first to look at the prognosis of cirrhotic patients with NCI.

In conclusion, Patients with decompensated liver cirrhosis are at risk of contracting a variety of infections. In such patients, NCI is one of the most common infections. In addition, NCI had a poor prognosis in these patients, with a higher mortality rate.

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Conflicts of Interest: Authors declared no conflict of interest

Ethical consideration: This work was conducted in accordance with the Code of Good Practice and the guidelines of Declaration of Helsinki, 7th revision, 2013 and after being approved by the Medical Ethics Committee of the Faculty of Medicine at the Assiut University with IRB No. 17100439. The study was registered on *clinicaltrials.gov* with IDNCT03413293. All patients were informed about the study and a written consent was obtained from each patient.

Abbreviations: NCI: nosocomial chest infection; LC: liver cirrhosis; SBP: spontaneous bacterial peritonitis; ICU: intensive care unit**.**

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